The role of ECMO in neonatal & paediatric patients

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Abstract

ECMO or Extracorporeal Membrane Oxygenation has now been part of healthcare for over 40 years. During that time, changes in circuit technology have resulted in improved survival and have facilitated the use of ECMO in more challenging patient groups in whom ECMO was previously considered to be contraindicated. Further advances have allowed ECMO to progress out of the specialist centres and nearer to patients, in the form of mobile ECMO. Patient selection remains key to a successful outcome since ECMO is a supportive therapy utilised whilst waiting for a reversible condition to resolve through other treatment strategies.

Keywords ECLS; ECMO; extracorporeal membrane oxygenation; paediatric intensive care; PICU

The basics

ECMO involves the drainage of blood via a cannula into an extracorporeal circuit including an artificial membrane where gas and heat exchange occurs, before returning it to the patient. Blood can be returned via an artery "VA" (veno-arterial) or a vein "VV" (veno-venous) ECMO. VA ECMO bypasses and supports both the heart and lungs, whilst VV supports gas exchange but does not bypass any organs. Due to the improvement in oxygenation, VV ECMO often improves cardiac function despite there being no direct mechanical arterial support.

The keys to successful ECMO are:

- Case selection
- Patient monitoring
- The ability to react to sudden mechanical or patient events

Epidemiology

Worldwide, ECMO has supported over 65,000 patients with approximately 35,000 of those being neonates and 15,000 children. The commonest conditions supported with ECMO are listed in Table 1. Each year in the United Kingdom (Total population 65 million, 15 million children), roughly 200–250 neonates and children receive ECMO support. Of whom, 100 neonates and 45 children receive respiratory support whilst approximately 80 neonates and children receive cardiac support. Nearly double that number will be referred, receive advice or be transferred for on-going conventional therapy whilst their need for ECMO is assessed. The proportion of neonatal and paediatric patients requiring support each year remains relatively low, which is why the expertise to provide it is concentrated in only a few centres.

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Evidence

Respiratory failure

Neonates: in 1975 a baby called Esperanza presented with Meconium Aspiration Syndrome (MAS) and severe Persistent Pulmonary Hypertension of the Newborn (PPHN). She received 72 hours of ECMO support, and was the first baby to survive thereby. She now leads a normal life. As a 'new' technology, ECMO was initially used to support patients with poor prognoses (expected mortality >80%) despite this ECMO appeared to increase survival rates to 75%.

The first randomised, controlled trial (RCT) evaluating neonatal respiratory ECMO was led by Dr. Bartlett at the University of Michigan in 1985. Whilst it demonstrated that ECMO provided a clear survival advantage, the unorthodox "play-the-winner" design led to significant debate amongst the medical community. This led to a second larger "play-the-winner" study from Dr Pearl O'Rourke at Boston Children's Hospital in 1989, with a similar survival advantage. By the mid-1990s, the UK Collaborative ECMO Trial Group published a 55-centre conventionally designed RCT randomising neonates with PPHN to either stay in their referral centre for standard therapy or be transferred to a regional ECMO centre. Survival was again higher in those receiving ECMO compared with those without (60% vs. 40%).

More recently (2008), a Cochrane review by Mugford and colleagues combined these three and a further non-randomised study comparing ECMO and conventional management for neonatal respiratory failure. All four studies demonstrated that ECMO support increased survival to hospital discharge when compared to conventional therapeutic strategies. Of the total 244 infants, 77% survived in the ECMO group compared with 44% in the conventionally managed group ($p < 0.00001$). This equates to one additional survivor for every three babies supported on ECMO.

