# EXTRACORPORAL MEMBRANE OXYGENATION FOR PERTUSSIS: PREDICTORS OF OUTCOME INCLUDING PULMONARY HYPERTENSION AND LEUKODEPLETION

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## Author contribution

Drs Domico, Brown, MacLaren, Barbaro and Annich helped in concept, design and grant application. Drs Domico, Brown and Ms. Ridout worked on data collection and analysis. Drs Domico, Brown, MacLaren, Barbaro, Schlapbach, Annich and Ms. Ridout contributed to drafting and/or revising the article for important intellectual content.

## Conflicts of Interest and Source of Funding

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## ABSTRACT

OBJECTIVE

The recent increase of pertussis cases worldwide has generated questions regarding the utility of extracorporeal membrane oxygenation (ECMO) for children with pertussis. We aimed to evaluate factors associated with ECMO outcome.

DESIGN

The study was designed in two parts: a retrospective analysis of the Extracorporeal Life Support Organization Registry to identify factors independently linked to outcome, and an expanded dataset from individual institutions to examine the association of white blood cell count, pulmonary hypertension and leukodepletion with survival.

SETTING

ELSO Registry database from 2002 though 2015, and contributions from 19 international centers

PATIENTS

200 infants from the ELSO Registry and expanded data on 73 children

INTERVENTIONS

None

MEASUREMENTS AND MAIN RESULTS

Of the 200 infants who received ECMO for pertussis, only 56 survived (28%). In a multivariable logistic regression analysis, the following variables were independently associated with increased chance of survival: older age (OR 1.43 [1.03, 1.98] p=0.034), higher $PaO_2/FiO_2$ ratio (OR 1.10 [1.03, 1.17] p=0.003) and longer intubation time prior to the initiation of ECMO (OR 2.10 [1.37, 3.22] p=0.001). The use of vasoactive medications (OR 0.33 [0.11, 0.99] p=0.047), and renal neurological or infectious complications (OR 0.21 [0.08, 0.56] p=0.002) were associated with increased mortality.

In the expanded dataset (n =73), leukodepletion was independently associated with increased chance of survival (OR 3.36 [1.13, 11.68] p=0.03) while the presence of pulmonary hypertension was adverse (OR 0.06 [0.01, 0.55] p=0.01).

CONCLUSIONS

The survival rate for infants with pertussis who received ECMO support remains poor. Younger age, lower $PaO_2/FiO_2$ ratio, vasoactive use, pulmonary hypertension and a rapidly progressive course were associated with increased mortality. Our results suggest pre-ECMO leukodepletion may provide a survival advantage.

KEY WORDS

Extracorporeal membrane oxygenation, pertussis, leukodepletion, pulmonary hypertension, infants, Extracorporeal life support organization.

## Introduction

Pertussis is a highly contagious respiratory illness caused by the Gram-negative bacterium *Bordetella pertussis*. Severe disease occurs predominantly in infancy and can include respiratory failure/apnea, pulmonary hypertension and neurologic complications. Estimates from the World Health Organization in 2008 suggested that 16 million cases of pertussis occurred worldwide and 195,000 children died from this vaccine-preventable disease [1]. In 2012, the Centers for Disease Control reported over 48,000 pertussis cases in the United States, the most since 1955. [2]. Due to waning acellular pertussis vaccine immunity, epidemics are expected to continue [3].

Extracorporeal membrane oxygenation (ECMO) has been used in children with respiratory failure for over 40 years. Since 2002, a resurgence of pertussis cases worldwide has correlated with increased utilization of ECMO for this disease [4]. Many have questioned the utility of ECMO in pertussis patients, citing concerns about low survival rates and a potentially irreversible process once pulmonary hypertension develops. Prior reports from the Extracorporeal Life Support Organization (ELSO) Registry demonstrated survival rates of 30% for pertussis patients receiving ECMO support [5, 6], which is significantly lower than most other ECMO respiratory indications.

Factors associated with increased mortality include younger age, elevated white blood cell (WBC) count and pulmonary hypertension (PHTN) [7, 8]. Following encouraging single institution reports, leukodepletion via exchange transfusion or leukofiltration has been introduced as a management strategy to attenuate the disease severity of critical pertussis patients with hyperleukocytosis, [6, 9-14].

