Extracorporeal Membrane Oxygenation (ECMO) for Neonates

Number: 0546

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Extracorporeal Membrane Oxygenation (ECMO) for Neonates:

Aetna considers ECMO medically necessary in neonates who meet all of the following criteria:

I. Diagnosis of any of the following:
   
   A. Congenital diaphragmatic hernia; or
   B. Hyaline membrane disease; or
   C. Meconium aspiration; or
   D. Persistent fetal circulation; or
   E. Possible cardiac anomaly; or
   F. Refractory neonatal septic shock; or
   G. Respiratory distress syndrome; or
   H. Uncontrollable air leak.

   and

II. Gestational age of at least 34 weeks; and
III. Birth weight of 2,000 grams or greater; \textit{and}

IV. Age less than 10 days (preferably less than 7 days).

Aetna considers ECMO for neonates experimental and investigational when criteria are not met because of insufficient evidence of its safety and effectiveness.

\textbf{ECMO for Children and Adults:}

Aetna considers ECMO and extracorporeal life support (ECLS) medically necessary for children and adults with any of the following diagnoses when the risk of death is very high despite optimal conventional therapy:

1. Adult respiratory distress syndrome (ARDS); \textit{or}
2. As a short-term (i.e., hours to a few days) bridge to heart, lung or heart-lung transplantation; \textit{or}
3. As a short-term bridge to durable mechanical circulatory support; \textit{or}
4. Following heart surgery to ease transition from cardiopulmonary bypass to ventilation; \textit{or}
5. Non-necrotizing pneumonias (both bacterial and viral); \textit{or}
6. Primary graft failure after heart, lung or heart-lung transplantation; \textit{or}
7. Pulmonary contusion; \textit{or}
8. Refractory pediatric septic shock; \textit{or}
9. Smoke inhalation injury; \textit{or}
10. Other reversible causes of respiratory or cardiac failure (e.g., myocarditis, cardiogenic shock) that is unresponsive to all other measures.

Aetna considers ECMO/ECLS for children and adults experimental and investigational for all other indications (e.g., acute massive pulmonary embolism, and pregnant and post-partum women with H1N1-related acute respiratory distress syndrome) because of insufficient evidence of its safety and effectiveness.
See also CPB 0518 - Nitric Oxide, Inhalational (INO) (0518.html).

**Background**

**ECMO in Neonates:**

Extra-corporeal membrane oxygenation (ECMO) is a term used to describe prolonged (days to weeks) mechanical support for patients with reversible heart or lung failure. The technology is similar to cardiopulmonary bypass as used during cardiac surgery, only modified for prolonged use at the bedside intensive care unit. Extra-corporeal membrane oxygenation is capable of effectively and safely supporting respiration and circulation in neonates with severe reversible respiratory failure and a moribund clinical presentation. When applied early in the course of severe failure, newborns who would have otherwise died will regularly survive. Contraindications to ECMO therapy in neonates include any severe diagnosis which would decrease the probability of survival of the neonate candidate. Some of the limiting diagnoses include: intracerebral hemorrhage; severe brain damage; multiple congenital anomalies; irreversible brain damage; and age greater than 10 days.

In a randomized controlled study (n = 59), Griffin and colleagues (2004) concluded that dexamethasone given during the first 3 days of ECMO results in significant improvement in lung injury scores by day 3 of ECMO but does not significantly decrease the duration of ECMO or improve survival. The preponderance of evidence would not support the use of dexamethasone in this setting.

The American College of Critical Care Medicine's clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock (Brierley et al, 2009) noted that children with septic shock, compared with adults, require ECMO for refractory shock.

**ECMO in Children and Adults:**
ECMO and extra-corporeal life support (ECLS) are used in children and adults with irreversible heart or lung failure for prolonged (days to weeks) mechanical support. The goal of ECMO/ECLS for pediatric or adult patients is to provide lung rest from the high levels of oxygen and higher airway pressures that are necessary to support oxygenation and ventilation. Proper selection involves determining in which patients the disease process itself is reversible (with 1 to 2 weeks of ECMO/ECLS). Contraindications to ECMO/ECLS in pediatric and adult patients include: necrotizing pneumonia; multiple organ failure in addition to respiratory or cardiac failure; metastatic disease; major central nervous system injury; quadriplegia; and more than 10 days on mechanical ventilation prior to the start of ECMO/ECLS.

An assessment of ECMO by the National Institute for Clinical Excellence (NICE, 2004) stated that its use is established in post-neonatal children to treat respiratory or cardiac failure that is unresponsive to all other measures, but is considered to have a reversible cause. According to NICE guidelines, ECMO may also be used following heart surgery in post-neonatal children to ease the transition from cardiopulmonary bypass to ventilation. National Institute for Clinical Excellence (2004) concluded that the use of ECMO for these indications in adults is currently the subject of investigation in the CESAR trial (Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure).