Adults: Evidence for the benefit of ECMO in adult respiratory patients was not rapidly forthcoming. Early studies did not demonstrate a survival advantage, but were hampered by ventilation techniques not employing a 'lung protective strategy', the enrolment of moribund patients and the utilisation of many centres with little or no previous experience of providing ECMO support. The multicentre CESAR trial found that transfer to an ECMO centre reduced the chance of death or severe disability at 6-months in adults with advanced respiratory failure (ECMO survival 63% vs. 47%, RR 0.69 [0.05–0.97], NNT 6.25). Following this, reporting of favourable outcomes from use of ECMO in adults with respiratory failure secondary to H1N1 has lead to a significant increase in use of ECMO for adult advanced respiratory failure.

Children: Paediatric ECMO is less common and the clinical indications for initiation of ECMO are more hetrogenous. This may explain the lack of a large RCT looking at the efficacy of ECMO in advanced respiratory failure. Evidence for outcome associated with paediatric ECMO is mostly limited to Class III evidence in

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The commonest respiratory ECMO indications by age (frequency %)

Neonatal	Paediatric	Adult
CDH (30%)	Non-ARDS, respiratory failure (20%)	Non-ARDS, Respiratory failure (20%)
MAS (25%)	Viral pneumonia (20%)	Bacterial pneumonia (17.5%)
PPHN (20%)	Bacterial pneumonia (8%)	ARDS (10%)
Sepsis (5%)	ARDS (6%)	Viral pneumonia (5%)
RDS/pneumonia (1.5%)	Aspiration pneumonia (1%)	Aspiration pneumonia (1.5%)
Other (18.5%)	Other (45%)	Other (46%)

Comments:
Neonatal – In the last decade, the number of babies needing ECMO for MAS has reduced with concomitant changes in obstetric practice and improvements in conventional NICU. The frequency of other neonatal diagnoses has remained static, bar an increase in less conventional indications.
Paediatric – There is an increasing frequency of pneumonias and other indications.
Adult – There has been an almost exponential increase in ECMO use in adults since the publication of the CESAR trial in 2009 and the successful utilisation in the treatment of the H1N1 virus. Adult cardiac ECMO has also greatly increased.

Table 1

the form of retrospective reviews. In 1996, Green published a multicentre, retrospective cohort study of paediatric patients with acute respiratory failure admitted to 32 US hospitals. A second analysis was performed of ECMO patients paired with severity and respiratory diagnosis matched controls. They found a reduction in mortality with the use of ECMO (26.4% vs 47.2%, $p < 0.01$).

Over the last 15 years survival has been consistent at 57% despite increasing comorbidities. Those without comorbidities had an increased survival from 57% to 72% over the study period. Higher survival figures were associated with status asthmaticus (83%), aspiration pneumonia (71%) and respiratory syncytial virus pneumonia (70%). Poor prognostic indicators included patients 10–18 years of age, hepatic or renal failure, evidence of immune dysfunction, or those with a diagnosis of pertussis, fungal pneumonia or ARDS secondary to sepsis.

Cardiac failure

Mechanical support for non-structural heart failure in children is uncommon with on average 10–15 patients per annum referred to UK ECMO centres. Of these, approximately 80% survive with around half of the survivors recovering and half requiring transplantation. ECMO is used to provide temporary circulatory support for patients with potentially reversible disease or as a bridge to decision, device or transplant.

ECMO is used to stabilise and assess patients prior to Ventricular Assist Device (VAD) insertion (Bridge-to-bridge). A VAD does not provide any respiratory support, is more expensive and is harder to implant but has better outcomes than both ECMO and mechanical ventilatory support, when used as a bridge to cardiac transplantation. The risk of embolic stroke necessitates anticoagulation and device insertion almost always requires a sternotomy with cardiac bypass.

In a recent (2012) prospective study of paediatric VADs, 88–92% of children successfully bridged to either recover or transplant compared to 67–75% of those supported by ECMO alone. VAD use is not without its problems however, 29% of children suffered a stroke, making balancing when or if to institute the support even more challenging. In the UK VAD use is currently limited to transplant centres.

