

## Neurologic complications and neurodevelopmental outcome with extracorporeal life support

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### Abstract

Extracorporeal life support is used to support patients of all ages with refractory cardiac and/or respiratory failure. Extracorporeal membrane oxygenation (ECMO) has been used to rescue patients whose predicted mortality would have otherwise been high. It is associated with acute central nervous system (CNS) complications and with long-term neurologic morbidity. Many patients treated with ECMO have acute neurologic complications, including seizures, hemorrhage, infarction, and brain death. Various pre-ECMO and ECMO factors have been found to be associated with neurologic injury, including acidosis, renal failure, cardiopulmonary resuscitation, and modality of ECMO used. The risk of neurologic complication appears to vary by age of the patient, with neonates appearing to have the highest risk of acute central nervous system complications. Acute CNS injuries are associated with increased risk of death in a patient who has received ECMO support. ECMO is increasingly used during cardiopulmonary resuscitation when return of spontaneous circulation is not achieved rapidly and outcomes may be good in select populations. Economic analyses have shown that neonatal and adult respiratory ECMO are cost effective. There have been several intriguing reports of active physical rehabilitation of patients during

ECMO support that is well tolerated and may improve recovery. Although there is evidence that some patients supported with ECMO appear to have very good outcomes, there is limited understanding of the long-term impact of ECMO on quality of life and long-term cognitive and physical functioning for many groups, especially the cardiac and pediatric populations. This deserves further study.

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**Key words:** Respiratory failure; Cardiopulmonary resuscitation; Pediatrics; Extracorporeal life support; Congenital heart disease; Stroke

**Core tip:** Extracorporeal life support is used to support patients of all ages with refractory cardiac and/or respiratory failure. It is associated with acute central nervous system complications and with long-term neurologic morbidity. Many patients treated with extracorporeal membrane oxygenation (ECMO) have acute neurologic complications, including seizures, hemorrhage, infarction, and brain death. In this review paper, we review the incidence of and factors associated with neurologic complications associated with the use of ECMO and the associated long term neurologic outcomes of patients treated with ECMO.

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### INTRODUCTION

Extracorporeal life support (ECLS) is used to provide pulmonary, cardiac, or cardiopulmonary support in neonate, pediatric, and adult patients refractory to con-

ventional management. Deployment of ELCS may be planned, urgent/emergent, or associated with cardiopulmonary resuscitation (ECPR). Various cannulation strategies exist with the dominant differentiating factor being veno-venous (VV) vs veno-arterial (VA) circuits. Survival has improved since extracorporeal membrane oxygenation (ECMO) was first utilized in the 1970s and indications and populations supported have expanded as techniques and strategies of deployment have evolved.

Patients supported by ECLS are at risk of neurologic injury from pre-ECLS factors including hypoxia, acidosis, hypotension and low cardiac output, infection, and organ failure, and from ECLS factors including hemorrhage, infarction, seizures, disrupted cerebral circulation, and development of new organ failure. Functional outcome after critical care, including ECLS support, is difficult to assess on a systematic basis, as follow up studies are limited and not standardized. Although children and adults are treated with ECMO, nearly 50% of treated patients are neonates<sup>[1]</sup> and assessing their long-term outcomes requires both time and an appropriate comparison population to account for severity of illness and social factors<sup>[2,3]</sup>. Neurodevelopmental and longitudinal outcomes after ECLS are most important to assess but are largely limited to neonatal and limited adult studies. More information is available on the incidence and risk factors for acute neurologic complications associated with ECLS.

The Extracorporeal Life Support Organization (ELSO) collects utilization, mortality, and complication data from 200 centers internationally on all technologies used to support cardiopulmonary function. Acute neurologic complications (seizures, infarction, hemorrhage, and brain death) are reported but functional outcome or disability is not. Administrative databases such as the Pediatric Health Information System or the Kids Inpatient Database also collect complication diagnoses but do not collect functional outcome specifically. Most reports of functional outcome after ECMO support are from single centers or multiple centers over a small time period<sup>[4-9]</sup>.

## ANATOMY AND PHYSIOLOGY OF NEUROLOGIC INJURY ASSOCIATED WITH ECLS

Neurologic injury associated with ECLS ranges from subtle neurocognitive defects to devastating intracranial hemorrhage to brain death. Injury may be sustained prior to ECLS support, during ECLS support, or after ECLS support has been discontinued. Neurologic complications reported to ELSO include hemorrhage and infarction documented by ultrasound and or computed tomography, clinical seizures, EEG documented seizures, and brain death (Table 1). The incidence of complications may be underreported due to the difficulty of obtaining reliable imaging in critically ill patients during extracorporeal support, and many patients who sustain

neurologic injury likely have increased risk of death and may die without imaging<sup>[10-12]</sup>.

