

Extracorporeal Membrane Oxygenation for Neonatal Respiratory Failure

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Introduction

Extracorporeal Membrane Oxygenation (ECMO) Systems

ECMO Methods

Patient Selection

Pre-ECMO Therapies

Mobile ECMO

Congenital Diaphragmatic Hernia

ECMO in the Delivery Room

Outcomes

Hospital Survival

Neurodevelopmental

Pulmonary

Economic

Complications

Summary

Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass adapted for long-term use. Blood is drained from the patient, pumped through an artificial lung or membrane where gas exchange is augmented, and then re-infused back to the patient. ECMO provides support for the neonate with severe respiratory failure so that potentially deleterious ventilator settings can be minimized and the disease process given time to resolve. Survival rates and long-term neurodevelopmental outcomes in newborns supported with ECMO for hypoxemic respiratory failure remain favorable, although the use of ECMO has decreased in the most recent decade because of the availability of alternative treatment options. Key words: extracorporeal membrane oxygenation, ECMO, neonatal, mechanical ventilation, respiratory failure. [Respir Care 2009;54(9):1244–1251. © 2009 Daedalus Enterprises]

Introduction

In 1975 Bartlett et al described the application of extracorporeal membrane oxygenation (ECMO), a modifica-

tion of cardiopulmonary bypass, in the management of a newborn with profound respiratory failure.¹ This pioneer-

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ing case ultimately led to a series of clinical investigations aimed at determining if ECMO could support newborns with severe respiratory failure and reduce the associated morbidity and mortality that were still prevalent. The hypothesis of these early studies was eventually realized, and ECMO became an important life-saving modality in the management of critically ill newborns.

A recent meta-analysis conducted by the Cochrane Collaborative confirmed this and concluded: "A policy of ECMO in mature infants with severe but potentially reversible respiratory failure results in significantly improved survival without risk of severe disability."² This paper will address the use of ECMO in this population and will describe the technical aspects, outcomes, and changing patterns.

ECMO Systems

The classic ECMO system, a modification of cardiopulmonary bypass technology, consists of a durable circuit, artificial lung or membrane oxygenator, pump, and heat exchanger. An updated description of ECMO circuits and techniques has been conveyed by Frenckner et al.³ In brief, the contiguous circuit has drainage and re-infusion limbs, and the membrane oxygenator and heat exchanger are situated midstream. De-oxygenated blood drained from the patient is pumped by either a non-occlusive centrifugal pump or occlusive roller pump to a silicone or hollow-fiber type membrane oxygenator. As de-oxygenated blood traverses the membrane, O₂ and CO₂ exchange occurs by diffusion across the silicone membrane or hollow fibers. Gas exchange is influenced by the surface area of the membrane and the flow rate and composition of the gas supplied to the membrane, known as the sweep gas. The arterialized blood is returned to the patient after it is re-warmed by a heat exchanger.

ECMO support for the neonate is continuously monitored, with anticoagulation, circuit function, and end-organ function being the principle focus. Anticoagulation is necessary to maintain circuit patency and is achieved with a continuous heparin infusion, which is titrated based on the periodic point-of-care measurement of activated clotting time. Current ECMO systems have built-in safeguards that alert the ECMO specialist to acute changes in venous drainage, changing circuit resistance from thrombus, and pump and membrane function. Monitoring end-organ function includes the periodic assessment of renal, neurologic, and cardiopulmonary function, which is influenced by ECMO pump rate, hemostasis, and gas exchange.

ECMO Methods

Two methods for providing ECMO support in newborns are used, venous-arterial and venous-venous. The method

of ECMO is defined or described by the blood drainage site, which is always the venous system, and the re-infusion site, which is either arterial or venous.³

Venous-arterial ECMO provides support for the heart and lungs, as drainage is from the right side of the heart and reinfusion to the left side. The cannula configuration consists of drainage of de-oxygenated blood from the right internal jugular vein and re-infusion of arterialized blood into the right common carotid artery. An ECMO flow rate of 100 mL/kg is typically used, which augments an estimated 80% of an infant's cardiac output. In the early ECMO era, venous-arterial was the only method available, and while carotid ligation is well tolerated in the newborn, techniques to avoid this were developed and venous-venous ECMO has become the preferred method.