Thiagarajan et al (2007) reported on outcomes and predictors of in-hospital mortality after ECMO used to support cardiopulmonary resuscitation (E-CPR). Outcomes for patients aged less than 18 years using E-CPR were analyzed with data from the Extracorporeal Life Support Organization, and predictors of in-hospital mortality were determined. Of 26,242 ECMO uses reported, 695 (2.6 %) were for E-CPR (n = 682 patients). Survival to hospital discharge was 38 %. In a multivariable model, pre-ECMO factors such as cardiac disease (odds ratio [OR] 0.51, 95 % confidence interval [CI]: 0.31 to 0.82) and neonatal respiratory disease (OR 0.28, 95 % CI: 0.12 to 0.66),
white race (OR 0.65, 95 % CI: 0.45 to 0.94), and pre-ECMO arterial blood pH greater than 7.17 (OR 0.50, 95 % CI: 0.30 to 0.84) were associated with decreased odds of mortality. During ECMO, renal dysfunction (OR 1.89, 95 % CI: 1.17 to 3.03), pulmonary hemorrhage (OR 2.23, 95 % CI: 1.11 to 4.50), neurological injury (OR 2.79, 95 % CI: 1.55 to 5.02), CPR during ECMO (OR 3.06, 95 % CI: 1.42 to 6.58), and arterial blood pH less than 7.2 (OR 2.23, 95 % CI: 1.23 to 4.06) were associated with increased odds of mortality. The authors concluded that ECMO used to support CPR rescued one-third of patients in whom death was otherwise certain. Patient diagnosis, absence of severe metabolic acidosis before ECMO support, and uncomplicated ECMO course were associated with improved survival. This is in agreement with the observations of Alsoufi et al (2007) who noted that acceptable survival and neurological outcomes (30 %) can be achieved with E-CPR in children after prolonged cardiac arrest (up to 95 minutes) refractory to conventional resuscitation measures.

In a review and quantitative analysis, Chawlin and colleagues (2008) stated that the role of ECMO has not been formally validated for patients with adult respiratory distress syndrome (ARDS). In anticipation of publication of the conventional ventilation versus ECMO in severe adult respiratory failure (CESAR) trial, the role of ECMO in this setting was reviewed. An electronic search for studies reporting the use of ECMO for the treatment of ARDS revealed 2 randomized controlled trials (RCTs) and 3 non-controlled trials. Bayesian analysis on the 2 RCTs produced an odds ratio mortality of 1.28 (CI: 0.24 to 6.55) showing no significant harm or benefit. Pooling was not possible for the non-controlled studies because of differing admission status and ECMO selection criteria and an inability to control for these differences in the absence of individual patient data. A large number (n = 35) of case series have been published with generally more positive results. The authors concluded that ECMO, as rescue therapy for ARDS, appears to be an unvalidated rescue treatment option. Analysis and review of trial data does not support its application; however the body of reported cases suggests otherwise.
The primary results for the CESAR trial, a multi-center randomized controlled clinical trial comparing conventional ventilation methods with ECMO for the treatment of severe acute respiratory failure in adults, has been published in the *Lancet*. Peek et al (2009) examined the safety, clinical efficacy, and cost-effectiveness of ECMO compared with conventional ventilation support. These investigators used an independent central randomization service to randomly assign 180 adults in a 1:1 ratio to receive continued conventional management or referral to consideration for treatment by ECMO. Eligible patients were aged 18 to 65 years and had severe (Murray score greater than 3.0 or pH less than 7.20) but potentially reversible respiratory failure. Exclusion criteria were: high pressure (greater than 30 cm H(2)O of peak inspiratory pressure) or high fraction of inspired oxygen [FiO(2)] (greater than 0.8) ventilation for more than 7 days; intra-cranial bleeding; any other contraindication to limited heparinization; or any contraindication to continuation of active treatment.

The primary outcome was death or severe disability at 6 months after randomization or before discharge from hospital. Primary analysis was by intention-to-treat. Only researchers who did the 6-month follow-up were masked to treatment assignment. Data about resource use and economic outcomes (quality-adjusted life-years) were collected. Studies of the key cost generating events were undertaken, and these researchers did analyses of cost-utility at 6 months after randomization and modelled lifetime cost-utility. A total of 766 patients were screened; 180 were enrolled and randomly allocated to consideration for treatment by ECMO (n = 90) or to receive conventional management (n = 90); 68 (75 %) patients actually received ECMO; 63 % (57/90) of patients allocated to consideration for treatment by ECMO survived to 6 months without disability compared with 47 % (41/87) of those allocated to conventional management (relative risk 0.69; 95 % CI: 0.05 to 0.97, p = 0.03). Referral to consideration for treatment by ECMO led to a gain of 0.03 quality-adjusted life-years (QALYs) at 6-month follow-up [corrected]. A lifetime model predicted the cost per QALY of ECMO to be 19,252 pounds (95 % CI: 7622 to 59 200) at a discount rate of 3.5 %.
The authors recommended transferring of adult patients with severe but potentially reversible respiratory failure, whose Murray score exceeds 3.0 or who have a pH of less than 7.20 on optimum conventional management, to a center with an ECMO-based management protocol to significantly improve survival without severe disability. They stated that this strategy is also likely to be cost-effective in settings with similar services to those in the United Kingdom.

