Extracorporeal Membrane Oxygenation for Neonates with Congenital Renal and Urological Anomalies and Pulmonary Hypoplasia: A Case Report and Review of the Extracorporeal Life Support Organization Registry

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Abstract

Keywords

- ▶ extracorporeal membrane oxygenation
- ▶ Extracorporeal Life Support Organization
- ▶ pulmonary hypoplasia
- ▶ congenital renal anomalies
- ▶ outcomes

Objective Congenital anomalies of the kidney and urinary tract constitute up to 30% of anomalies identified in the neonatal period. In utero oligohydramnios is often associated with pulmonary hypoplasia and respiratory failure in the neonate who may not be responsive to mechanical ventilation. Placement of these neonates on extracorporeal membrane oxygenation (ECMO) remains controversial and is considered in most centers to be a relative contraindication. The objective of this study is to use the Extracorporeal Life Support Organization (ELSO) database to describe the outcomes and complications of patients with congenital renal and urogenital anomalies with pulmonary hypoplasia who underwent ECMO in the neonatal period.

Data Sources Data from the ELSO registry were retrospectively reviewed for all patients with congenital renal and urogenital anomalies with pulmonary hypoplasia treated with ECMO support between 1990 and November 2014 using ICD-9 diagnosis codes.

Data Synthesis We identified 45 patients. The average age of the patient at the time of ECMO was 1.7 days (range: 0–14 days) and weight was 3.1 kg (interquartile range [IQR]: 2.5–3.3). Patients spent an average of 162 hours on ECMO (IQR: 81–207). The majority of patients were managed with venoarterial ECMO (60%), and the overall survival of this cohort was 42%. Survivors had higher weights (3.4 vs. 2.8 kg; $p < 0.019$) and were more likely to be male (90 vs. 44%; $p < 0.002$). Patients with obstructive urogenital lesions had an overall survival of 71 versus 16.6% in patients with a primary intrinsic renal diagnosis ($p = 0.004$). Renal replacement therapy was required in 51% of the patients during their ECMO support.

Conclusion Neonates with renal or urogenital disease and pulmonary hypoplasia have an overall survival rate of 42%. Patients with a diagnosis of urogenital obstruction have much more favorable outcomes when compared with those with intrinsic renal disease such as polycystic kidney disease.

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Introduction

The patient is a male neonate with a prenatal diagnosis of multicystic kidneys on fetal ultrasound and anhydramnios with autosomal recessive polycystic kidney disease. He was born at 37 weeks through spontaneous vaginal delivery with Apgar scores of 5 and 8. He was intubated secondary to hypoxic respiratory failure and placed on high-frequency oscillator ventilator (HFOV) with a mean airway pressure of 12, requiring 100% FiO₂ (oxygenation index: 29) and inhaled nitric oxide. Complications within the first hours of life included bilateral pneumothoraces and pneumomediastinum. The patient was cannulated for venoarterial extracorporeal membrane oxygenation (ECMO) at hour 5 of life with a pre-ECMO blood gas of pH 6.98, PCO₂ >100, PaO₂ 41, and HCO₃ 26. During his ECMO course, continuous hemofiltration was initiated to control fluid balance, and hypertension was controlled with a nicardipine infusion. The patient was decannulated from ECMO at hour 87 and a peritoneal dialysis (PD) catheter was placed. He was originally managed on conventional ventilation and escalated to the jet ventilator 8 days after decannulation. On day 43 of life, he underwent bilateral nephrectomy due to the enlarged size of his kidneys causing significant respiratory compromise. During hospitalization, the patient had tracheostomy, gastrostomy tube placement, Nissen fundoplication, and removal and replacement of PD catheter. He was also found to have hepatic fibrosis and ultrasound findings consistent with Caroli's disease. The hospital course was complicated by chyloperitoneum after nephrectomy, multiple pneumothoraces requiring chest tubes, circulatory collapse requiring cardiopulmonary resuscitation, and fungal peritonitis causing septic shock, subdural hygroma, sedation withdrawal syndrome, and deep venous thrombosis. He was discharged from the pediatric intensive care unit to home at 8 months of age on chronic mechanical ventilation and PD with a plan to evaluate for kidney transplantation.