Newborns with primary respiratory failure are commonly supported with venous-venous, in which blood is drained and returned to the venous system. Venous-venous can be accomplished by accessing 2 veins, but specially designed double-lumen cannulas for neonates are more commonly used, and the configuration is referred to as venous-venous double-lumen. These cannulas require cannulation only of the right internal jugular vein. Blood is drained from one lumen and arterialized blood is simultaneously re-infused into the adjacent lumen. Proper placement is important in order to optimize the introduction of arterialized blood into the pulmonary vasculature and subsequently the systemic circulation.

Patient Selection

The fundamental and indisputable indication for ECMO is a reversible disease process, since ECMO is not a therapy but a supportive measure that is highly invasive and associated with risks. Historically, newborns with severe respiratory failure being considered for ECMO have a > 80% risk of death, as determined by an oxygenation index of > 40–60 or an alveolar-arterial oxygen difference of > 600 mm Hg.^{3,4} The oxygenation index is calculated as:

$$(\text{Mean airway pressure} \times F_{\text{IO}_2} \times 100) / P_{\text{aO}_2}$$

The alveolar-arterial oxygen difference is calculated as:

$$P_{\text{AO}_2} - P_{\text{aO}_2}$$

While the oxygenation index has never been prospectively validated, it continues to be used. An oxygenation index calculated from a conventional mechanical ventilation mean airway pressure is likely to be lower than that during high-frequency oscillatory ventilation, and no correlations have been established. The trajectory of these

measurements is usually evaluated over a relatively short period of time, such as 2–4 hours, during which time serial blood gas results are monitored. Identifying high mortality risk as soon as possible is vital in the decision to initiate ECMO, particularly if transfer to an ECMO center has to be factored in.

The profile of a newborn who is considered for ECMO includes the presence of an underlying disease such as meconium aspiration syndrome, congenital diaphragmatic hernia, respiratory distress syndrome, pneumonia, or sepsis, which is often manifested as persistent pulmonary hypertension of the newborn and subsequent cardiopulmonary failure.^{2,3} An additional factor influencing the decision to use ECMO is the patient's response to advanced therapies, including inhaled nitric oxide, high-frequency ventilation, and surfactant-replacement therapy.²

Contraindications to ECMO continue to be debated, and their boundaries extended beyond historical conventions. A ventilator course of greater than 7–10 days prior to ECMO was considered a contraindication because of the potential of lung disease becoming increasingly irreversible. Severe respiratory failure associated with the aforementioned diseases is typically manifested early in the newborn period, with ECMO being initiated within 2 days.⁴ The need for ECMO after a prolonged mechanical ventilator course in a newborn may be suggestive of atypical lung pathology that may not be reversible.⁴

Patient size and gestational age limitations also need to be taken into consideration. The premature brain is more susceptible to intracranial hemorrhage, and even at greater risk in the presence of anticoagulation during ECMO; therefore, ECMO has been considered contraindicated in newborns < 32 weeks gestation. The presence of an existing intracranial hemorrhage does not necessarily preclude the use of ECMO unless it is staged beyond a grade I or II. Antifibrinolytic agents have been administered during ECMO to patients with existing intracranial hemorrhage and those at risk.⁵ These agents help minimize the extension of bleeding by stabilizing clot formation. Size limitations to ECMO are mainly due to the challenges of cannulating the tiny vessels of patients < 2.0 kg.

Another consideration that may negatively impact ECMO outcome is a pre-ECMO cardiopulmonary arrest, although it may be reasonable to proceed with ECMO if spontaneous circulation resumes following a short arrest time.⁶ Recently an expanded use of ECMO is for cardiopulmonary resuscitation, referred to as E-CPR.⁷ This entails the rapid deployment and initiation of ECMO during or around resuscitative measures. While this has been mainly used in patients with cardiac disease, with a survival rate of around 30%, it may be a reasonable approach in newborns with respiratory failure when an arrest occurs during preparation for ECMO or upon arrival to the ECMO center.