In a retrospective review, Tissot et al (2009) analyzed the indications and outcome of ECMO for early primary graft failure and determined its impact on long-term graft function and rejection risk. A total of 28 (9 %) of 310 children who underwent transplantation for cardiomyopathy (n = 5) or congenital heart disease (n = 23) required ECMO support. The total ischemic time was significantly longer for ECMO-rescued recipients compared with the authors' overall transplantation population (276 +/- 86 mins versus 242 +/- 70 mins, p < 0.01). The indication for transplantation, for ECMO support, and the timing of cannulation had no impact on survival. Hyperacute rejection was uncommon; 15 children were successfully weaned off ECMO and discharged alive (54 %). Mean duration of ECMO was 2.8 days for survivors (median of 3 days) compared with 4.8 days for non-survivors (median of 5 days). There was 100 % 3-year survival in the ECMO survivor group, with 13 patients (46 %) currently alive at a mean follow-up of 8.1 +/- 3.8 years. The graft function was preserved (shortening fraction 36 +/- 7 %), despite an increased number of early rejection episodes (1.7 +/- 1.6 versus 0.7 +/- 1.3, overall transplant population, p < 0.05) and hemodynamically comprising rejection episodes (1.3 +/- 1.9 versus 0.7 +/- 1.3, overall transplant population, p < 0.05). The authors concluded that overall survival was 54 %, with all patients surviving to at least 3 years after undergoing transplantation. None of the children requiring more than 4 days of ECMO support survived. Despite an increased number of early rejection and hemodynamically compromising rejection episodes, the long-term graft function is similar to the overall transplantation population.
Bermudez and colleagues (2009) analyzed outcomes after ECMO use for primary graft dysfunction (PGD) after lung transplantation at a single center over a 15-year period and assessed long-term survival. From March 1991 to March 2006, 763 lung or heart-lung transplants were performed at the authors' center. A total of 58 patients (7.6 %) required early (0 to 7 days after transplant) ECMO support for PGD. Veno-venous or veno-arterial ECMO was implemented (32 and 26 cases) depending on the patient's hemodynamic stability, surgeon's preference, and the era of transplantation. Mean duration of support was 5.5 days (range of 1 to 20). Mean follow-up was 4.5 years. Thirty-day and 1-year and 5-year survivals were 56 %, 40 %, and 25 %, respectively, for the entire group. Thirty-nine patients were weaned from ECMO, 21 veno-venous and 18 veno-arterial (53.8 % and 46.2 %), with 1-year and 5-year survivals of 59 % and 33 %, inferior to recipients not requiring ECMO (p = 0.05). Survival at 30 days and at 1 and 5 years was similar for the patients supported with veno-arterial or veno-venous ECMO (58 % versus 55 %, p = 0.7; 42 % versus 39 %, p = 0.8; 29 % versus 22 %, p = 0.6). The authors concluded that ECMO can provide acceptable support for PGD irrespective of the method used.

Hammäinen and colleagues (2011) examined early outcome in patients with end-stage pulmonary disease bridged with ECMO with the intention of lung transplantation (LTx) in 2 Scandinavian transplant centers (n = 16). Most patients were late referrals for LTx, and all failed to stabilize on mechanical ventilation. A total of 13 patients (7 men) with a mean age of 41 +/- 8 years (range of 25 to 51 years) underwent LTx after a mean ECMO support of 17 days (range of 1 to 59 days). Mean follow-up at 25 +/- 19 months was 100 % complete. Three patients died on ECMO while waiting for a donor, and 1 patient died 82 days after LTx; thus, by intention-to-treat, the success for bridging is 81 % and 1-year survival is 75 %. All other patients survived, and 1-year survival for transplant recipients was 92 % +/- 7 %. Mean intensive care unit stay after LTx was 28 +/- 18 days (range of 3 to 53 days). All patients were doing well at follow-up; however, 2 patients underwent
re-transplantation due to bronchiolitis obliterans syndrome at 13 and 21 months after the initial ECMO bridge to LTx procedure. Lung function was evaluated at follow-up, and mean forced expiratory volume in 1 second was 2.0 +/- 0.7 l (62 % +/- 23 % of predicted) and forced vital capacity was 3.1 +/- 0.6 l (74 % +/- 21 % of predicted). The authors concluded that ECMO used as a bridge to LTx results in excellent short-term survival in selected patients with end-stage pulmonary disease.

Haneya et al (2011) describes the successful use of different extra-corporeal circulatory systems as a bridge to LTx at remote centers. Between January 2003 and December 2009, these investigators had 10 requests for implantation of extra-corporeal circulatory systems (pumpless extra-corporeal lung assist [PECLA] or ECMO) in patients decompensating on the waiting list to bridge to LTx at 3 different transplant centers between 150 km and 570 km apart. Cannulas were inserted percutaneously with Seldinger's technique. The median patient age was 36 years (range of 24 to 53). Three patients were supported with PECLA and 7 with ECMO. The median duration of support was 23 days (range of 5 to 73). Two patients were initially provided with ECMO and then changed to PECLA after hemodynamic stabilization in the face of persisting pulmonary failure. Two patients died of multi-organ failure on ECMO while on the waiting list. One PECLA patient was successfully weaned and waiting for LTx. Before transplantation, 5 patients (4 PECLA and 1 ECMO) were successfully weaned from mechanical ventilation, and 3 PECLA patients were successfully weaned from the system. Seven patients were successfully bridged and transplanted; 5 of 7 patients were discharged from the transplant centers. The authors concluded that these findings suggested that implantation of extra-corporeal circulatory systems is a safe method to bridge patients decompensating on the waiting list for LTx. Support intervals of several weeks are possible.