The aim of this study was to determine the predictors of survival in pertussis patients placed onto ECMO in the current era. As part of this investigation, we also sought to explore the impact of highest white blood cell (WBC) count, presence of PHTN and use of leukodepletion (LD) techniques prior to ECMO initiation. We hypothesized the presence of PHTN and an elevated WBC count would decrease the chances of survival and that LD would improve the chance of survival for children with pertussis who received ECMO support.

## Materials and Methods

### Data Collection and Study Population:

The study was designed in two parts. The first was an analysis of the ELSO Registry database (Ann Arbor, Michigan) to identify factors independently associated with outcome [4]. The registry contains data from over 35,000 neonates and children with respiratory failure from > 300 centers worldwide. The second was a non-ELSO expanded dataset to test the hypothesis regarding the relationship between WBC count, PHTN, LD and survival. Survival to hospital discharge was defined as the primary outcome. The additional de-identified data from 19 contributing centers, obtained their own institutional permission if required. Children's Hospital of Orange County granted IRB exemption.

A retrospective review of the ELSO database was performed for all patients with a primary or secondary diagnosis of pertussis between January 1, 2002 and January 1, 2015. The specific time period was selected due to a previous ELSO report [5], and because leukocyte reduction for pertussis was increasingly adopted after a publication in

the year 2000 suggesting exchange transfusion [15]. To isolate patients most vulnerable to pertussis, we excluded patients over 1 year of age. Patients who required more than one ECMO course were excluded, as it was unclear if the impetus for a repeat course was related to pertussis or a subsequent complication.

Data examined included the following: patient demographic details, diagnoses, duration of ECMO, mode of ECMO, survival to hospital discharge or transfer, and time to death or transfer. Pre-ECMO variables included: ventilator days, calculated oxygenation index (OI), serum pH, positive end expiratory pressure (PEEP), $PaO_2/FiO_2$ (P/F) ratio, $PaCO_2$, inotrope infusion requirement, cardiac arrest, use of high frequency ventilation (HFOV), inhaled nitric oxide (iNO) administration and pre-ECMO co-infection.

A complete organ assessment prior to ECMO initiation can be difficult in the setting of rapid disease progression. Therefore, we considered neurologic complications and renal complications during ECMO as risk factors, recognizing these may in part be caused by pertussis and may be present before ECMO commencement. Neurologic and renal complications were based on defined ELSO Registry fields as follows: the presence of seizures, intracranial bleed or stroke while on ECMO support, and the use of renal support (such as hemodialysis or hemofiltration). A further risk factor considered was infection acquired during ECMO support.

Since hyperleukocytosis and the PHTN are not captured in the ELSO database, the investigators contacted ELSO-contributing pediatric centers to retrospectively obtain these data. The 19 centers were selected based on personal communication from one or more of the investigators and their willingness to submit data from every patient placed onto ECMO with pertussis between 2002 through 2015. Additional information sought

included highest WBC count at any time from intensive care unit (ICU) admission until ECMO commencement, the use of LD techniques at any time from ICU admission until ECMO commencement, and evidence of PHTN or right ventricular (RV) failure at any time from ICU admission throughout the course of ECMO.

Use of LD techniques was defined as exchange transfusion, leukopheresis, plasmapheresis or leukofiltration. Evidence of RV failure or PHTN (right ventricle pressure > 50% systemic) was defined by set echocardiographic parameters including but not limited to: tricuspid regurgitation pressure estimate, flattened septum and/or right ventricular systolic dysfunction.

**Statistical Analysis**

Variables are presented as number with percentage, mean with standard deviation (SD) or median and inter quartile range (IQR) for skewed data.

Part 1: ELSO Registry analysis

Univariate logistic regression analysis was undertaken to examine the association of each of the following pre-ECMO factors: age, pH, P/F ratio, OI, pre-ECMO ventilation days, inotrope use, cardiac arrest, co-infection, iNO usage, and year of ECMO on survival to hospital discharge. Due to large numbers of missing data for PEEP and $PaCO_2$, these factors were not included in the univariate analysis. Similarly examined variables while receiving ECMO support included mode of ECMO, co-infection, and neurologic or renal complications.

Although ECMO duration was not included in the regression analyses, a

descriptive analysis of the relationship between ECMO duration and survival was undertaken using fractional polynomials.

All factors were selected *a priori* and those found to be significant ($p<0.05$) on univariate analysis were assessed further in multivariable analyses. In the multiple variable models P/F ratio was considered instead of OI due to larger numbers of missing values for OI. A multiple logistic regression model was constructed including all variables meeting the preset criteria (Multiple Model I) and second a multiple logistic regression model was constructed including only variables definitively known prior to commencing ECMO (Multiple Model II).