Table 1. Indications for Extracorporeal Membrane Oxygenation in Newborns With Severe Respiratory Failure

Oxygenation index > 40–60
Alveolar-arterial oxygen difference > 600 mm Hg
Diagnosis associated with persistent pulmonary hypertension of the newborn
Meconium aspiration syndrome
Respiratory distress syndrome
Sepsis
Pneumonia
Congenital diaphragmatic hernia

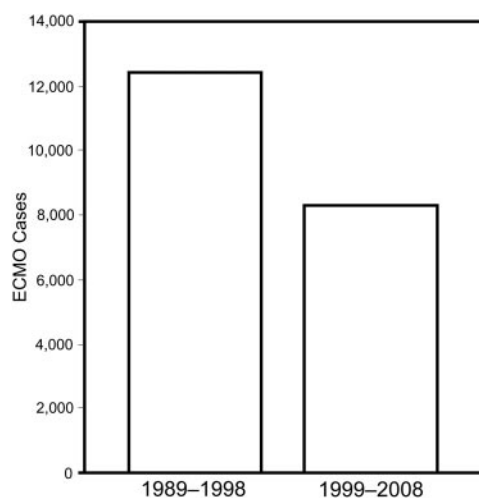


Fig. 1. Neonatal respiratory failure extracorporeal membrane oxygenation (ECMO) cases reported over 2 decades. (Data from Reference 8.)

Other considerations for not employing ECMO include the presence of other potentially fatal congenital abnormalities, impaired neurologic status, and bleeding disorders that may be exacerbated with anticoagulation. Patient-selection criteria for ECMO are presented in Table 1.

Pre-ECMO Therapies

Advances in neonatal intensive care, particularly inhaled nitric oxide, high-frequency ventilation, and surfactant-replacement therapy, have influenced the use of ECMO. The Extracorporeal Life Support Organization,⁸ an association of clinicians dedicated to the science of extracorporeal techniques, has reported through its international registry an average of around 800 cases per year reported in the most recent decade, versus approximately 1,200 cases in the prior decade (Fig. 1). ECMO is somewhat of “safety-net” for the exploration of therapeutic alternatives; for an example, it is unlikely that inhaled nitric oxide would have been as enthusiastically studied and subse-

quently approved by the Food and Drug Administration without an ECMO requirement as an end point.

The impact of pre-ECMO therapies has been described by Fliman et al, who sought to determine if there was a potential associated mortality in neonates supported with ECMO.⁶ During this study period, which included 4 years prior to and after Food and Drug Administration approval of inhaled nitric oxide, ECMO use declined by 27%, and inhaled nitric oxide, high-frequency ventilation, and surfactant use increased. Patients with respiratory distress syndrome, meconium aspiration syndrome, and sepsis required less ECMO, suggesting that pre-ECMO therapies benefited these diagnoses more. There was not a significant reduction in ECMO requirement for patients with persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, or the category for “other” indications. This study suggested that there was no increased mortality associated with the application of newer therapies, and the use of inhaled nitric oxide prior to cannulation may provide greater stability and lessen the risk of cardiopulmonary arrest.

During the same period investigators in the United Kingdom conducted follow-up studies to determine if changes in neonatal practice impacted developmental outcomes.⁹ This study concluded that developmental outcomes for newborns with severe respiratory failure supported with ECMO have favorable survival rates and normal developmental testing results. This study also suggested that pre-ECMO strategies do not prolong the time of ECMO, as most referrals occurred in less than 2 days.

A recently published 15-year retrospective appraisal of the United Kingdom neonatal experience reports that advanced respiratory therapies are widely used but have not significantly reduced the need for ECMO, and the survival rate remains at a favorable 80%.¹⁰ This review suggested that current therapies lessen the severity of illness at the time of ECMO initiation, and that prolonging the time to cannulation and a concomitantly rising oxygenation index increase the risk of mortality.