Noah et al (2011) compared the hospital mortality of patients with H1N1-related ARDS referred, accepted, and transferred for ECMO with matched patients who were not referred for ECMO.
A cohort study in which ECMO-referred patients were defined as all patients with H1N1-related ARDS who were referred, accepted, and transferred to 1 of the 4 adult ECMO centers in the United Kingdom during the H1N1 pandemic in winter 2009 to 2010. The ECMO-referred patients and the non-ECMO-referred patients were matched using data from a concurrent, longitudinal cohort study (Swine Flu Triage study) of critically ill patients with suspected or confirmed H1N1. Detailed demographic, physiological, and co-morbidity data were used in 3 different matching techniques (individual matching, propensity score matching, and GenMatch matching). Main outcome measure was survival to hospital discharge analyzed according to the intention-to-treat principle. Of 80 ECMO-referred patients, 69 received ECMO (86.3%) and 22 died (27.5%) prior to discharge from the hospital. From a pool of 1,756 patients, there were 59 matched pairs of ECMO-referred patients and non-ECMO-referred patients identified using individual matching, 75 matched pairs identified using propensity score matching, and 75 matched pairs identified using GenMatch matching. The hospital mortality rate was 23.7% for ECMO-referred patients versus 52.5% for non-ECMO-referred patients (relative risk [RR], 0.45 [95% confidence interval (CI): 0.26 to 0.79]; p = 0.006) when individual matching was used; 24.0% versus 46.7%, respectively (RR, 0.51 [95% CI: 0.31 to 0.81]; p = 0.008) when propensity score matching was used; and 24.0% versus 50.7%, respectively (RR, 0.47 [95% CI: 0.31 to 0.72]; p = 0.001) when GenMatch matching was used. The results were robust to sensitivity analyses, including amending the inclusion criteria and restricting the location where the non-ECMO-referred patients were treated. The authors concluded that for patients with H1N1-related ARDS, referral and transfer to an ECMO center was associated with lower hospital mortality compared with matched non-ECMO-referred patients.

In an editorial that accompanied the afore-mentioned study, Checkley (2011) stated that "the study by Noah et al was an observational, prospective study ... does not replace a randomized clinical trial .... the current study may have been
underpowered to determine if ECMO was associated with a survival advantage when using hospitals as the unit of analysis .... despite several decades of investigation into potential treatment strategies, use of low tidal volumes remains the only proven therapy to decrease mortality in ARDS. In light of the large observed differences in mortality with and without ECMO, large consortia of trialists may be enticed to consider ECMO as a potential target for a randomized controlled trial early in the course of severe ARDS from all causes".

Moran et al (2010) noted that the role of ECMO in the treatment of the acute respiratory distress syndrome (ARDS) is controversial, notwithstanding the recent publication of the results of the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial. Using Bayesian meta-analytic methods from 3 randomized controlled trials (RCTs) of ECMO in ARDS, these researchers estimated the mortality odds ratio (OR) to be 0.78 (95% credible interval, 0.25 to 3.04), p (OR > 1) = 30%. Thus, a null effect of ECMO is not excluded and there appears only weak evidence of efficacy. These investigators surveyed particular problems associated with the conduct of the "pragmatic" CESAR trial: composite endpoints, sample size estimation under uncertainty of baseline mortality rates, the generation of unbiased treatment comparisons, the impact of treatment non-compliance, and the uncertainty associated with cost-effectiveness and cost-utility analysis. The authors concluded that the CESAR trial is problematic in terms of both the clinical and economic outcomes, although observational series suggested plausible efficacy. They suggested that ECMO finds rationale as rescue therapy and that the current uncertainty of its role mandates a further RCT.

Park et al (2011) stated that the role of ECMO in supporting adult refractory respiratory failure continues to evolve. Technical advances and the clinical challenges of H1N1 associated severe ARDS have spurred a resurgence of interest in ECMO. Published systematic review and pooled analyses pointed out the limitations of available studies, however, a
growing body of evidence suggested potential for benefit.

Wong and Vuylsteke (2011) noted that a large proportion of critically ill H1N1/2009 patients with respiratory failure subsequently developed ARDS and, to date, about 400 patients receiving ECLS have been accounted for globally, with a reported survival rate from 63 % to 79 %. The survival rates of patients with ARDS due to non-H1N1/2009 infections are similar. There is no definite evidence to suggest that patient outcomes are changed by ECLS, but its use is associated with serious short-term complications. Extra-corpooreal life support relies on an extra-corpooreal circuit, with ECMO and pumpless interventional lung assist (ILA) being the 2 major types employed in ARDS. Both have the potential to correct respiratory failure and related hemodynamic instability. There are only a very limited number of clinical trials to test either and, although ECLS has been used in treating H1N1/2009 patients with ARDS with some success, it should only be offered in the context of clinical trials and in experienced centers.

Combes et al (2012) reviewed case series and trials that evaluated ECMO for respiratory failure and describes patient and circuit management in the modern era of ECMO support. In recent years, pivotal progress has been made in the conception and construction of ECMO circuits. They are now simpler, safer, require less anticoagulation and are associated with fewer bleeding complications. The encouraging results of the efficacy and economic assessment of conventional ventilatory support versus ECMO for severe adult respiratory failure (CESAR) trial performed in the United Kingdom and good outcomes of patients who received ECMO as rescue therapy during the recent H1N1 influenza pandemic, in which the latest generation of ECMO technology was used, reignited interest in ECMO for severe ARDS. The authors concluded that the latest generation of ECMO systems is more biocompatible, better performing and longer lasting. Although recent studies suggested that veno-venous ECMO might improve the outcomes of patients with ARDS, indications for ECMO use remain uncertain. They stated that future trials of ECMO for
severe ARDS should strictly control for standard-of-care mechanical ventilation strategies in the control group and early transportation on ECMO for patients in the intervention arm.