The goodness of fit of the final models was assessed using the Hosmer-Lemeshow test. The c statistic or area under the receiver operator curve (AUC) was used to assess model discrimination. Results are presented as odds ratios (OR) for survival to hospital discharge, with 95% confidence intervals (CI) and p values.

Part 2: Expanded dataset

Data was acquired from 19 centers worldwide (see acknowledgements), including demographic information, survival, highest pre-ECMO WBC count, use of LD techniques, and evidence of PHTN or RV failure. Univariate logistic regression was used to assess the the relationship between survival rate and each of these factors in turn. A multiple logistic regression model was generated to evaluate which factors were independently linked to outcome.

A value of $p < 0.05$ was deemed significant. Analysis was performed using the statistics package Stata (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

## Results

Part 1: ELSO Registry analysis

A search of the *entire* ELSO database (1989-2015) revealed a total of 275 patients placed on ECMO for pertussis with a survival rate of 80/275 (29%), this included adults, children and neonates. For completeness of information we listed all pertussis patients from the ELSO database in Table 1 along with the number and proportion of survivors. Patients were excluded from further analysis if they did not meet inclusion criteria. A total of 200 infants formed the study group. There was no increase in survival from 2002-2015 (p= 0.43). The study group survival rate was 56/200 (28%) with a median (IQR) age of 39 [27 – 59] days and a median (IQR) duration of 13 [5, 26] days on ECMO support (Table 2).

The most frequent pre-ECMO intervention was inotrope use, utilized in 176/200 (88%) of patients. Additional therapy included iNO in 154/200 (77%). Pre-ECMO co-infection occurred in 44/200 (22%) of patients and 36/200 (18%) suffered a cardiac arrest preceding ECMO. Five infants were classified as ECPR and all 5 died. VA ECMO support was initiated in 164/200 (82%) of patients.

High rates of renal, neurologic and infectious complications were reported. Renal complications were reported in 154/200 (77 %) and neurologic complications in 80/200

(40%) of patients. In addition, 56/200 (28%) were noted to have a co-infection while receiving ECMO.

Univariate analysis of factors associated with survival is shown in Table 2, with variable results presented separately for survivors and non-survivors. Older age (OR 1.65 [1.17, 2.32] p=0.004), higher pH (OR 1.29 [1.05, 1.59] p=0.015), increased P/F ratio (OR 1.06 [1.007, 1.12] p=0.03) and a longer intubation time prior to ECMO cannulation (log transformed because of skewed distribution, OR, 2.20 [1.40, 3.45] p= 0.001) were significantly associated with improved survival when each was considered in isolation. There was no difference in survival between VV and VA ECMO modes (OR 1.92 [0.63, 5.83] p=0.25). Inotrope use (OR 0.30 [0.13, 0.71] p= 0.006), higher OI (OR 0.78 [0.65, 0.93] p = 0.006) and one or more complication (infection, renal or neurologic) while on ECMO (OR 0.27 [0.12, 0.60] p=0.001) were significantly associated with a reduced chance of survival.

The primary multivariable logistic regression analysis (Multiple Model I) identified the following variables as independently and significantly associated with the chance of survival: increased age (OR 1.43 [1.03, 1.98] p=0.034), increased P/F ratio (OR 1.10 [1.03, 1.17] p=0.003), and increased intubation time prior to the initiation of ECMO (OR 2.10 [1.37, 3.22] p=0.001) were all protective. The use of vasoactive medication (OR 0.33 [0.11, 0.99] p=0.047), and any complication on ECMO (infection, renal or neurologic) was adverse (OR 0.21 [0.08, 0.56] p=0.002) (Table 3). The c statistic was 0.80, displayed as AUC (Figure 1), with Hosmer-Lemeshow p=0.52. The secondary multivariable model (Multiple Model II) consisting of pre-ECMO variables only (Table 3) contained the same risk factors with the exception of the “on-ECMO” complications and had a c statistic of 0.78 with Hosmer-Lemeshow p=0.55.

The duration of ECMO support as it relates to chance of survival in pertussis patients is depicted in Figure 2. Survival was at an optimum with an ECMO duration of 15 days and starts to decline thereafter.

