The use of ECMO to treat infection in paediatric patients

The use of extracorporeal membrane oxygenation (ECMO) in term babies with severe but potentially reversible respiratory failure results in significantly improved survival without increased risk of severe disability. This article describes a case series of children referred for sepsis to a tertiary referral centre for ECMO over an eight-year period. The age range of the patients was between zero days and 16 years; two babies were referred in the first week of life. In most cases there was a quick onset of respiratory failure and/or multi-organ failure; the survival rate was 45%.

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Key points

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1. The survival rate in children with infection who receive ECMO can be up to 80%. In this case series the survival rate was 45%.
2. In the survivors group, the added co-morbidities were treatable.
3. There was variation in the management of patients prior to ECMO. Standardisation of practice may improve outcomes.
4. There appears to be some correlation between lactate levels prior to ECMO and survival to discharge, suggesting that lactate could be used as a predictor for survival.

Extracorporeal membrane oxygenation (ECMO) was initially used as respiratory support in neonates and is now widely used in paediatric and adult patients with respiratory and/or cardiac failure. Technological advances have led to improved safety and patient survival. It is recognised that the earlier use of ECMO to prevent or reverse multi-organ failure (MOF) can lead to better outcomes.[1,2] ECMO can provide complete cardio-respiratory support and has become a standard of care in paediatrics to support respiratory and/or cardiac function when conventional treatment is failing.[3]

ECMO treatment: outcomes

Outcome after ECMO treatment is variable, depending on the primary diagnosis. Survival rate for children with sepsis is comparable with the adult population and may be up to 76% in neonates.[4] Von Bahr studied 400 ECMO patients over 27 years and examined 10-year survival rates;[5] 84% of the neonates and 74% of the paediatric patients survived ECMO. Approximately 10% of ECMO survivors died within 90 days of weaning leading to 76% and 66% 90-day survival rates for neonatal and paediatric patients, respectively. Cardiac patients were excluded from this study. Von Bahr reported a long-term survival rate of up to 90% for those children who survived the first three months following ECMO.

The prognosis is favourable in patients with reversible conditions.[5] The 10-year survival rate for babies with congenital diaphragmatic hernia (CDH) is only 53% compared to 99% for babies treated for meconium aspiration syndrome (MAS). In neonates, a Cochrane review showed that using ECMO in term babies with severe but potentially reversible respiratory failure results in significantly improved survival without increased risk of severe disability.[6] The ECMO Collaborative UK Study data also showed that ECMO support for cardiorespiratory failure in term infants reduces the risk of death without a rise in severe disability. In this study, one in four survivors had evidence of impairment with or without disability.[7] A US study showed that ECMO improves survival, and most US centres have reported a relatively low morbidity rate for the entire ECMO population. However, the CDH population appears to have a higher incidence of neurodevelopmental, respiratory, and feeding abnormalities in the first year of life.[8]

Types of ECMO

There are two types of ECMO:

1. Venovenous ECMO (VV-ECMO) supports lung function by oxygenating venous blood and removing carbon dioxide. By improving the delivery of oxygen to the tissues, VV-ECMO improves cardiac function as well.
2. Venoarterial ECMO (VA-ECMO) provides full cardiac and respiratory support, allowing the lungs and heart to rest and recover (**FIGURE 1**).

ECMO in neonates

In 1973, the first neonate was successfully treated with ECMO for MAS. Since then,

approximately 30,000 neonatal respiratory ECMO cases have been reported to the Extracorporeal Life Support Organization (ELSO) registry, and the survival rate to discharge from the ECMO centre at Freeman Hospital was 75% overall. The most common neonatal conditions treated with ECMO include MAS, CDH, pulmonary hypertension, sepsis, and respiratory distress syndrome. The population benefiting most from ECMO treatment are the patients found on the 50-75th mortality risk centile who fail to improve with conventional therapies. The mortality risk centile is calculated using the oxygenation index (OI) and the paediatric risk mortality (PRISM) score. In these patients the benefit of ECMO outweighs the complications associated with treatment.[9,10]

The inclusion criteria for ECMO are:

- gestational age >34 weeks
- birth weight >2kg
- reversible lung disease
- absence of uncontrolled bleeding or coagulopathy
- absence of intraventricular haemorrhage (IVH) grade 3/4
- correctable congenital heart disease
- failure of optimal conventional treatment.