Basic physiology of ECMO support

With VA ECMO, the venous drainage into the ECMO circuit unloads the right side of the heart, reducing pulmonary blood flow, which in turn reduces left sided preload by reducing both left ventricular end diastolic pressure (LVEDP) and volume (LVEDV). However the left ventricular afterload is increased by the flow from the ECMO circuit and if left ventricular or lung function is severely impaired this can lead to problems that will prevent recovery. If the heart is ejecting, the coronary arteries are perfused with blood from the left ventricle, if the lungs have also failed this blood will be hypoxic and this in turn can lead to poor LV function "stunning". If the heart is not ejecting and the aortic valve remains closed the left ventricle will gradually distend and sub-endocardial perfusion will fail when the LVEDP exceeds the non-pulsatile mean arterial pressure provided by the ECMO machine. In this setting, the coronaries are perfused with blood from the pump, but the myocardium will die. In addition, the high LVEDP leads to dilatation of the LA with pulmonary hypertension, oedema and haemorrhage. In this setting, it is vital that the left ventricle is decompressed, by venting either directly or across the atrial septum. The greatly augmented systemic blood flow from VA ECMO leads to immediate restitution of end organ function as long as ECMO has been initiated before multi-system organ failure is well established.

Specific conditions

Congenital diaphragmatic hernia

The presence of a congenital diaphragmatic hernia (CDH) is the commonest single indication for ECMO in neonates. When assessing neonates with a CDH, a key question is how much of the respiratory failure is due to direct lung compression by the abdominal contents (potentially reversible), rather than due to underlying lung hypoplasia (potentially fatal). The late development of a CDH in utero would suggest adequate lung development but the early presence of a CDH does not preclude ECMO use. In practice, those who can be supported to some degree with conventional therapy would be eligible for ECMO support. Counselling needs to be appropriate as even with a

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successful repair, decannulation from ECMO or extubation from a ventilator may not be possible. Successful survival of neonates with a CDH requiring ECMO is in the region of 50–60% with a rising trend. Factors associated with survival to discharge include; greater birth weight and gestational age, higher APGAR score, the presence of a unilateral lesion and a shorter run on ECMO. Those associated with a poorer outcome include; associated cardiac defect, pre-ECMO cardiac arrest, pH < 7.2, $PaCO_2 > 8$ KPa, $PaO_2 < 5.3$ KPa and oxygen saturations $<80\%$.

Meconium aspiration syndrome (MAS)

The increased use of surfactant, nitric oxide and HFOV have reduced the need for ECMO in MAS. MAS remains the second commonest neonatal indication and has the highest survival and lowest complication rate of all conditions treated with ECMO. Survival rates are around 90–97%. This high survival rate in conjunction with research suggesting that late institution of ECMO may results in a lung reperfusion injury, has led to international recommendation that infants in this cohort with an oxygen index ≥ 25 are discussed and/or cared for in an ECMO centre. This then allows for the timely institution of ECMO if there is further deterioration.

Persistent pulmonary hypertension of the newborn (PPHN)

Persistent Pulmonary Hypertension of the Newborn is a failure of normal postnatal reduction in the pulmonary vascular resistance (PVR). With increased PVR, blood diverts through the path of least resistance of the foramen ovale and ductus arteriosus thereby bypassing the lungs. ECMO is useful when conventional techniques fail to lower the PVR enough to improve oxygenation and ventilation.

PPHN is usually secondary to an external insult. Primary pulmonary hypertension due to hypertrophy of the pulmonary vessel musculature is very rare, as are Alveolar Capillary Dysplasia and Surfactant Protein deficiency; these conditions are usually fatal. At initiation of ECMO, primary and secondary PPHN is largely impossible to differentiate, so the early identification through awareness, genetic testing or lung biopsy, is vital to prevent prolonged futile ECMO support.