Cai and colleagues (2012) evaluated the effects of ECMO on mortality in adult patients with ARDS. Literature concerning RCTs, case-control studies and prospective cohort studies from January 1966 to July 2011 on ECMO for the treatment of ARDS patients was retrieved by electronic and manual search. Meta-analysis of the use of ECMO in the treatment of ARDS patients was conducted using the methods recommended by the Cochrane Collaboration's software RevMan 5.0. A total of 3 papers reporting RCTs and 6 papers concerning observational cohort studies of using ECMO in patients with severe ARDS were enrolled for analysis. Meta-analysis of the 3 RCTs (310 patients, 159 of them treated with ECMO) revealed ECMO did not decrease the mortality of ARDS patients [OR = 0.75, 95% CI: 0.45 to 1.24, p = 0.27]. Meta-analysis of the all 9 studies (1,058 patients, 386 of them treated with ECMO) revealed ECMO increased the mortality of ARDS patients (OR = 1.58, 95% CI: 0.94 to 2.67, p = 0.08). The authors concluded that there is no evidence to prove that ECMO is beneficial in adult patients with ARDS, therefore further investigation with a large sample of high quality RCT is warranted.

Chou et al (2012) presented their experience of heart transplantation (HTx) using ECMO with Thoratec pneumatic ventricular assist device (TpVAD). From May 1996 to June 2011, among 410 patients who underwent HTx, 23 required mechanical circulatory support (MCS) with implantation of the TpVAD and 15 (65%) of them received grafts. The 23 patients included 4 female and 19 male patients (age range of 10 to 80 years). Eighteen (78%) of them needed ECMO before TpVAD implantation. Twelve (67%) were implanted with a TpVAD double bridge to HTx. The demand for MCS among patients with acute hemodynamic collapse has led to major improvements in the existing systems such as ECMO with double bridge to TpVAD. These researchers used ECMO as a rescue procedure for acute hemodynamic deterioration.
However, during ECMO support, left ventricular afterload increased. If prolonged support is required, TpVAD might be required: 15 (65 %) of patients supported by ECMO with TpVAD needed to wait a suitable donor. The authors recommended the application of ECMO for short-term support (within 1 week), and TpVAD as a bridge for medium- or long-term support.

Asmussen et al (2013) performed a systematic review and meta-analysis to evaluate the level of evidence for the use of ECMO in hypoxemic respiratory failure resulting from burn and smoke inhalation injury. These investigators searched any article published before March 01, 2012. Available studies published in any language were included. Five authors rated each article and assessed the methodological quality of studies using the recommendation of the Oxford Centre for Evidence Based Medicine (OCEBM). The search yielded 66 total citations but only 29 met the inclusion criteria of burn and/or smoke inhalation injury. There were no available systematic reviews/meta-analyses published that met inclusion criteria. Only a small number of clinical trials, all with a limited number of patients, were available. The overall data suggested that there is no improvement in survival for burn patients suffering acute hypoxemic respiratory failure, with the use of ECMO. Extra-corporeal membrane oxygenation run times of less than 200 hours correlate with higher survival compared to 200 hours or more. Scald burns show a tendency of higher survival than flame burns. The authors concluded that the presently available literature is based on insufficient patient numbers; and the data obtained as well as the level of evidence generated are limited. They stated that the role of ECMO in burn and smoke inhalation injury is therefore unclear; further research on ECMO in burn and smoke inhalation injury is warranted.

Combes et al (2014) stated that the use of ECMO for severe acute respiratory failure (ARF) in adults is growing rapidly given recent advances in technology, even though there is controversy regarding the evidence justifying its use. Because
ECMO is a complex, high-risk, and costly modality, at present it should be conducted in centers with sufficient experience, volume, and expertise to ensure it is used safely. On behalf of the International ECMO Network, these investigators presented a position paper, which represented the consensus opinion of an international group of physicians and associated health-care workers who have expertise in therapeutic modalities used in the treatment of patients with severe ARF, with a focus on ECMO. These researchers provided physicians, ECMO center directors and coordinators, hospital directors, health-care organizations, and regional, national, and international policy makers a description of the optimal approach to organizing ECMO programs for ARF in adult patients. They noted that this position paper will help ensure that ECMO is delivered safely and proficiently, such that future observational and randomized clinical trials assessing this technique may be performed by experienced centers under homogeneous and optimal conditions. The authors concluded that given the need for further evidence, they encourage restraint in the widespread use of ECMO until there is a better appreciation for both the potential clinical applications and the optimal techniques for performing ECMO.