Contraindications for ECMO treatment have been defined. Absolute contra-indications for ECMO are lethal congenital malformations or anomalies, eg trisomy 13 or 18, severe irreversible brain injuries and IVH grade 3/4. Some contraindications are relative:

- gestational age <34 weeks, because of the increased risk of intracranial haemorrhage
- birth weight <2kg, because of higher mortality associated with lower birth weight and technical difficulties related to cannula size
- irreversible organ damage, unless the patient is considered for organ transplant. In the case of patients with lung disease, the presence of chronic lung disease and prolonged mechanical ventilation (>14 days) with exposure to high oxygen concentrations are considered relative contraindications. Irreversible conditions such as surfactant B protein deficiency, alveolar capillary dysplasia or pulmonary hypoplasia are considered contraindications for ECMO, however they may remain undiagnosed prior to ECMO.

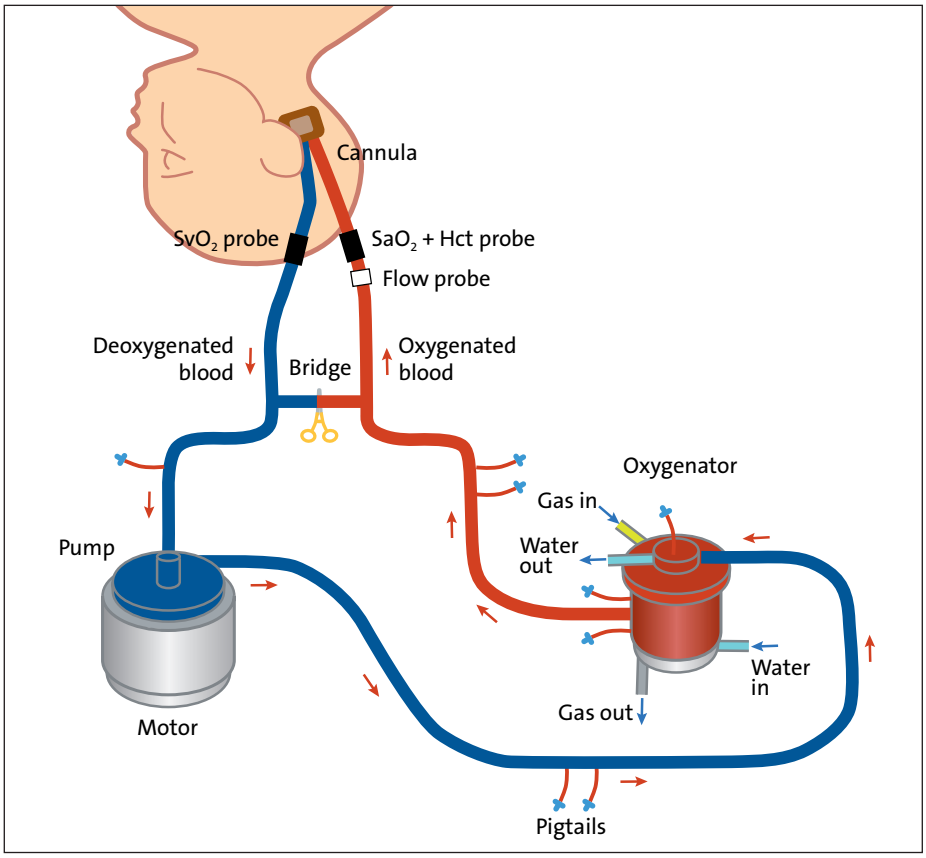

FIGURE 1 Example of a circuit in a case of VA-ECMO via the neck vessels. Key: SaO_2 = arterial blood oxygen saturation, SvO_2 = venous blood oxygen saturation, Hct = haematocrit.

These criteria represent a guide and each case should be individually assessed. ECMO can be used as a bridge to definitive treatment such as transplant, and this option should be explored in individual cases.