The use of ECMO in newborns with hypoxemic respiratory failure has declined in our program.¹¹ The referral base for our program consists mainly of the New England states, and transfers for ECMO from other tertiary-care centers are fairly low, although the denominator is not fully understood. In our experience, ECMO is required in about 20% of referrals, with most patients successfully managed with non-ECMO therapies, and mortality is low and only in ECMO patients (Fig. 2). Our low initiation rate in newborns referred for ECMO from other tertiary-care centers does not suggest an inappropriate transfer decision but a thoughtful judgment in which a more stable patient is presented for ECMO if it is warranted. Successful outcomes are very much dependent on the decision and timing of transferring a patient for ECMO and the continua-

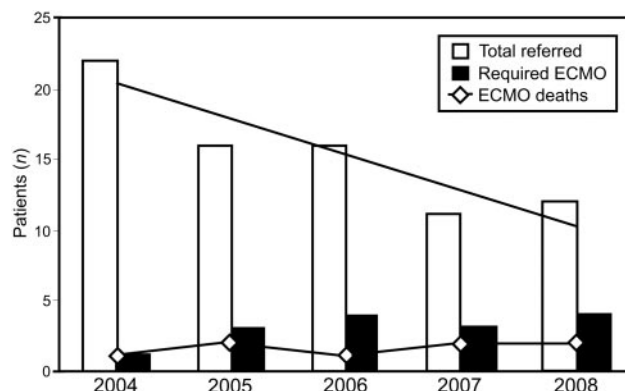


Fig. 2. Five-year review of extracorporeal membrane oxygenation (ECMO) referrals from tertiary-care neonatal intensive care units in Children's Hospital Boston ECMO registry. (Approved by the Children's Hospital Boston institutional review board.)

tion of advanced therapies en route, so that ECMO is not applied in an unsalvageable situation.

Mobile ECMO

While movement of ECMO patients within the confines of a hospital for diagnostic and surgical procedures is not uncommon, the transport of patients connected to an ECMO circuit between hospitals is less so. There are a small number of ECMO programs that have created mobile ECMO systems capable of safely transporting patients via ground and air.¹² When pre-ECMO strategies fail and patients become more unstable, ECMO can be initiated at a referring hospital, and the patient can then be returned to an ECMO center for further management. ECMO transport capabilities are particularly beneficial in regions where ECMO is not readily available, or the distance or weather conditions prohibit a routine ground transfer.¹³

Congenital Diaphragmatic Hernia

Over the past decade, advances in the care of the patient with congenital diaphragmatic hernia, including delayed surgical repair, gentle ventilation with permissive hypercapnia, high-frequency oscillatory ventilation, and inhaled nitric oxide, have improved overall survival.¹⁴ Despite this improved survival, the diagnosis of congenital diaphragmatic hernia carries the highest morbidity and mortality of any of the neonatal indications for ECMO.⁸ The reversibility of the major components of the disease, primarily pulmonary hypoplasia and associated pulmonary hypertension, is variable and difficult to predict, and has led to some controversy as to the utility of ECMO in this population. For this reason we have chosen to discuss the use of ECMO for congenital diaphragmatic hernia separately.

The most commonly used criterion for ECMO in the congenital diaphragmatic hernia patient is a failure to respond to conventional therapy. Although conventional therapy varies among institutions, a strategy of limiting peak inspiratory pressure and the avoidance of over-distention is a widely accepted ventilator strategy. Criteria for failure include a pH < 7.15 with a peak inspiratory pressure requirement of > 25 cm H₂O, failure to maintain preductal oxygen saturation > 85%, and an oxygenation index > 40.¹⁵ The role of ECMO in the congenital diaphragmatic hernia patient is considered to be primarily a lung-protective approach that prevents ventilator-induced lung injury in the preoperative period. It is widely accepted that congenital diaphragmatic hernia is no longer a surgical emergency, and, depending on the institution, patients who require ECMO support are repaired early in the ECMO course, prior to separation from ECMO, or in the immediate post-ECMO period.¹⁶