Part 2: Expanded dataset

Expanded data was collected on 74 children from 19 international centers and is shown in Table 4. One teenager was excluded as to remain consistent with the study population defined above. The overall survival in this selected group was 23/73 (32%). The mean (SD) WBC was 78,000 (35,000) white blood cells per microliter in survivors and 77,000 (26,000) white blood cells per microliter in those who died. Pre-ECMO LD was used in 9 of 23 survivors and in 9 of 50 non-survivors. The survival rate amongst leukodepleted infants was 9/18 (50%), whilst the survival rate was only 14/55 (25%) in the non-leukodelpeted. PHTN was present in 18/23 (78%) survivors and in 49 of 50 (98%) non-survivors.

In univariate analyses, WBC count did not relate to survival (OR 1.01 [0.85, 1.20] p=0.88), nor did age (neonatal versus infant age group) (OR 2.45 [0.72, 8.34] p=0.15). The presence of PHTN or RV failure (n=67) was associated with a reduced chance of survival (OR 0.07 [0.01, 0.67] p=0.02). Only 18 of 73 patients received LD, and in the univariate analysis, there was no statistically significant association with increased survival (OR 2.93 [0.97, 8.84] p=0.06).

In a multiple analysis, both LD and PHTN were independently associated with outcome. Those patents with evidence of PHTN or RV failure had a decreased chance

of survival (OR 0.06 [0.01, 0.55] p=0.01). Children who received LD had an increased chance of survival (OR 3.36 [1.13, 11.68] p=0.03).

## Discussion

Based on ELSO Registry data, the overall survival rate for infants with critical pertussis who received ECMO support remains low and has not improved over the past decade. We present analysis of risk factors for survival outcome with the aim of assisting in clinical decision making, both from the perspective of the entire course of critical pertussis (Multiple Model I) and from the perspective of clinical features definitively known prior to ECMO (Multiple Model II).

Many studies have demonstrated that pertussis in younger age groups (particularly those < 2 months) is associated with severe disease and higher mortality [7, 16- 20]. Consistent with those previous studies, we observed a decreased chance of survival in younger infants with pertussis. In 2011, Zabrocki et al. reviewed the ELSO Respiratory database from 1993 to 2007 [21]. They reported a survival of 38% for pertussis patients (n=85) as compared to 28% in our cohort (n=200). Since that time, the number of centers contributing to ELSO has doubled, and our study isolated children most vulnerable to pertussis, those less than 1-year of age.

A longer duration of mechanical ventilation (up to 13 days) was associated with increased survival, perhaps due to a less fulminant disease process. Pertussis patients who had a rapidly progressive course (time from intubation to ECMO) had a decreased chance of survival. Other studies have suggested a rapidly progressive course with pertussis is associated with higher mortality [17, 20, 22-24] with many patients requiring

intubation within 24 hours of hospital arrival and either ECMO support or death within 2 days.

Infectious, neurologic and renal complications while on ECMO support were much higher in our pertussis study group than what is currently reported for respiratory ECMO cases [4], and this suggests that underlying pertussis disease was a contributor to these complications. The co-infection rate during ECMO was 28% in our study population (organisms included streptococcus, staphylococcus, gram negative bacteria, respiratory viruses and yeast) whereas the ELSO registry reports infectious complications at 5.8% (neonatal respiratory database) and 17% (pediatric respiratory database) [4]. The increased co-infection rate may be a reflection of the longer duration of ECMO, however this was not explored further and is a limitation of the study. Neurologic complications and the use of renal replacement therapy are known hazards of ECMO [25] but are also frequently described in patients with pertussis who did not receive ECMO support [7,8,17, 26-28]. It is not possible to discern whether the high neurologic and renal complication rates in this study (3 to 5 times higher than the ELSO Registry data) are a result of ECMO or the underlying disease. Since both neurologic and renal complications can result from ECMO therapy and can occur as an indicator of multi-organ involvement with pertussis, every effort should be made to assess other organs prior to ECMO initiation.

PHTN has been linked to worse outcome in pertussis [5, 7, 8, 15, 17]. Many authorities believe that once a pertussis patient develops PHTN, it becomes irreversible [7, 19, 29], possibly due to leukocyte vascular plugging, veno-occlusive disease, and/or lung necrosis, [5, 19, 23, 24, 27, 30]. While the exact mechanism is unknown, pertussis toxin-mediated hyperinflammation and leukocyte activation has been shown to be

involved [19]. Only a handful of case reports have described patients with pertussis and PHTN surviving after ECMO [31-34]. We report that pulmonary hypertension was significantly and independently related to mortality; however, the majority of the patients in our study (69 of 73) had PHTN or RV failure.