Hemorrhage is generally poorly tolerated due to the anti-coagulation that is needed during ECLS support. Most common hemorrhagic injuries include intraventricular, intracerebral, and subdural hemorrhages. Risk factors for intraventricular hemorrhage have been most clearly demonstrated in neonatal patients<sup>[13]</sup>. Intracerebral hemorrhages are thought to be at significant risk of extension due to anti-coagulation but there is little published information on the natural history of intracranial pathology during ECMO<sup>[14]</sup>.

Infarctions may be small and related to micro emboli of clot or air, or may be large and related to large embolic clots. The incidence of image documented infarction is roughly similar to that of hemorrhage. Clinical seizures occur in 5%-10% of neonatal and pediatric patients, and 1%-2% of adult patients<sup>[1]</sup>. The difference between the adult and pediatric incidence of seizures may be related to trends in VV versus VA cannulation techniques<sup>[12]</sup> or may be due to relative sparing of cerebral vessels given that adults are more likely to be cannulated through femoral vessels or may be due to increase likelihood of infants to seizures due to developmental vulnerability<sup>[15]</sup>.

Hypoxic ischemic damage due to poor cardiac output or acidosis prior to, during, or after mechanical support is difficult to quantify and makes outcome studies difficult to interpret in the absence of appropriate control groups.

## HISTORICAL TRENDS

ECMO was developed in the 1970's and although the first reported case was an adult, the first series of neonates<sup>[16,17]</sup> reported success whereas the first series of adults reported dismal survival (9%)<sup>[18]</sup>. It became clear that ECMO was efficacious for patients with reversible disease and that prematurity or other risk factors for bleeding posed a significant risk. The importance of early recognition of intraventricular hemorrhage in neonates became evident. It appears that after the first week of life premature infants have reduced risk of intracranial hemorrhage<sup>[19]</sup>.

Neonatal respiratory ECMO volume peaked in the early 1990s and has remained relatively stable since the early 2000's. Overall survival has diminished likely reflecting advances in standard therapies and application of ECMO to more diverse and ill patients. Neonates with congenital diaphragmatic hernia continue to be a high-risk group with high mortality among respiratory patients. The majority of neonatal respiratory ECMO support is VA. Pediatric respiratory ECMO has increased substantially in the past 3 decades with a peak in 2009 coincident with the H1N1 influenza pandemic. About half of pediatric respiratory ECMO support is VA but there is increasing utilization of VV support modes. Adult ECMO was rarely performed until late in

**Table 1** Survival and cumulative incidence of neurologic complications by age and indication for extracorporeal membrane oxygenation (Extracorporeal Life Support Organization 2013)

	Cumulative survival to discharge or transfer	2012 survival to discharge or transfer	Clinical seizures	Central nervous system hemorrhage
Neonatal				
Respiratory	75%	69%	9.20%	7.10%
Cardiac	40%	45%	7.20%	11.10%
ECPR	39%			
Pediatric				
Respiratory	56%	58%	5.70%	6.00%
Cardiac	49%	55%	6.80%	4.90%
ECPR	41%			
Adult				
Respiratory	55%	57%	1.10%	4.00%
Cardiac	39%	39%	2.00%	2.00%
ECPR	28%			

ECPR: Extracorporeal membrane oxygenation support initiated during cardiopulmonary resuscitation.

the 2000s and has also increased substantially in 2009, with further increases since. The significant majority of adult ECMO support is VV.

ECMO support for cardiac indications in all age groups has increased steadily since the early 1990s<sup>[1]</sup>. ECPR was first described in 1992<sup>[20]</sup> and its application has expanded substantially in the past several years though indications remain controversial.