OI remains the most widely used tool to predict outcome and define the failure to respond to conventional therapy. OI is calculated by:

$$\frac{\text{mean airway pressure x } FiO_2 \text{ x } 100}{\text{post-ductal } PaO_2}$$

Most centres use an OI range of 40-45 as indication for initiating ECMO. Existing data suggest that earlier initiation of ECMO improves outcome, by reducing the reperfusion injury, therefore most ECMO centres recommend referring for ECMO any neonate receiving optimal conventional therapy with an OI greater than 25. One study found that mortality increased by 16 times when OI was greater than 33.2.[11]

ECMO in infants

ECMO has a defined role in managing severe respiratory failure in infants with viral pneumonia or bronchiolitis. Approximately 5% of infants admitted with bronchiolitis will require mechanical ventilation and a small number will be referred for ECMO. Often these infants have a significant underlying condition, such as chronic lung disease of prematurity. The most often involved pathogen is respiratory syncytial virus (RSV); metapneumovirus has also been quoted. Selection criteria for ECMO in this population are similar to those used for neonates. An OI of greater than 25 for more than 12 hours of optimal conventional ventilation with nitric oxide should prompt referral. Previously, prolonged ventilation (>7 days) and home oxygen treatment preceding the illness were considered a relative contraindication for this population. Brown et al disproved this approach, and while most will accept that the less the number of ventilation days the better outcome, ECMO treatment should still be considered for these patients.[12]

ECMO and sepsis

Sepsis is a well-known cause of infant mortality and pneumonia is the worldwide leading cause of death in children under five years. ECMO can be used in refractory

septic shock to support the cardiac output and oxygenation while antibiotics control underlying infection. By July 2006, 2,906 cases had been reported to the ELSO registry, with 72% survival rate to discharge.

Methodology

This article reports on the authors' experiences of ECMO in children with infection associated with refractory septic shock and/or respiratory failure. A retrospective description of a case series of children admitted to a national ECMO referral centre in Newcastle, primarily for treatment of septic shock and/or respiratory failure, is presented.

The paediatric intensive care unit (PICU) at Freeman Hospital in Newcastle is a cardiac intensive care unit for children recovering from heart surgery or with end stage heart failure requiring heart transplantation and/or mechanical heart support. The centre delivers mechanical heart support in the form of extra-corporeal cardiopulmonary support or a ventricular assist device, and heart and lung transplantation.

The case series

Between April 2008 and August 2016, 11 children were referred to Freeman PICU with refractory septic shock and/or respiratory failure secondary to infection who received ECMO for haemodynamic and respiratory support. The case descriptions and status at discharge were obtained from the PICU database and case notes.

There were four boys and seven girls. Age at referral was widespread: two newborn babies, three toddlers, four children and two teenagers. The overall survival rate was 45% (five children); in the survivors' group, the age range was zero days to 14 years.

The clinical picture at onset of disease was non-specific with upper respiratory tract symptoms in more than half of the cases, which then quickly evolved to full blown pneumonia, respiratory failure, and septic shock. The median time between onset of primary symptoms and onset of multi-organ and/or respiratory failure was less than four days, with children being referred for ECMO within the first four days of illness in more than half of the cases. No difference in survival was noted in the case series between cases referred in the first 48 hours from the onset of signs of septic shock and/or respiratory failure and those referred after 48 hours.

Case	Primary infection	Secondary infection
1	Group A streptococcus	
2	Pseudomonas	*Escherichia Coli*, enterococcus
3	Rhino syncytial virus, *Haemophilus influenzae*	Proteus, *Enterobacter cloacae*, stenotrophomonas
4	Meningococcus group B	
5	Pneumococcus type 19A	Candida
6	Adenovirus	*Haemophilus influenzae*, coagulase negative staphylococcus, pseudomonas
7	*Haemophilus influenzae, Streptococcus pneumoniae*	
8	*Legionella pneumophilia ST48*	*Haemophilus influenzae*, stenotrophomonas
9	Group A streptococcus	
10	Rhinovirus	
11	Group B streptococcus	Enterococcus

TABLE 1 The infecting microorganisms in each case.

Referral

Eight out of 11 cases (72%) were referred from the northern region of England, and three cases were referred from out of region. No specific criteria or form for referral were used. The patients were showing either refractory septic shock (three cases) or respiratory failure (seven cases). One patient was referred for empyema drainage, however cardiovascular collapse occurred prior to intervention and the patient received eCPR (the use of ECMO in cardiovascular resuscitation).

Organ failure

Prior to starting ECMO, nine out of 11 cases (81%) had MOF and, of those, a third survived. Four cases developed a new organ failure while on ECMO, of which two children died. There was no obvious correlation in the case series between the pre-existence of MOF on admission and survival, or between the number of organs affected and survival. Also, it did not appear that the pre-existence of kidney failure was a predictor for poor outcome, nor was the development of new kidney failure while on ECMO.