Recently, several authors have questioned whether exchange transfusion or other leukoreduction techniques can improve outcome. Romano and colleagues published the first report of an infant with pertussis and suprasystemic PHTN who survived without ECMO, but with a double volume exchange transfusion [10]. Over the past decade, investigators at Great Ormond Street Hospital adopted an aggressive LD strategy for children with pertussis. They observed significantly better outcomes than predicted for the patients who received LD [6]. Our results of additional data collected from 19 international centers indicate that LD techniques prior to ECMO commencement increased survival rates (50%, 9 of 18). We did not explore leukoreduction while on the ECMO circuit (such as using a leukofilter) but this approach may also improve survival [6,12,33]. Our study did not evaluate which type of LD method was preferred (exchange transfusion versus leukopheresis).

When ECMO is used for pertussis the average duration is relatively long and resource utilization is high, inflicting a heavy financial burden worldwide. An infant with pertussis in Oregon who required 43 days of ECMO support and a 90-day hospital stay totaled $1.5 million dollars. [34] The Australia and New Zealand Paediatric Intensive Care group (ANZPIC) also report a heavy financial burden of over $1 million per year in direct pertussis-related hospitalization costs [20].

One of the most difficult tasks for an intensive care clinician is to determine if ECMO provides a survival advantage. A rapidly deteriorating young infant with pertussis-induced PHTN and multi organ involvement has a low chance of survival even with ECMO support. A decision to offer ECMO in such cases should take into consideration local protocols and the circumstances of each individual case.

**Limitations**

This was a retrospective database review with the limitations inherent in databases. The ELSO registry is a voluntary database and there is no standardized quality measurement for the accuracy of data reported. There is no verification process to confirm a polymerase chain reaction or culture proven diagnosis of pertussis. Although there are various types of neurologic and renal complications, we were limited to the complication categories reported in the ELSO database. Despite basing the study on the ELSO Registry and multiple center involvement, the findings are limited by their retrospective nature, non-randomization and small numbers, particularly in the area of leukoreduction (n=18).

Pertussis patients who present with pneumonia (as compared to those presenting with apnea) may have worse outcomes [18, 26]. Unfortunately, we cannot address mortality related to symptoms at presentation because this data is not routinely available in the ELSO registry. We are unable to report on the long-term outcome of these patients particularly regarding neurodevelopmental sequelae, as this data was not available.

**Conclusion**

The survival rate for children with pertussis who received ECMO support remains poor (28%). Younger age, lower $PaO_2/FiO_2$ ratio, vasoactive use, pulmonary

hypertension and a rapidly progressive course were independently and significantly associated with increased mortality. However, pre-ECMO leukodepletion techniques may provide a survival advantage.

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**References**

1. World Health Organization. Immunization, Vaccines and Biologicals, Pertussis: 2008 Report. Retrieved from http://www.who.int/immunization/topics/pertussis/en. Accessed February 1 2017

2. Centers for Disease Control and Prevention. Pertussis outbreak trends: 2012 Report. Retrieved from https://www.cdc.gov/pertussis/outbreaks/trends.html. Accessed February 1 2017

3. Klein NP, Bartlett J, Rowhani-Rahbar A, et al:. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med* 2012; 367:1012-1019

4. ECMO Registry of the Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan. Accessed January 5 2015

5. Halasa NB, Barr FE, Johnson JE, et al:. Fatal pulmonary hypertension associated with pertussis in infants: does extracorporeal membrane oxygenation have a role? *Pediatrics* 2003; 112:1274-1278

6. Rowlands HE, Goldman AP, Harrington K, et al:. Impact of rapid leukodepletion on the outcome of severe clinical pertussis in young infants. *Pediatrics* 2010. 126: e816-827

7. Winter K, Zipprich J, Harriman K, et al: Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study. *Clin Infect Dis* 2015; 61: 1099-1106

8. Berger JT, Carcillo JA, Shanley TP, et al: Critical pertussis illness in children: a multicenter prospective cohort study. *Pediatr Crit Care Med* 2013; 14: 356-365

9. Onoro G, Salido AG, Martinez IM, et al: Leukoreduction in patients with severe pertussis with hyperleukocytosis. *Pediatr Infect Dis J* 2012; 31: 873-876