## NEUROLOGIC COMPLICATIONS AND NEURODEVELOPMENTAL OUTCOME BY AGE GROUP

### Neonatal

Neonates have the highest rate of neurologic complications when examining the ELSO reports by patient age. Cumulative ELSO data on neonates who undergo ECMO for respiratory support report a 9.2% incidence of clinical seizures and a 7.1% incidence of intracranial hemorrhage<sup>[1]</sup>. Neonates who are undergoing support for cardiac indications have a 7.2% incidence of seizures and an 11.1% incidence of hemorrhage. An initial assessment of risk factors for intracranial hemorrhage included lower gestational age, sepsis, acidosis, coagulopathy, and inotropic support<sup>[13]</sup>. Gestational age less than 34 wk has repeatedly been associated with unacceptably high rates of intracranial hemorrhage<sup>[13,17]</sup>. In a recent analysis of the ELSO registry<sup>[21]</sup>, for those neonatal patients supported with ECMO from 2005-2010, a 20% incidence of neurologic complications was noted. Risk factors for neurologic complications included birth weight less than three kg, gestational age less than 34 wk, need for CPR, acidosis, and use of VA ECMO support.

Studies of long-term neurodevelopmental outcomes of infants who undergo ECMO support suggest that impairment is similar to that of comparable conventionally treated infants. Single institutions series have noted impairment or disability in 20%-50% of surviving infants<sup>[4,22,23]</sup>. Factors that may influence the determination of disability include differences in socioeconomic status

of those who complete follow-up<sup>[4]</sup>, time from ECMO support to evaluation<sup>[22]</sup>, and institutional selection criteria. Long-term outcome studies highlight the changing neurologic function over time, with some initial disabilities likely resolving, and new more subtle learning and language deficits emerging. The 1996 United Kingdom collaborative randomized trial of neonatal ECMO versus conventional management<sup>[24]</sup> demonstrated similar proportions of survival without disability at seven years of age, and overall severe disability is less common than that in earlier reports. Sensorineural hearing loss is increasingly recognized as an important consequence of ECMO<sup>[23,25]</sup>. Sensorineural hearing loss has been found to be associated with pre-ECLS seizures<sup>[26]</sup>.

In neonates treated with ECMO, those with seizures were found to have lower IQ at preschool age than those without seizures<sup>[27]</sup>. In another small group of neonatal ECMO patients, seizures were found to be a risk factor for the subsequent development of cerebral palsy or developmental delay<sup>[28]</sup>.

An understanding of baseline characteristics of patients undergoing ECMO including ECPR is critical to any evaluation of outcome. Patients who receive ECMO support have generally had periods of serious illness including underlying congenital heart disease or hypoxemia which may play an important role in modifying outcome. Long-term neurodevelopmental outcomes of children who undergo cardiopulmonary bypass for congenital heart disease reveal a range of outcomes including mild cognitive and psychomotor delays<sup>[29,30]</sup> as well as speech and language abnormalities<sup>[31]</sup> in a substantial proportion of survivors. Newborns with congenital heart disease have brain abnormalities including white matter injury prior to cardiac surgery<sup>[32]</sup>.

### Pediatric

Pediatric ECMO patients represent a population of patients that are substantially more varied than the neonatal group. Cumulative ELSO data on pediatric patients who undergo ECMO for respiratory support report a 5.7% incidence of clinical seizures and a 6% incidence

of intracranial hemorrhage. Pediatric cardiac ECMO patients have a slightly greater incidence (6.8%) of clinical seizures and a 4.9% incidence of hemorrhage<sup>[1]</sup>. Acute neurologic complications including CNS hemorrhage or infarct, and EEG-determined or clinically determined seizures are associated with reduced hospital survival<sup>[1,14]</sup>. Similar to neonates, risk factors for severe CNS complications in pediatric patients include metabolic acidosis, inotrope or vasopressor requirement, renal failure, cardiopulmonary resuscitation, or left ventricular assist device prior to initiation of ECMO<sup>[33]</sup>.

There is little data on long-term neurodevelopmental outcomes in the extremely heterogeneous pediatric ECMO population<sup>[7]</sup>. Zabrocki *et al.*<sup>[34]</sup> demonstrated that over a 15-year period from 1993-2007 the survival of pediatric patients supported for respiratory indications did not change, but ECMO was offered to increasingly medically complex patients, which could easily confound assessments of disability after ECMO.

## Adult

Adults comprise the smallest, though growing, population of ECMO patients. Cumulative ELSO data on adult patients who undergo ECMO for respiratory support report a 1.1% incidence of clinical seizures and a 4% incidence of intracranial hemorrhage. Adults supported for cardiac indications have a 2% incidence of seizures and a 2% incidence of intracranial hemorrhage<sup>[1]</sup>. The lower incidence of severe CNS complications may be due to patient factors, selection factors, or technical factors. Adult patients are almost exclusively supported with VV ECMO and this has been shown to lower the rate of neurologic complications in pediatric patients<sup>[12]</sup> although this association may not remain consistent in adults<sup>[35]</sup>. When adult patients are supported with VA ECMO, cannulation of the cervical vessels is avoided, which may decrease the incidence of neurologic complications.