Children with severe congenital renal anomalies can have pulmonary hypoplasia, which is thought to be a consequence of oligohydramnios.¹ Manifestations of pulmonary hypoplasia in neonatal period can range from an asymptomatic infant to severe respiratory failure.^{2,3} With severe congenital renal anomalies and subsequent pulmonary hypoplasia, the postnatal management of these children is often complicated or marked by ventilator associated lung injury and pulmonary hypertension.

ECMO for primary pulmonary indications in the neonatal period is used as a rescue therapy to avoid high ventilator settings, allow for resolution of pulmonary hypertension, and prevent ventilator associated lung injury. One of the primary considerations for ECMO use is the determination of reversibility of the underlying disease process as prolonged ECMO runs are associated with high mortality and morbidity.⁴⁻⁷ Patients with congenital diaphragmatic hernia (CDH) associated pulmonary hypoplasia tend to show improvement in lung function over time.⁸ Other disease processes associated with pulmonary hypoplasia, such as omphalocele and congenital malformation of the lung, also appear to have similar

long term outcomes.⁹ However, little is known about the long-term lung function in patients with pulmonary hypoplasia associated with oligohydramnios. Outcomes for the patient population with pulmonary hypoplasia related to oligohydramnios and congenital renal anomalies requiring ECMO remain uncertain.

The purpose of this study was to use data from the Extracorporeal Life Support Organization (ELSO) international registry to describe the clinical characteristics of neonates with congenital renal anomalies and pulmonary hypoplasia who have been placed on ECMO and to assess the differences between survivors and nonsurvivors.

Methods

The ELSO is an international registry compiled from more than 320 institutions of all known cases in which ECMO was performed. This registry has more than 45,000 cases of newborns, children, and adults with respiratory and cardiac failure. ELSO was developed for the benefit of individual centers to make decisions on using ECMO and for quality assurance. Updated reports are collected biannually by participating institutions. The data are submitted voluntarily by each organization with no patient identifiers. Information collected includes gender, race, nature and severity of illness, technical details of extracorporeal support used, complications, and outcome. Queries of the registry for purposes of research presentations or publications are permitted through local internal review boards (IRB). It was determined by the IRB at the University of Maryland that oversight was not required due to the nature of study.

The data requested from the ELSO registry included all patients with a diagnosis of renal agenesis, dysgenesis, or other urogenital malformation (ICD-9 codes 753.0–753.9) from 1990 to November 2014. These patients were then evaluated for pulmonary hypoplasia (ICD-9 code 748.5). Patients were excluded if their age was outside the neonatal period (>30 days). For any patient requiring multiple courses of ECMO, the first course only was considered for analysis.

Descriptive statistics were calculated in Microsoft Excel. The distributions of continuous variables were compared between patients who survived hospital discharge and those who died using Mann–Whitney U test (IBM SPSS Statistics for Windows, 2013). The proportions of categorical variables were compared using the chi-square test. Statistical significance will be defined as $p < 0.05$. The research team grouped patients into diagnostic categories or either intrinsic renal disease or urogenital obstructive disease based on ICD-9 codes. To determine possible predictors of survival, we conducted multivariate analysis of variance (MANOVA) to assess the maximal main effects of physiological measures.

Results

Patient Demographics and Mortality

During the study period, 45 patients were treated with ECMO support for respiratory failure related to primary renal or urogenital disease associated with pulmonary hypoplasia.

Table 1 Patient demographics

	Survivors (n = 19)	Nonsurvivors (n = 26)	p-Value
Age (d)	1.26 (0–4)	2 (0–14)	0.72
Weight (kg)	3.41 (2.3–5)	2.83 (1.9–4.98)	0.019
Sex (male)	17 (89.5%)	11 (44%)	0.002
Race (white)	8 (42%)	13 (50%)	0.057

Note: Two patients did not have weight recorded and two patients did not have race recorded.