In a Cochrane review, Tramm et al (2015) examined if the use of veno-venous (VV) or venous-arterial (VA) ECMO in adults is more effective in improving survival compared with conventional respiratory and cardiac support. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid) and EMBASE (Ovid) on August 18, 2014. They searched conference proceedings, meeting abstracts, reference lists of retrieved articles and databases of ongoing trials and contacted experts in the field. They imposed no restrictions on language or location of publications. These researchers included RCTs, quasi-RCTs and cluster-RCTs that compared adult ECMO versus conventional support. Two review authors independently screened the titles and abstracts of all retrieved citations against the inclusion criteria. They independently reviewed full-text copies of studies that met the inclusion criteria. They
entered all data extracted from the included studies into Review Manager. Two review authors independently performed risk of bias assessment. All included studies were appraised with respect to random sequence generation, concealment of allocation, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The authors included 4 RCTs that randomly assigned 389 participants with acute respiratory failure. Risk of bias was low in 3 RCTs and high in 1 RCT. These researchers found no statistically significant differences in all-cause mortality at 6 months (2 RCTs) or before 6 months (during 30 days of randomization in 1 trial and during hospital stay in another RCT). The quality of the evidence was low to moderate, and further research is very likely to impact the confidence in the estimate of effects because significant changes have been noted in ECMO applications and treatment modalities over study periods to the present. Two RCTs supplied data on disability. In 1 RCT survival was low in both groups but none of the survivors had limitations in their daily activities 6 months after discharge. The other RCT reported improved survival without severe disability in the intervention group (transfer to an ECMO center ± ECMO) 6 months after study randomization but no statistically significant differences in health-related quality of life. In 3 RCTs, participants in the ECMO group received greater numbers of blood transfusions. One RCT recorded significantly more non-brain hemorrhage in the ECMO group. Another RCT reported 2 serious adverse events in the ECMO group, and another reported 3 adverse events in the ECMO group. Clinical heterogeneity between studies prevented meta-analyses across outcomes. These investigators found no completed RCT that had investigated ECMO in the context of cardiac failure or arrest. They found 1 ongoing RCT that examined patients with acute respiratory failure and 2 ongoing RCTs that included patients with acute cardiac failure (arrest). The authors concluded that ECMO remains a rescue therapy. Since the year 2000, patient treatment and practice with ECMO have considerably changed as the result of research findings and technological advancements over time. Over the past 4 decades, only 4 RCTs have been published that compared the
intervention versus conventional treatment at the time of the study. Clinical heterogeneity across these published studies prevented pooling of data for a meta-analysis. The authors recommended combining results of ongoing RCTs with results of trials conducted after the year 2000 if no significant shifts in technology or treatment occur. They stated that 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 can play in patient care.

Noly and colleagues (2014) stated that right ventricular failure (RVF) after implantation of left ventricular assist device (LVAD) is a dramatic complication. These researchers compared retrospectively 2 techniques of temporary right ventricular support after LVAD (HeartMate II, Thoratec Corp, Pleasonton, CA) implantation. From January 1, 2006 to December 31, 2012, a total of 78 patients [mean age of 52 ± 1.34 years; 15 women (19 %)] received a HeartMate II at the authors’ institution. Among these, 18 patients (23 %) suffered post-implant RVF treated by peripheral temporary right ventricular support. Etiology of heart failure was ischemic in 12 (67 %) and dilated cardiomyopathy in 6 (33 %) patients. The pre-implant RV risk-score averaged 5.1 ± 0.59. Ten patients were treated using a femoro-femoral veno-arterial ECLS and 8 patients were treated using ECMO as a right ventricular assist device (RVAD) established between a femoral vein and the pulmonary artery via a Dacron prosthesis (RVAD). Duration of RV support was 7.12 ± 5.4 days and 9.57 ± 3.5 days in veno-arterial ECLS and vein and the pulmonary artery RVAD groups, respectively (p = 0.32). Three patients (17 %) died while under RV support (veno-arterial ECLS, n = 2; and vein and the pulmonary artery RVAD, n = 1, p = 0.58). In the veno-arterial ECLS group, 6 (60 %) patients suffered major thromboembolic complications including thrombosis of the ECLS arterial line (n = 2), ischemic stroke (n = 2) and thrombosis of the ascending aorta (n = 2). No major complication was observed in the vein and the pulmonary artery RVAD group (p = 0.01). Right ventricular
support was successfully weaned in 8 (80%) patients of the veno-arterial ECLS group and in 7 (87.5%) of the vein and the pulmonary artery RVAD group (p = 0.58). The duration of post-implant intensive care unit stay was not different (respectively, 27.5 ± 18.7 days and 20.0 ± 12.0 days; p = 0.38) between both groups. The authors concluded that temporary support of the failing RV after LVAD implantation using temporary vein and the pulmonary artery RVAD is a promising therapeutic option.

Furthermore, an UpToDate review on “Extracorporeal membrane oxygenation (ECMO) in adults” (Haft and Bartlett, 2015) states that “Future -- Applications for ECMO may expand in the future to include percutaneous temporary left ventricular assistance and low flow ECMO for CO2 removal (ECOOR)

**Acute Massive Pulmonary Embolism:**

Yusuff et al (2015) stated that massive pulmonary embolism (PE) can present with extreme physiological dysfunction, characterized by acute right ventricular failure, hypoxemia unresponsive to conventional therapy and cardiac arrest. Consensus regarding the management of patients with persistent shock following thrombolysis is lacking. These investigators described the application of ECMO in the treatment of acute massive PE. They were unable to identify any RCTs comparing ECMO with other support systems in the setting of massive PE. They reviewed case reports and case series published in the past 20 years to evaluate the mortality rate and any poor prognostic factors. Overall survival was 70.1% and none of the definitive treatment modalities was associated with a higher mortality (thrombolysis - OR - 0.99, p - 0.9, catheter embolectomy - OR - 1.01, p - 0.99, surgical embolectomy - OR - 0.44, p - 0.20). Patients who had ECMO instituted while in cardio-respiratory arrest had a higher risk of death (OR - 16.71, p - 0.0004).

Furthermore, an UpToDate review on “Overview of acute pulmonary embolism in adults” (Thompson, 2016) does not
mention ECMO as a therapeutic option; and an UpToDate review on “Extracorporeal membrane oxygenation (ECMO) in adults” (Haft and Bartlett, 2016) does not mention pulmonary embolism as an indication of ECMO.