In addition to the previously mentioned contraindications, newborns with congenital diaphragmatic hernia and a concomitant lethal anomaly are considered poor candidates for ECMO, as disease reversibility is uncertain. ECMO is not offered in some institutions if the degree of pulmonary hypoplasia is considered to be irreversible, although there are no established standards used to grade hypoplasia. Clinically, hypoplasia is considered more severe if hypercarbia persists and there is an inability to maintain an acceptable pre-ductal saturation.¹⁷ Predictors of mortality in the patient who requires ECMO support have been examined. Haricharan et al described independent risk factors associated with mortality, including a 5-min Apgar score of 6 or lower, a birth weight of < 2 kg, P_{aCO₂} higher than 60 mm Hg during the 6-hour period before ECMO, and an ECMO duration of 15 days or longer.¹⁸

The aforementioned Cochrane review of ECMO for severe respiratory failure in newborn infants evaluated trials that either excluded patients with congenital diaphragmatic hernia or included studies with limited numbers. The conclusions of the review suggested that ECMO may offer short-term benefits but that the overall benefit in this group remains unclear.²

The Congenital Diaphragmatic Hernia Study Group, established in 1995, maintains a multi-institutional registry of patients with congenital diaphragmatic hernia.¹⁹ This international association was created to provide participants with a forum to pose clinical questions, discuss therapeutic approaches, and monitor outcomes. This forum is particularly beneficial to centers with relatively low case volumes that may have difficulty reaching conclusions based on their own experience. Data from the Congenital Diaphragmatic Hernia Study Group have been used to identify tendencies in this population. For example, the timing of delivery and birth weight are 2 variables that

have been recognized as influencing survival and the use of ECMO, with 37–38-week gestation infants weighing > 3.1 kg showing the greatest survival and the least use of ECMO.²⁰ Another objective of the Congenital Diaphragmatic Hernia Study Group is to provide a foundation for future protocol-driven studies for the management of newborns with congenital diaphragmatic hernia.

ECMO in the Delivery Room

Few reliable predictors of survival and severity of disease exist for the fetus with the diagnosis of congenital diaphragmatic hernia. The most commonly used variable is the lung-to-head ratio, which is measured via prenatal ultrasound.²¹ Unfortunately, this measurement has only been validated for left-sided defects during a limited gestational window and has not successfully predicted postnatal survival. Another biometric variable under investigation is the observed-to-expected fetal lung volume, measured via magnetic resonance imaging. A multicenter prospective study conducted in France found that fetal lung volume measurement via magnetic resonance imaging is a good predictor of postnatal mortality related to pulmonary hypoplasia.²² Prenatal measurements may assist with determining risk, which may improve prenatal parental counseling and aid in the selection of the optimal conditions for delivery.

An antenatal diagnosis of congenital diaphragmatic hernia that is categorized as severe via any of the above variables may be considered for delivery in a center with immediate ECMO availability. The goal is to avoid the potential hemodynamic instability and barotrauma that may occur during the transport of an infant to an ECMO center. The availability of an ECMO circuit for the delivery of an infant with congenital diaphragmatic hernia is debatable, as this approach almost certainly requires a planned cesarean section and the availability of a team of specialists and resources.