The median age of these patients was approximately 1 day at the time of ECMO cannulation. The median time from intubation to ECMO cannulation was 19.5 hours, with a median duration of ECMO of 148 hours. Overall survival to hospital discharge was 42% (19/45). One patient did not have demographic data recorded. The demographics of survivors and nonsurvivors are described in ►Table 1.

Survival for individual diagnoses could not be determined. Those patients with intrinsic renal disease had a higher risk of mortality compared with patients with urogenital obstructive disease ($p = 0.004$; ►Table 2). There were no patients in the database who survived with the diagnosis of renal agenesis/dysgenesis or cystic kidney disease. One patient survived with a diagnosis of unspecified polycystic kidney disease.

To determine possible predictors of survival, we conducted MANOVA to assess the maximal main effects of physiological measures (HCO_3 , MAP, pH, hours on ECMO, and weight) on survival outcome (survivors versus nonsurvivors). This analysis confirmed that weight was the only predictor of mortality ($p < 0.029$).

►Table 3 demonstrates the patient management of physiological parameters prior to ECMO cannulation. Survivors and nonsurvivors had similar ventilator management strate-

Table 3 Survivor and nonsurvivor pre-ECMO parameters

Variable average, (range)	Survivors (n = 19)	Nonsurvivors (n = 26)	p-Value
Intubation to ECMO (hr)	27.8 (4–82)	49.7 (3–327)	0.21
HFOV	18 (94.7%)	21 (80.7%)	0.26
MAP	21.3 (17–30)	20.6 (13–33)	0.46
Hertz	8.44 (4–10)	9.1 (6–15)	0.99
100% FiO_2 at time of ECMO	19 (100%)	21 (80.1%)	0.041
pH	7.17 (6.83–7.45)	7.19 (6.87–7.41)	0.54
pCO_2	64.8 (35–130)	61.2 (27–120)	0.68
pO_2	33.6 (19–47)	38.4 (18–91)	0.85
HCO_3	22.6 (14–30)	21.4 (16–31)	0.3
SaO_2	56.7 (16–89)	55.8 (6–90)	0.9
Mean arterial pressure	38 (24–54)	38 (18–67)	0.96

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillator ventilator; MAP, mean average pressure.

gies using HFOV as the main mode of ventilation. There was a shorter period of time between intubation and ECMO in the survivor group, although this was not statistically significant (27.8 vs. 49.7 hours; $p = 0.21$).

Both groups were primarily managed on venoarterial ECMO (89 vs. 69%; $p = 0.15$). After initiating ECMO, 17 of 19 patients in the survivor group were switched to a conventional ventilator, and 18 of 26 patients in the nonsurvivor groups were switched to a conventional ventilator ($p = 0.15$). Conventional ventilator settings were not statistically significantly different between the two groups, including rate, peak

Table 2 Mortality for intrinsic renal diagnosis and urological diagnosis

Primary renal/urological diagnosis (ICD-9)	Survivors (n = 19)	Nonsurvivors (n = 26)	Percent survival
Intrinsic renal disease	4	20	4/24; 16.6% ($p < 0.0001$)
Renal agenesis/dysgenesis (753.0)	0	2	
Cystic kidney disease (753.1)	0	2	
Polycystic kidney, unspecified (753.12)	1	5	
Polycystic kidney, autosomal recessive (753.14)	0	5	
Renal dysplasia (753.15)	2	4	
Other cystic kidney disease (753.19)	0	1	
Other specified anomalies of the kidney (753.3)	1	1	
Primary obstructive/urological diagnosis	15	6	15/21; 71.4%
Unspecified obstructive defects of renal pelvis and ureter (753.2)	0	3	
Other obstructive defects of renal pelvis and ureter (753.29)	8	1	
Atresia and stenosis of the urethra and bladder neck (753.6)	5	2	
Unspecified anomaly of the urinary system (753.9)	2	0	