Pregnant and Post-Partum Women With H1N1-Related Acute Respiratory Distress Syndrome:

Saad et al (2016) evaluated available evidence regarding the use of ECMO in pregnant and post-partum women with acute respiratory distress syndrome secondary to swine flu (H1N1) infection. Databases from Medline (U.S. National Library of Medicine, 1946 to April 1, 2015), the Cochrane Library Controlled Trials Register, ClinicalTrials.gov, and Web of Science were queried for studies on ECMO in pregnant or post-partum patients with acute respiratory distress syndrome. Search terms included: "ARDS", "ECMO", "pregnant" and "postpartum"; all relevant references in any language were reviewed. Literature for inclusion and methodological quality were reviewed based on the meta-analyses and systematic reviews of observational studies (Meta-analysis Of Observational Studies in Epidemiology) guidelines. Of 266 citations, 5 retrospective studies (39 patients) fulfilled the inclusion criteria; no RCTs were found. The pooled estimate of the survival rate among pregnant and post-partum patients who received ECMO for acute respiratory distress syndrome secondary to H1N1 was 74.6 % (95 % CI: 60.7 to 88.6 %). Neonatal outcomes were reported in 2 studies and the rate of live-birth was 70 % (95 % CI: 43.7 to 95.2). Heterogeneity was not significant among studies (I ranged from 0 % to 21 %; p > 0.25). The authors concluded that the role of ECMO in pregnant and post-partum women with acute respiratory distress syndrome from H1N1 remains unclear and the benefits suggested from this review should be interpreted with caution. The main drawback of this review were: (i) the small number of available studies in the literature (only 39 patients in this analysis). Moreover, the relevant studies were mainly retrospective with fair quality and high selection and comparability biases; thus susceptible to confounding, (ii)
stochastic variation is a likely significant source of bias because the sample sizes, individually and in aggregates, are small and there was essentially no difference between the meta-analysis version of survival proportion compared with simply aggregating survivors and total, and (iii) neonatal outcome estimate should be taken with a significant caveat since it is not stated for 3 of the 5 studies, and the numbers of neonates reported is only 7 of 10.

Anand and colleagues (2016) stated that ECMO provides complete or partial support of the heart and lungs. Ever since its inception in the 1960s, it has been used across all age groups in the management of refractory respiratory failure and cardiogenic shock. While it has gained widespread acceptance in the neonatal and pediatric physician community, ECMO remains a controversial therapy for acute respiratory distress syndrome in adults. Its popularity was revived during the H1N1 pandemic and advancements in technology have contributed to its increasing usage. Acute respiratory distress syndrome continues to be a potentially devastating condition with significant mortality rates. Despite gaining more insights into this entity over the years, mechanical ventilation remains the only life-saving, yet potentially harmful intervention available for acute respiratory distress syndrome. Extracorporeal membrane oxygenation shows promise in this regard by offering less dependence on mechanical ventilation, thereby potentially reducing ventilator-induced injury. However, the lack of rigorous clinical data has prevented ECMO from becoming the standard of care in the management of acute respiratory distress syndrome. Therefore, the results of 2 large ongoing randomized trials, which will hopefully throw more light on the role of ECMO in the management of this disease entity, are keenly awaited.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”:*
**ICD-10 codes will become effective as of October 1, 2015:**

<table>
<thead>
<tr>
<th>CPT codes covered if selection criteria are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td>33946 - 33986 Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician</td>
</tr>
<tr>
<td>33987 Arterial exposure with creation of graft conduit (eg, chimney graft) to facilitate arterial perfusion for ECMO/ECLS (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>33988 Insertion of left heart vent by thoracic incision (eg, sternotomy, thoracotomy) for ECMO/ECLS</td>
</tr>
<tr>
<td>33989 Removal of left heart vent by thoracic incision (eg, sternotomy, thoracotomy) for ECMO/ECLS</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33120</td>
<td>Excision of intracardiac tumor, resection with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33305</td>
<td>Repair of cardiac wound; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33315</td>
<td>Cardiotomy, exploratory (includes removal of foreign body, atrial or ventricular thrombus); with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33322</td>
<td>Suture repair of aorta or great vessels; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33335</td>
<td>Insertion of graft, aorta or great vessels; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33403</td>
<td>Valvuloplasty, aortic valve; using transventricular dilation, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33405</td>
<td>Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or stentless valve</td>
</tr>
<tr>
<td>33406</td>
<td>with allograft valve (freehand)</td>
</tr>
<tr>
<td>33410</td>
<td>with stentless tissue valve</td>
</tr>
<tr>
<td>33422</td>
<td>Valvotomy, mitral valve; open heart, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>33425</td>
<td>Valvuloplasty, mitral valve, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33426</td>
<td>with prosthetic ring</td>
</tr>
<tr>
<td>33427</td>
<td>radical reconstruction, with or without ring</td>
</tr>
<tr>
<td>33430</td>
<td>Replacement, mitral valve, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33460</td>
<td>Valvectomy, tricuspid valve, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33465</td>
<td>Replacement, tricuspid valve, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33474</td>
<td>Valvotomy, pulmonary valve, open heart; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33496</td>
<td>Repair of non-structural prosthetic valve dysfunction with cardiopulmonary bypass (separate procedure)</td>
</tr>
<tr>
<td>33500</td>
<td>Repair of coronary arteriovenous or arteriocardiac chamber fistula; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33504</td>
<td>Repair of anomalous coronary artery from pulmonary artery origin; by graft, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33641</td>
<td>Repair atrial septal defect, secundum, with cardiopulmonary bypass, with or without patch</td>
</tr>
<tr>
<td>33702</td>
<td>Repair sinus of Valsalva fistula, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33710</td>
<td>with repair of ventricular septal defect</td>
</tr>
<tr>
<td>33720</td>
<td>Repair sinus of Valsalva aneurysm, with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33736</td>
<td>Atrial septectomy or septostomy; open heart with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33814</td>
<td>Obliteration of aortopulmonary septal defect; with cardiopulmonary bypass</td>
</tr>
<tr>
<td>33853</td>
<td>Repair of hypoplastic or interrupted aortic arch using autogenous or prosthetic material; with cardiopulmonary bypass</td>
</tr>
</tbody>
</table>
### Ascending aorta graft, with cardiopulmonary bypass
Includes valve suspension, when performed