Sepsis

ECMO support is no longer seen as controversial or contra-indicated in advanced septic shock and there are numerous studies suggesting that high flow VA ECMO reverses shock, improves multi-organ dysfunction and improves survival rates. Survival amongst neonatal and paediatric patients supported with ECMO seems to be inversely proportional to their age with figures ranging from 30% in adolescents up to 75% in neonates.

eCPR

eCPR (the use of ECMO during cardiac arrest to support the heart through to recovery) is considered to be accepted treatment in both adult cardiology/cardiac surgery and paediatric cardiac intensive care practice, where most cardiac arrests are cardiac in origin. Most paediatric cardiac arrests outside of a paediatric cardiac intensive care unit are secondary to a respiratory arrest and therefore due to hypoxia. For the heart to stop following a respiratory arrest there will have been a period of hypoxia that makes recovery less likely.

The highest survival from eCPR amongst paediatric patients is found amongst post-cardiotomy patients already within the PICU or catheter laboratory environment. The survival in this group within the published literature ranges from 33 to 75%, with the larger studies all finding survival to hospital discharge at approximately 40–50%. The International Summary ELSO database (January 2015) identified 3482 neonates and children less than 18 years of age who received ECMO support during cardiopulmonary resuscitation between 1992 and 2014. Of those, 41% ($n = 1425$) survived to hospital discharge, with a near identical survival rate between neonatal and paediatric patients. Whilst eCPR is being increasingly utilised, survival was not shown to improve over a 14-year period between 1992 and 2005. Predictors of mortality include the presence of non-cardiac disease, acute kidney injury on ECMO, neurological complication whilst on ECMO, a high lactate, a low pH on ECMO and the use of sodium bicarbonate during the resuscitation.

Neurological morbidity is highest amongst neonates requiring eCPR and is more prevalent than with conventional ECMO deployment. A review of the International Extracorporeal Life Support Organisation (ELSO) database identifies 22% of neonates and children requiring eCPR have an acute neurological injury, $\sim$ 10–12% have an incidence of seizures, a similar frequency have radiological evidence of infarct or haemorrhage and a similar number again fulfil brain death criteria.

Neurological outcome following in hospital cardiac arrest and ECMO support is most frequently assessed utilising the pediatric cerebral performance category (PCPC) scoring system. Detailed long-term neurological follow up of survivors of paediatric eCPR is lacking within the medical literature bar that of single institutions, however, an analysis of the US National Registry of CPR in 2010 identified 6288 reported arrests between 2000 and 2008, of which 199 (3.2%) received eCPR following in-hospital arrest. Survival to hospital discharge was 43.7% ($n = 87$) and of those, 59 had a PCPC score recorded. Fifty-six (94.9%) had a favourable PCPC score, defined as categories 1–3 or no change from baseline score – see Table 2. Including the 28 survivors who had no PCPC score recorded, a minimum of 64% had a favourable outcome.

Less common indications

Air leak syndrome

The ability to oxygenate and ventilate using ECMO support without requiring high-pressure respiratory support makes air-leak syndrome highly reversible. Most cases of pneumothorax will resolve with the placement of a pleural drain. When ECMO support is required, on going air leak often resolves with the reduction in ventilatory pressures. If the age of the child permits, reducing sedation and extubating the patient will allow the return of spontaneous unsupported negative pressure ventilation, which in turn will aid in the resolution of the air leak syndrome.

Pertussis

Since 2011, the incidence of pertussis infection in the UK has risen due to a fall in vaccination rates.

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Pediatric cerebral performance Category (PCPC) Scale

Score	Category	Description
1	Normal	Normal, age appropriate, regular school
2	Mild disability	Age appropriate interaction, regular school but mild neurological deficit or lower grade
3	Moderate disability	Age appropriate independent functioning, special educational needs
4	Severe disability	Conscious but dependent on others for daily support
5	Coma or vegetative state	Unaware, even if appears awake. No evidence of cortical interaction with their environment.
6	Brain dead	Apnoeic, without brainstem reflexes

Table 2

Due to the aggressive nature of *Bordetella pertussis*, widespread pulmonary necrosis is often irreversible by the time pre-vaccination infants present for ECMO support. This has led to a consensus amongst the UK respiratory ECMO community to only offer ECMO to infants who have had at least their first pertussis vaccination (or maternal vaccination). Prevention of a poor outcome in this cohort requires focus on preventative strategies rather than the utilisation of ECMO support. Infants who have had their first set of vaccinations seem to have an attenuated response and improved survival but this remains an aggressive disease in the very young. Overall survival rates are approximately 30% (40% after 6 weeks of age), but this drops to 15% in those under 6 weeks of age.