Table 4 Comparison of complications between survivors and nonsurvivors

	Survivors (n = 19)	Nonsurvivors (n = 26)
CAVHD	21% (4/19)	15% (4/26)
Hemodialysis	0% (0/19)	0% (0/26)
Hemofiltration	47% (9/19)	26% (10/26)
Creatinine 1.5–3	42% (8/19)	58% (11/26)
Creatinine > 3	21% (4/19)	8% (2/26)
Cardiovascular: inotropes	26% (5/19)	35% (9/26)
Cardiovascular: HTN requiring vasodilators	21% (4/19)	19% (5/26)
Respiratory: pneumothorax	11% (2/19)	0% (0/26)
Respiratory: pulmonary hemorrhage	5% (1/19)	15% (4/26)
Neurologic: CNS hemorrhage	0% (0/19)	23% (6/26)
Neurologic: CHS infarction by US/CT	11% (2/19)	4% (1/26)
Total complications	39	52

Abbreviations: CAVHD, continuous arterial venous hemodialysis; CHS, cerebral hyperperfusion syndrome; CNS, Central nervous system; CT, computed tomography; HTN, hypertension; US, ultrasound.

inspiratory pressure, and positive-end expiratory pressure. The survivor group had a longer duration of time on ECMO (173.5 hours) versus the nonsurvivor group (153.5 hours). This was not statistically significant ($p = 0.21$).

Complications on ECMO

The frequency of complications with patients on ECMO in both groups is shown in ▶Table 4. The most common complications were associated with renal replacement therapy. In the survivor group, 53% of patients required some form of renal replacement therapy (three patients requiring both continuous arterial venous hemodialysis [CAVHD] and hemofiltration). In the nonsurvivor group, 50% required renal replacement therapy, with one requiring both CAVHD and hemofiltration. An elevated creatinine above 1.5 was noted in 42% of survivors and 58% of nonsurvivors ($p = 1$); however, a creatinine elevated above 3 was noted in only 21% of survivors and 8% on nonsurvivors ($p = 0.38$). Central nervous system complications of hemorrhage or stroke were also more common in nonsurvivors (27 vs. 10.5%; $p = 0.18$). The average number of complications per patient was 2 in both survivors and nonsurvivors ($p = 1$).

Discussion

We report the first published case of a neonate with autosomal polycystic kidney disease and pulmonary hypoplasia who was managed on ECMO and survived to discharge. Furthermore, the registry demonstrated no other patient with this combination of diagnoses who survived to discharge. We then queried the ELSO registry for all patients

with a combination of renal/urogenital anomalies and pulmonary hypoplasia. Our analysis of the ELSO registry shows an overall survival rate of 42% in this patient population, which is not statistically different from the survival of neonates born with CDH (42 vs. 48%; $p = 0.2$).¹⁰ However, the survival rate for patients with intrinsic renal pathology and pulmonary hypoplasia was 16.6%, significantly less when compared with obstructive urological pathology survival of 71.4%. Congenital renal anomalies amenable to surgical interventions have been associated with better outcomes in children requiring ECMO.¹¹

Patients in the nonsurvivor group had a longer duration on mechanical ventilation prior to the initiation of ECMO than those in the nonsurvivor group, but this was not >14 days, which has been associated with increased mortality.¹² Our study did not demonstrate that ECMO mode (venovenous vs. venoarterial) was a predictor of mortality and is similar to the finding of Zahraa et al.¹³ A large percentage of both survivors and nonsurvivors required some form of continuous renal replacement therapy (CRRT) on ECMO. The need for CRRT on ECMO has been shown to be a safe and effective way to provide fluid removal and maintain electrolyte balance. However, the use of CRRT is associated with high mortality and longer duration of ECMO, likely indicating a higher severity of illness in this patient population.¹⁴