The ex-utero intrapartum treatment (EXIT) procedure has been used in some centers as a strategy for initiating early ECMO support. During an EXIT procedure the baby is partially delivered via cesarean section and maintained on placental support while the neonatal surgical team evaluates the infant's condition. The procedure was originally developed as a delivery method to reverse the temporary tracheal occlusion in patients who had undergone fetal surgery for severe congenital diaphragmatic hernia. In addition, this method of delivery has been used for infants who were diagnosed prenatally with life-threatening airway conditions.²³ This technique was described in a case series of 14 patients, in which an EXIT-to-ECMO delivery strategy was employed. This study reported a 64% survival rate and noted that, despite a risk stratification of severe, 3 patients did not require ECMO, leading to spec-

ulation that the prenatal screening was imperfect, and that there was additional risk to the mother, as this procedure is not a typical cesarean section.^{24,25}

Outcomes

Hospital Survival

Since its inception in the 1980s, the Extracorporeal Life Support Organization has reported the use of ECMO in nearly 23,000 cases of respiratory failure in newborns, with an overall hospital survival rate of 76%. Infants with meconium aspiration syndrome have the highest survival rate, at 94%.⁸ The combined survival rate for the more typical newborn respiratory disorders, including meconium aspiration syndrome, respiratory distress syndrome, persistent pulmonary hypertension of the newborn, sepsis, and pneumonia, has been consistently over 85%.

The survival rate for congenital diaphragmatic hernia patients requiring ECMO has been reported at 52% by the Congenital Diaphragmatic Hernia Study Group and 51% by the Extracorporeal Life Support Organization.^{8,18} Similarly, our institution's cumulative 24-year ECMO survival rate for congenital diaphragmatic hernia is 56%. A review of our most recent 10-year-period experience with congenital diaphragmatic hernia patients demonstrated an average of 16 patients admitted per year, with an ECMO requirement of about 44%. The hospital survival rate for the total group of congenital diaphragmatic hernia patients was 78%, and 61% for ECMO patients (Fig. 3).

Neurodevelopmental

ECMO and the pre-ECMO condition predispose the neonate to potentially substantial morbidity, in particular neurologic injury. Short has written a comprehensive description of the effects of ECMO on the brain.²⁶ Cerebral blood flow is disrupted by the ligation of carotid and internal jugular blood vessels, and prolonged periods of pre-ECMO hypoxemia place the neonatal brain at substantial risk. Adding to these risks are the need for systemic anticoagulation, fluctuations in blood pressure, and the non-pulsatile nature of ECMO flow. Despite these risks, animal experiments and clinical observations suggest that the brain responds by the development of collateral circulation and other adaptive processes.

ECMO programs in the earlier eras were justifiably concerned with the long-term well being of the infants that were rescued, and attempted to follow these infants' progress into childhood. A number of early studies identified neurodevelopmental trends in children in the 3–5-year age range who required ECMO support in infancy.²⁷ These earlier observations were encouraging, as the majority of infants surviving a course of ECMO had few or

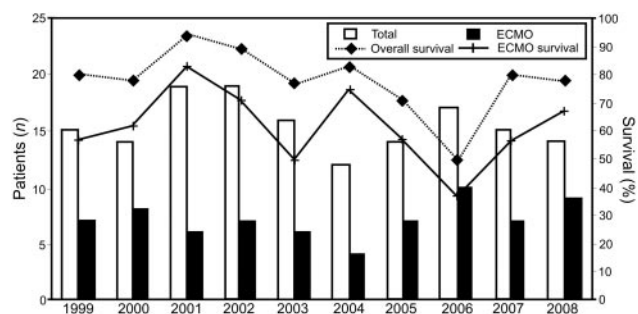


Fig. 3. Ten-year trend of newborns with congenital diaphragmatic hernia, extracorporeal membrane oxygenation (ECMO), and non-ECMO cases in Children's Hospital Boston ECMO registry. (Approved by the Children's Hospital Boston institutional review board.)

no long-term deficits. Attempts at identifying risk factors, such as diagnosis, pre-ECMO severity of illness, ECMO and post-ECMO hospital duration, and type of ECMO support, have been varied.

The United Kingdom Collaborative ECMO trial clearly established the benefits of an ECMO policy for severe respiratory failure in newborns, and provided further confirmation by means of 4-year and 7-year follow-up evaluations.^{28,29} Throughout these post-study years, ECMO graduates had similar neurodevelopmental patterns, including cognitive and behavioral targets, to the non-ECMO groups, with no level of disability being categorized as severe. The congenital diaphragmatic hernia cohort had a 26% incidence of disability, and over 50% were found to have chronic or recurrent gastrointestinal problems, with poor weight gain and growth observed in 33% of long-term survivors.³⁰

The risks associated with ECMO for neonatal respiratory failure are well balanced with a good survival rate and favorable neurodevelopmental outcomes.