As for pediatric patients there is relatively little long-term functional outcome data for adult patients. The CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory Failure) trial, demonstrated no difference in severe disability of any measure of health care quality between patients randomized to the consideration for ECMO group versus the control group<sup>[36]</sup>.

## Cardiac and ECPR outcome

The use of ECMO to support low cardiac output, failure to wean from bypass, or cardiac arrest has been steadily increasing for the past 20 years and during that time the use of ECPR has emerged as an important strategy. Although somewhat variable year to year, overall survival of ECMO for cardiac indications has not shown definitive trends over time and cumulative ELSO survival now averages 39% in adults, 49% in pediatric patients, and 39% in neonates. ECPR survival is slightly lower at 28% in adults, 41% in children, and 39% in neonates<sup>[1]</sup>. ECPR survival does not appear to have changed significantly over time<sup>[37,38]</sup>.

The incidence of major neurologic morbidity in cardiac patients as reported to ELSO is highest in neonates, with 7.2% suffering seizures, 3.5% infarction, and 11.1% intracranial hemorrhage. Children have slightly lower incidence of seizures and hemorrhage and a slightly higher incidence of infarction. Adults have the lowest incidence of major neurologic morbidity with 2% suffering seizures, 3.7% infarction, and 2% hemorrhage. In all age groups those patients who suffer major neurologic complications have a lower hospital survival<sup>[1]</sup>.

Several single institution studies have reported neurologic outcomes after cardiac ECMO<sup>[5,6,39-42]</sup>. Evaluations included chart review, telephone interviews, and neurodevelopmental testing but no studies that performed detailed neurologic and neurodevelopmental testing included control groups of normal infants or of infants who had similar cardiac defects or illnesses. Hospital survival was similar to that reported by ELSO and all series had patients who died following discharge and who were lost to follow-up. Time to evaluation was extremely variable ranging from months to years within individual cohorts. Those studies that performed detailed neurodevelopmental assessments<sup>[6,42]</sup> found 50% incidence of moderate to severe cognitive delay and 12%-25% incidence of neuromotor delay among long term survivors. Predictors of poor cognitive outcome included time to normalization of lactate, highest inotrope score, and chromosomal abnormality. As previously discussed, pre-morbid characteristics of cardiac patients undergoing ECMO support are critical to assessment of outcomes.

Significant neurologic complications during ECPR are more prevalent than during other support strategies, with a 12% incidence of seizures, 11.8% incidence of radiologic evidence of infarct or hemorrhage, and 11% incidence of brain death in one evaluation of the ELSO database<sup>[37]</sup>. Infarction or hemorrhage but not seizures were more common in nonsurvivors than survivors. Further evaluation of this data revealed that risk factors for major neurologic complication included acidosis, non-cardiac disease, pulmonary hemorrhage, need for dialysis, and CPR while on ECMO<sup>[11]</sup>. In this analysis, there was a trend towards less neurologic injury over time.

Limited long-term neurologic and neurodevelopmental outcome after ECPR data are available from several single institution series<sup>[38,43-48]</sup>. In these series survival to hospital discharge ranges from 33%-74%, with most ranging from 33%-41%. Some studies reported neurologic outcome based on chart review and some assigned Pediatric Cerebral Performance Category (PCPC) and Pediatric Outcome Performance Category (POPC) scores. None reported detailed neurodevelopmental evaluations<sup>[49]</sup> but the PCPC and POPC scores have been rigorously validated<sup>[50]</sup>. An early series<sup>[43]</sup> reported no change from baseline POPC or PCPC in 50% of patients, and several authors<sup>[38,46,48]</sup> reported post ECPR PCPC scores of 1-2 (normal or mild cerebral disability) in 3/4 of patients. A recent analysis of the National



Registry of Cardiopulmonary Resuscitation confirms favorable [PCPC 1-3 (normal, mild cerebral disability or moderate cerebral disability)] neurologic outcomes in at least 64% and up to 95% of ECPR survivors<sup>[51]</sup>. This is similar to an analysis of the National Registry of Cardiopulmonary Resuscitation database, which showed the outcome of pediatric survivors of in hospital cardiac arrest, where the overall hospital survival was lower than that usually reported for ECPR (27%) but 65% of surviving patients had good neurologic outcome<sup>[52]</sup>.