Our study population can be compared with patients with CDH and pulmonary hypoplasia. The introduction of ECMO, delayed repair outside of the hours of life, and having dedicated multidisciplinary teams have improved outcomes of children with CDH.^{15–17} Kays et al have recently reported that after multivariate modeling of severity to define the worst 10% for CDH, survival in this cohort approached 50%.¹⁸ They also reported mean time to discharge in survivors to be 3.25 months, indicating these children require a prolonged hospital course. It remains unclear how to risk stratify the degree of pulmonary hypoplasia to determine long-term survival or need for ECMO support in this more well-studied patient population.^{9,19} Investigators have shown that in pulmonary hypoplasia due to CDH, the prenatal difference between observed and expected lung volume based on fetal magnetic resonance imaging readings can predict outcomes.^{9,19} Similar analyses have not been conducted in patients with congenital renal anomalies and pulmonary hypoplasia due to the lower numbers at any single center and in the registry. We speculate that the difference in weight between the survivors and nonsurvivors in our study may be an indirect indication of the difference in lung volumes. Renal anomalies in the neonatal period pose an additional challenge as the ventilation strategies are greatly affected by fluid balance and can be affected by the overall size of the kidneys in polycystic kidney diseases. The literature remains inconclusive about the timing of nephrectomy in this population.²⁰

Overall, the use of ECMO has increased, and the ELSO registry shows a steady rise in the number of international cases from 1,644 cases in 1990 to 6,177 cases in 2015.²¹ The complexity of patients managed on ECMO and the diagnoses considered for ECMO have also increased in that time period. In patients with complex congenital disease processes

involving multiple organ systems such as renal dysgenesis, urogenital obstruction, and pulmonary hypoplasia the decision to offer ECMO is unclear. A survival-to-hospital discharge rate of 42% makes an argument to support the use of ECMO in this patient subset on an individual basis based on underlying congenital anomalies and other associated risk factors. The discussion of ECMO candidacy is center-specific and based on interdisciplinary expertise. Descriptive studies like ours that use the ELSO registry can help clinicians make informed decisions on rarer diagnoses or combinations of diagnoses.

This study is limited by the retrospective design and nature of the ELSO registry. The study is not randomized, and data are limited by information submitted to the registry. Data submitted by various institutions is voluntary, and therefore the comprehensiveness and diagnostic coding accuracy cannot be verified. There is lack of standardization for the use of ECMO at individual centers. The disease processes studied are rare, and patient population is small. There is no way to know if the pulmonary hypoplasia was caused by oligohydramnios secondary to pathology in utero or the degree of pulmonary hypoplasia. Oligohydramnios was only coded in two patients included in the study. However, this may be a prenatal diagnosis and not recorded as a diagnosis in the individual centers. This study is not able to provide data on longer term outcomes and overall resource utilization for this patient population.

Conclusion

We report the first case of a neonate with autosomal recessive polycystic kidney disease and pulmonary hypoplasia who was managed on ECMO in the initial newborn period and was subsequently discharged home on chronic mechanical ventilation and PD. Neonates with congenital renal and urogenital anomalies with pulmonary hypoplasia managed with ECMO in the ELSO registry had an overall survival of 42%. Weight at the time of ECMO was the only independent predictor of survival. However, when grouping these patients into primary intrinsic renal disease versus urogenital obstruction, survival was 16.6% in patients with intrinsic renal disease and 71.4% in patients with urogenital obstruction. These results may suggest careful consideration on a case-by-case basis prior to initiating ECMO support in the subset of patients with intrinsic renal disease and pulmonary hypoplasia. This study serves as a starting point for discussion when considering ECMO in this patient population and can assist physicians in making decisions to provide therapy as well as anticipatory guidance for parents.

Note

All the authors meet the criteria for authorship published by Frontiers in Pediatrics. N. T., D. B., K. W., A. B., and J. C. were involved in conception of the work. J. C., K. W., and A. B. were involved in data acquisition. J. W., A. B., and J. C. were involved in data analysis. N. T., D. B., K. W., J. W., A. B., and J. C. were involved in interpretation of data. N. T., D. B., K. W., J. W., A. B., and J. C. were involved in drafting the work and critically reviewing the manuscript.

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Conflict of Interest

None.

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