Pulmonary

The pulmonary function of newborn ECMO survivors has been described in a number of studies. The United Kingdom trial evaluated children at one year of age, and, although there were no significant differences in respiratory status between the 2 groups, the non-ECMO group tended to have indicators of mild airflow obstruction, when compared to the ECMO group.³¹ This was attributed to the need for greater ventilatory support and duration, whereas the ECMO group received a lung-rest approach to mechanical ventilation.

Exercise tolerance was evaluated in 10–15-year-old subjects who required ECMO as newborns.³² This trial demonstrated that ECMO graduates had a greater propensity for airflow obstruction following exercise, as compared to

controls, but that both groups had similar tolerance to exercise as indicated by measures of aerobic capacity.

Airflow abnormalities were also identified in children around the age of 11 years who were treated with ECMO as newborns.³³ This study suggested that impaired pulmonary function is influenced by the degree of post-ECMO ventilatory support and oxygen requirement. When patients with congenital heart disease and congenital diaphragmatic hernia were removed from the data analysis, the remainder of the ECMO group did not have significantly different pulmonary function than the non-ECMO group.

There does appear to be some evidence that an ECMO requirement for newborn respiratory failure may affect pulmonary function later in life. The factors that influence this predisposition may be related to diagnosis, post-ECMO assisted ventilation, and oxygen requirement.

Economic

The number of ECMO centers reporting data to the Extracorporeal Life Support Organization has not varied significantly, with 100 centers in the United States and 25 at other international locations.⁸ This may in part be attributed to a relatively steep learning curve, the availability of other centers in certain regions, and costs. Instituting an ECMO policy requires a tremendous amount of technical, human, and financial resources. Guidelines governing the reimbursement of ECMO services vary from payer to payer, with some providing reimbursement only for evidenced-based ECMO practices such as newborn respiratory failure.³⁴ There are 3 current procedural terminology (CPT) codes associated with ECMO, including the cost of the cannulation, the initial day of support, and the subsequent days of ECMO management.³⁴

Determining if ECMO is worth the associated expenses is difficult to deliberate, because in many circumstances its availability and use means the difference between life and death. The United Kingdom Collaborative has managed to provide detailed analysis of cost-effectiveness as part of their randomized ECMO study in newborns with respiratory failure, and has determined ECMO to be cost-effective relative to the non-ECMO control groups, and at years 1, 4, and 7.³⁵⁻³⁷ As ECMO indications broaden, it may become even more difficult to ascertain the overall economic impact.

Complications

The common complications associated with ECMO are generalized as either technology-related or physiologic. The Extracorporeal Life Support Organization registry includes complications data, and reports an average of 2.5 complications per neonatal respiratory case.⁸ Prevalent

technology-related events include clotting of circuit components, for which troubleshooting procedures are required. The need for systemic anticoagulation predisposes the neonate to bleeding, which is common and may range from minor oozing from cannula sites to more extensive bleeding such as an intracranial hemorrhage. Other patient-related complications include renal insufficiency, seizures, and cardiovascular instability. The physiologic complication rate may increase in patients who receive a second course of ECMO, which occurs in only about one percent of neonates and mainly in patients with congenital diaphragmatic hernia.³⁸

Summary

While advances in newborn intensive care have led to a decline in the use of ECMO in respiratory failure, it remains an important life-saving intervention. ECMO for congenital diaphragmatic hernia patients continues to be a reasonable alternative, although its exact position in the treatment algorithm is somewhat unclear. Newborns with severe respiratory failure who have been supported with ECMO have a consistently good survival rate and favorable long-term developmental and cardiopulmonary outcomes.

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