Hypothermia

Severe paediatric hypothermia is extremely rare in the United Kingdom. Since 2005, the European Resuscitation Council have recommended ECMO as the preferred method for rewarming following hypothermic cardiac arrest. Survival from hypothermia is multifactorial but is significantly poorer if the mechanism causing the hypothermia also causes hypoxia whilst they are still warm e.g. drowning or avalanches with airway obstruction. Serum potassium can be useful for both differentiation and prognostication. ECMO needs to be thought of early and the presence of local and regional guidelines will aid in this process.

Outcome

Specific disease populations drastically alter the outcome of extracorporeal support and patient selection is key within an environment of limited resources. However, as techniques are refined and concurrent medical therapy progresses, extracorporeal support is likely to be offered to an increasingly diverse population with increasingly positive outcomes (See Table 3).

Morbidity

The UK Collaborative ECMO trial group publications provide key evidence of the benefit of neonatal ECMO and also followed up their study cohort at 1, 4 and 7 years. They identified that neonatal ECMO was effective not only at reducing mortality but the rate of severe disability too, compared to conventional therapy (RR Death or Severe Disability 0.64 [95% CI 0.47–0.86, p = 0.004]). This approximates to roughly one extra survivor without severe neurological disability for every four patients treated with ECMO. They also concluded that the underlying disease processes appear to be the major influence on morbidity. However, this cohort is now entering adulthood and during those 18 years, intensive care monitoring, interventions and ECMO management have changed significantly. This influences the conclusions drawn when considering our current neonatal population and

Overall survival figures for children and neonates supported by ECMO as reported to the International Extracorporeal Life Support Organisation (ELSO)

Neonates	CDH	50% (Increasing to 60–70% in the EU over the past 2 years)
	MAS	90–97%
	PPHN	75–85%
	RDS	>70%
	Sepsis	50–70%
Paediatric	Viral pneumonia	60–80%
	Bacterial pneumonia	60% (70–90% in the EU)
	Aspiration pneumonia	75%
	ARDS	50–60% (60–70% in the EU)
	Non-ARDS Respiratory Failure	50–70% (60–80% in the EU)

EU = European Union.

Table 3

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may suggest that ECMO is more or less effective or associated with greater or fewer morbidities.

Neurological outcomes

Long-term neurological morbidity is not significantly greater than comparable infants treated conventionally without ECMO support. Two relatively recent studies from the Netherlands identified the incidence of severe neurological deficit at 5 years following neonatal ECMO to be between 6 and 13%. ELSO data suggests an overall risk of acute seizures or haemorrhage of between 5 and 10% with a greater risk amongst those requiring support for cardiac indications. High-risk groups include those with a lower gestational age, birth weight <3 kg, prior CPR or those with sepsis, acidosis, coagulopathy or an inotropic requirement. Neonates requiring veno-arterial ECMO are also at greater risk of neurological complications.

Making a referral

Early discussion of a potential ECMO patient with the ECMO service is a mutually beneficial process. The ECMO team provides supportive advice, which in many cases obviates the requirement for ECMO. If ECMO is required, the patient transfer to an ECMO centre can be achieved at a time most beneficial to the patient and within the constraints of a small specialist team. If ECMO is not appropriate, this can be identified early and prevent false hopes being raised.