Lactate, inotropes and hydrocortisone

Normal lactate range is 0.5-1mmol/L. In this case series, lactate range was 2-20mmol/L; however, in all cases that survived, lactate during admission was less than 6mmol/L. Mean arterial pressure range was 28-80mmHg, charting within normal for age in six out of 11 cases. There was significant variation in inotropic treatment prior to ECMO, with most cases receiving at least two inotropes prior to starting ECMO. Hydrocortisone treatment for refractory septic shock was added in four cases. Four out of seven children were weaned of inotropes while on ECMO and they all survived.

Ventilation parameters

Pre-ECMO ventilation parameters were available in the notes of eight cases. Five children received high pressure ventilation (with inspiratory pressure up to 30cmH_2O) in 100% FiO_2 and three cases received high frequency ventilation with nitric oxide.

Cause of infection

In seven cases, the primary cause of infection was respiratory and four children presented with overwhelming sepsis. One baby presented with overwhelming Group B streptococcus (GBS) sepsis and one with Legionella pneumonia. There was a wide range of microorganisms involved (**TABLE 1**). Treatment commenced with broad spectrum antibiotics, followed by targeted antimicrobial therapy once the micro-organisms had been identified.

ECMO treatment

The length of stay was between four days and four months (in one case). The length

of ECMO treatment was between one and 39 days, with a median of 10 days. Ten cases received peripheral ECMO, with cannula size appropriate to weight (as per the ELSO ECMO protocol), and achieved optimal flows according to age, with a range of 100-230mL/kg. Four out of nine cases of peripheral VA-ECMO achieved flows above 180mL/kg, however none survived, suggesting that the flows are more likely to reflect the severity of the disease, rather than the size of the cannulae (range 8-25Fr). Hypotension can be attributed to the inflammatory response and low systemic vascular resistance secondary to infection. As a result, the ECMO flows are increased to counteract the systemic hypotension and the status of shock with increased cardiac output.

Complications

Seven cases developed ECMO-related complications including bleeding, frequent 'clots cut out' and secondary infection. Bleeding is an expected complication during ECMO because of the anti-coagulant therapy, however it can be catastrophic in the setting of disseminated intravascular coagulation secondary to sepsis. Bleeding contributed to death in three of the cases. Six cases (54%) developed secondary infection during the ECMO course and in two of those cases the secondary infection was overwhelming and contributed to death (one case of Pseudomonas and one case of Candida, respectively). Five cases developed neurological complications post-coagulopathy and bleeding.

Weaning from ECMO

ECMO treatment was weaned in a planned manner in five cases who survived to discharge from Freeman Hospital. Three survivors had neurological morbidity at discharge, with one case of left-sided weakness, one critical illness myopathy and one cerebral abscess following cerebral haematoma. ECMO treatment was weaned in an unplanned manner in two cases; in one case due to precarious cannulae and in the other, due to need for a lifesaving intervention considered unsuitable while on ECMO. In four cases, ECMO treatment was withdrawn (one case where brain death was diagnosed and three cases where continuing treatment was considered futile).

Discussion

The survival rate in this case series was 45%, lower than previously quoted, however the small number of cases does not allow a meaningful statistical conclusion. The PICU in Freeman Hospital is not a general PICU and, therefore, the cases referred to Freeman PICU are likely to be at the most severe end of the spectrum. In general PICUs with ECMO the procedure can be started semi-electively, hence earlier and with better results. In the survivors group, the added co-morbidities were treatable.

Freeman PICU receives referrals from a wide geographical area and this leads to significant variation in the management of a patient prior to ECMO, such as inotropes used. Standardisation of practice may improve outcomes.

Early referral is critical, however in most cases there was a very quick onset of respiratory failure and/or MOF, suggesting that the innate aggressive nature of the bacteria associated with reduced defences of the host plays a big role despite adequate ECMO support. The unit operates a general ECMO referral form and a specific guideline for those patients with suspected infection will be developed, to rationalise the referral process and to facilitate better collection of data in the future.

There appears to be some correlation between a lower level of lactate prior to starting ECMO and survival to discharge. This was noted in previous studies[13,14] and may suggest that lactate could be used as a predictor for survival.

ECMO can be safely used to resuscitate and support children with sepsis, refractory shock and/or respiratory failure. Sepsis with MOF should not be considered a contraindication to ECMO. Further work is needed to define criteria for ECMO referral and outcome predictors in sepsis.

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