The effect of duration of CPR on outcome, either survival or neurodevelopmental outcome is difficult to determine. Several studies report no correlation between duration of CPR and survival<sup>[38,43,44,51]</sup> and several report remarkable grossly normal survival after prolonged (> 60 min of CPR) in a few patients<sup>[43,46,51]</sup>, yet this is not a universal finding<sup>[47]</sup>. Cardiac disease as the indication for ECPR appears to improve the odds of survival<sup>[51]</sup>. In general the term ECPR is reserved for those patients who do not achieve return of spontaneous circulation (ROSC) prior to cannulation. When evaluating these studies it is important to consider that the decisions to perform ECPR vary considerably between institutions and are not standardized. The development of rapid deployment teams, which could cannulate during CPR or after ROSC may lead to improved outcomes<sup>[53]</sup>. As with any form of ECMO support the premise of reversible disease as a prerequisite for ECMO support must be kept in mind.

## QUALITY OF LIFE ASSESSMENT

Increasingly quality of life and functional and school related outcomes are appreciated as important indicators of the efficacy of critical care. Several reports have described relatively subtle cognitive, physical, and school related problems in survivors of pediatric critical care. A recent report showed that pediatric survivors of critical illness had verbal, spatial, and memory problems, attention and problem solving difficulty, and school performance following paediatric intensive care unit (PICU) admission<sup>[54]</sup>. A different study evaluated health care related quality of life and adaptive behavior functioning and found it to be significantly reduced in survivors of urgent PICU admission<sup>[55]</sup>. In this study prolonged ECMO support was one factor associated with reduced quality of life.

Looking at the issue of quality of life differently, a study that looked at patients with prolonged ICU stays (> 28 d) found that the majority of children (57%) had a normal quality of life, with 22.9% having impaired quality of life and 20% having poor quality of life<sup>[56]</sup>. In a single institution cohort of cardiac ECMO survivors physical health related quality of life was lower than that of the general population but similar to those with complex congenital heart disease. Psychosocial quality of life as reported by parents and by older surviving patients was similar to that of the general population<sup>[8]</sup>.

There have been relatively few analyses of the cost-effectiveness of ECMO but there have been some positive reports. The United Kingdom Collaborative ECMO Trial was a randomized, controlled trial of neonatal respiratory ECMO. Over 7-year follow-up of enrolled subjects they found an incremental cost per disability-free life year gained to be below the nationally acceptable threshold<sup>[24]</sup>. Similarly the CESAR trial found referral to an ECMO center to be cost effective when evaluated in terms of quality of life year expense<sup>[36]</sup>. In a single institution evaluation of ECPR for patients with congenital heart disease, ECMO was found to be within acceptable cost efficacy<sup>[57]</sup>.

## TECHNICAL ISSUES INFLUENCING NEUROLOGIC OUTCOME

Along with evolving indications for ECMO, the support and monitoring technology has changed dramatically over the past 30 years. Most recently newer dual lumen VV cannulas for respiratory support have been introduced and centrifugal pumps are increasingly being used to support pediatric patients. There have been advances in anticoagulation strategies as well as the development of more biocompatible circuits and oxygenators. Near infrared spectroscopy monitoring is increasingly being used during ECMO support. With the exception of a VV cannulation strategy none of these technologies has yet been shown to improve neurologic outcome<sup>[34]</sup>.

## REHABILITATION

An intriguing development in the care of the ECMO patient is the concept of active rehabilitation during ECMO support. Critical illness of any sort leads to deconditioning due to immobility and this is especially problematic with highly invasive support technologies. If patients can be exercised and kept mobile during mechanical support they may be more able to progress quickly once liberated from invasive support. There have been several small series of patients who received active physical or occupational therapy, advancing to ambulation, while undergoing ECMO support<sup>[58-60]</sup>. Thus far this strategy has been limited to older patients supported for respiratory indications, almost exclusively with single dual lumen catheters.

## CONCLUSION

Neurologic outcomes after ECMO support vary by patient age, type of support, indications for support, and underlying diagnosis. There are not widely accepted standards for initiation of ECMO outside of the neonatal respiratory population so severity of illness and underlying conditions among patients supported by ECMO may vary widely between institutions. Acute severe neurologic complications are more prevalent in neonates and children than adults. The long-term impact of ECMO sup-

port on development, school performance, and quality of life is poorly defined and needs further study. Where it has been evaluated, ECMO appears to be cost effective.

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