Whilst an oxygen index of ≥40 has traditionally been considered the threshold for instituting neonatal ECMO support, more recent evidence suggests that those receiving ECMO when the OI is ≥25 and ≤40 had both a shorter hospital stay and utilised less costly resources with a trend towards an improved outcome. As such, the current UK respiratory ECMO commissioning document suggests referral with an OI of >25 (on nitric oxide) to allow discussion, planning and advice — see Boxes 1 and 2.

Whilst all children should ideally have ≤14 days of high-pressure ventilation, both the duration and intensity of ventilation is considered when assessing whether ECMO support is likely to be beneficial. Early referral remains preferable to minimise long-term pulmonary dysfunction.

Infants on home oxygen due to prior prematurity were thought to have a higher risk of mortality. Whilst they are more prone to neurodevelopmental disability, it is unclear whether this is due to pre-existing morbidity or ECMO itself. A retrospective survey published in 2004 identified that this cohort has the same mortality risk and whilst the baseline level of oxygen dependency was the greatest predictor of death, no parameters, nor combination of parameters, reliably predicted mortality that would preclude ECMO support.

Criteria for an ECMO referral (but if in doubt, ring for advice)

1. A neonate with an oxygenation index (OI) of >30–35 on optimal treatment for four hours, or >25 on nitric oxide.
2. An infant or child with a pneumonia/air leak/ARDS and an OI of 25 (assuming no right to left shunt).
3. An arterial CO_2 tension of >12 kPa for more than three hours despite optimal treatment.

Box 1

Practical Limitations when instigation of ECMO would be unlikely

- < 34 weeks — due to size and risks of intracerebral bleed
- < 2 Kg — due to size in relation to cannulae
- Grade II or above intraventricular bleed — anticoagulation risk
- Cardiac arrest **without** adequate CPR
- Irreversible underlying cardiac or lung pathology
- Greater than two weeks of high pressure ventilation
- Pulmonary hypertension in those with chronic lung disease
- Established multi-organ dysfunction i.e. not acute
- Lethal congenital anomalies

Box 2

UK Respiratory ECMO Centres

Glenfield Hospital, Leicester:	(0300) 300 3200
Great Ormond Street Hospital, London:	(0207) 405 9200
Freeman Hospital, Newcastle:	(0191) 233 6161
Yorkhill Hospital, Glasgow:	(0141) 201 0000

All paediatric cardiac surgical centres in the United Kingdom provide cardiac ECMO support. Current commissioning supports respiratory ECMO in some of these centres as part of a surge process when the respiratory ECMO centres are full.

Mobile ECMO

As ECMO technology has advanced, the practicalities of transporting patients on ECMO have become easier. Whilst a few paediatric patients are transported from one ECMO centre to another each year, the majority of paediatric patients being moved on ECMO are as a result of the ECMO team mobilising to a peripheral hospital to support an acutely deteriorating patient. The advantages of earlier respiratory and cardiovascular support seem to outweigh the risks of cannulation in a 'foreign' environment or high-risk transfer otherwise associated with these patients. There are institutional experiences within the medical literature detailing safe programmes with similar outcomes but there is little that clearly demonstrates a survival/time/morbidity advantage over the conventional approach to paediatric transport. Nevertheless good outcomes can only be obtained with mobile ECMO by a highly experienced expert team.

Summary

ECMO support is providing improved outcomes to a wider population as technology and expertise advances. The importance of appropriate patient selection remains paramount to prevent futile prolonging of life. ECMO is a supportive therapy instituted to maintain respiratory and/or cardiac support, whilst waiting for a reversible condition to resolve through other treatment

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strategies. Early discussion with the regional ECMO centre is encouraged. ◆

FURTHER READING

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Key learning points

- There is good evidence to support the use of ECMO in neonates and adults with advanced respiratory failure but studies in children are lacking
- ECMO is considered a last resort therapy for refractory septic shock in all ages and is recommended on the basis of level C evidence
- ECPR following in hospital arrest increases neurologically intact survival in infants and children, particularly if they have cardiac disease amenable to recover or transplantation and their arrest occurs in a highly monitored environment with skilled expertise available

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