### Ascending aorta graft, with cardiopulmonary bypass
With valve suspension, with coronary reconstruction and valve sparing aortic root remodeling (e.g., David Procedure, Yacoub Procedure)

### Transverse arch graft, with cardiopulmonary bypass

### Descending thoracic aorta graft, with or without bypass

### Repair of thoracoabdominal aortic aneurysm with graft, with or without cardiopulmonary bypass

### Pulmonary artery embolectomy; with cardiopulmonary bypass

### Pulmonary endarterectomy, with or without embolectomy, with cardiopulmonary bypass

### Transection of pulmonary artery with cardiopulmonary bypass

### Repair of pulmonary artery arborization anomalies by unifocalization; with cardiopulmonary bypass

### Neonates:

ICD-10 codes covered if selection criteria are met:

- P22.0 Respiratory distress syndrome of newborn
- P24.01 Meconium aspiration with respiratory symptoms
- P25.0 - P25.8 Interstitial emphysema and related conditions originating in the perinatal period [uncontrollable air leak]
- P28.5 Respiratory failure of newborn
- P29.3 Persistent fetal circulation
- Q79.0 Congenital diaphragmatic hernia
- R65.21 Severe sepsis with septic shock [neonatal and pediatric]

### Children and adults:

ICD-10 codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A22.1</td>
<td>Pulmonary anthrax [non-necrotizing]</td>
</tr>
<tr>
<td>A36.81</td>
<td>Diphtheritic cardiomyopathy</td>
</tr>
<tr>
<td>A37.01</td>
<td>Pneumonia in whooping cough [non-necrotizing]</td>
</tr>
<tr>
<td>A37.11</td>
<td></td>
</tr>
<tr>
<td>A37.81</td>
<td></td>
</tr>
<tr>
<td>A37.91</td>
<td></td>
</tr>
<tr>
<td>A39.52</td>
<td>Meningococcal myocarditis</td>
</tr>
<tr>
<td>A48.1</td>
<td>Legionnaires' disease [non-necrotizing]</td>
</tr>
<tr>
<td>A52.06</td>
<td>Other syphilitic heart involvement</td>
</tr>
<tr>
<td>B25.0</td>
<td>Cytomegaloviral pneumonitis [non-necrotizing]</td>
</tr>
<tr>
<td>B33.22</td>
<td>Viral myocarditis</td>
</tr>
<tr>
<td>B44.0</td>
<td>Invasive pulmonary aspergillosis [non-necrotizing]</td>
</tr>
<tr>
<td>B58.81</td>
<td>Toxoplasma myocarditis</td>
</tr>
<tr>
<td>B77.81</td>
<td>Ascariasis pneumonia [non-necrotizing]</td>
</tr>
<tr>
<td>I01.2</td>
<td>Acute rheumatic myocarditis</td>
</tr>
<tr>
<td>I09.0</td>
<td>Rheumatic myocarditis</td>
</tr>
<tr>
<td>I40.0 - I40.9</td>
<td>Acute myocarditis</td>
</tr>
<tr>
<td>I41</td>
<td>Myocarditis in diseases classified elsewhere</td>
</tr>
<tr>
<td>I50.1 - I50.9</td>
<td>Heart failure</td>
</tr>
<tr>
<td>I51.4</td>
<td>Myocarditis, unspecified</td>
</tr>
<tr>
<td>J10.00 - J18.1 J18.8 - J18.9</td>
<td>Influenza and pneumonia [non-necrotizing]</td>
</tr>
<tr>
<td>J70.5</td>
<td>Respiratory conditions due to smoke inhalation</td>
</tr>
<tr>
<td>J80</td>
<td>Acute respiratory distress syndrome [adult respiratory distress syndrome]</td>
</tr>
<tr>
<td>J95.1 - J95.3</td>
<td>Acute and chronic pulmonary insufficiency and postprocedural respiratory failure following thoracic and nonthoracic surgery [adult respiratory distress syndrome associated with trauma and surgery]</td>
</tr>
<tr>
<td>J95.821 - J95.822</td>
<td>Acute and chronic pulmonary insufficiency and postprocedural respiratory failure following thoracic and nonthoracic surgery [adult respiratory distress syndrome associated with trauma and surgery]</td>
</tr>
<tr>
<td>J96.00 - J96.02</td>
<td>Acute respiratory failure [reversible] [unresponsive to all other measures]</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:

2. Custer J, Fackler J. ECLS for children with acute respiratory distress syndrome. In: ECMO: Extracorporeal...


52. Asmussen S, Maybauer DM, Fraser JF, et al. Extracorporeal membrane oxygenation in burn and


60. Thompson BT. Overview of acute pulmonary embolism in adults. UpToDate Inc., Waltham, MA. Last reviewed March 2016.


Amendment to
Aetna Clinical Policy Bulletin Number: 0546
Extracorporeal Membrane Oxygenation (ECMO)

There are no amendments for Medicaid.