10. Romano MJ, Weber MD, Weisse ME, et al: Pertussis pneumonia, hypoxemia, hyperleukocytosis, and pulmonary hypertension: improvement in oxygenation after a double volume exchange transfusion. *Pediatrics* 2004; 114: e264-266

11. Donoso AF, Cruces PI, Camacho JF, et al: Exchange transfusion to reverse severe pertussis-induced cardiogenic shock. *Pediatr Infect Dis J* 2006; 25: 846-848

12. Grzeszczak MJ, Churchwell KB, Edwards KM, et al: Leukopheresis therapy for severe infantile pertussis with myocardial and pulmonary failure. *Pediatr Crit Care Med* 2006; 7: 580-582

13. Martinez M, Rochat I, Corbelli R, et al: Early blood exchange transfusion in malignant pertussis: a case report. *Pediatr Crit Care Med* 2011; 12: e107-109

14. Kuperman A, Hoffmann Y, Glikman D, et al: Severe pertussis and hyperleukocytosis: is it time to change for exchange? *Transfusion* 2014; 54: 1630-1633

15. Pierce C, Klein N, Peters M. Is leukocytosis a predictor of mortality in severe pertussis infection? *Intensive Care Med* 2000; 26: 1512-1514

16. Marshall H, Clarke M, Rasiah K, et al: Predictors of disease severity in children hospitalized for pertussis during an epidemic. *Pediatr Infect Dis J* 2015; 34: 339-345

17. Nieves D, Bradley JS, Gargas J, et al.: Exchange blood transfusion in the management of severe pertussis in young infants. *Pediatr Infect Dis J* 2013; 32: 698-699

18. Mikelova LK, Halperin SA, Scheifele D, et al: Predictors of death in infants hospitalized with pertussis: a case-control study of 16 pertussis deaths in Canada. *J Pediatr* 2003; 143: 576-581

19. Paddock CD, Sanden GN, Cherry JD, et al: Pathology and pathogenesis of fatal Bordetella pertussis infection in infants. *Clin Infect Dis* 2008; 47: 328-338

20. Straney L, Schibler A, Ganeshalingham A, et al: Burden and Outcomes of Severe Pertussis Infection in Critically Ill Infants. *Pediatr Crit Care Med* 2016; 17: 735-742

21. Zabrocki LA, Brogan TV, Statler KD, et al: Extracorporeal membrane oxygenation for pediatric respiratory failure: Survival and predictors of mortality. *Critical Care Med* 2011; 39: 364-370

22. Paksu MS, Akgun M, Karadag A, et al: Fulminant pertussis in very young infants: two cases and review of the literature. *Turk J Pediatr* 2013; 55: 426-429

23. Williams GD, Numa A, Sokol J, et al: ECLS in pertussis: does it have a role? *Intensive Care Med* 1998; 24:1089-92

24. Sawal M, Cohen M, Irazuzta JE, et al: Fulminant pertussis: a multi-center study with new insights into the clinico-pathological mechanisms. *Pediatr Pulmonol* 2009; 44: 970-980

25. Nasr VG, Faraoni D, DiNardo JA, et al: Association of Hospital Structure and Complications With Mortality After Pediatric Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2016; 17: 684-691

26 Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. *Pediatr Crit Care Med* 2007; 8: 207-211

27. Pooboni S, Roberts N, Westrope C, et al: Extracorporeal life support in pertussis. *Pediatr Pulmonol* 2003; 36: 310-315

28. Olsen M, Thygesen SK, Ostergaard JR, et al: Hospital-Diagnosed Pertussis Infection in Children and Long-term Risk of Epilepsy. *JAMA* 2015; 314:1844-1849

29. Sreenan CD, Osiovich H. Neonatal pertussis requiring extracorporeal membrane oxygenation. *Pediatr Surg Int* 2001; 17: 201-203

30. Burr JS, Jenkins TL, Harrison R, et al: The Collaborative Pediatric Critical Care Research Network Critical Pertussis Study: collaborative research in pediatric critical care medicine. *Pediatr Crit Care Med* 2011; 12: 387-392

31. Couchot E, Paut O, Ghez O, et al:. Extracorporeal membranous oxygenation in severe infant pertussis: a case report. *Ann Fr Anesth Reanim* 2009; 28: 74-77

32. De Berry BB, Lynch JE, Chung DH, et al: Pertussis with severe pulmonary hypertension and leukocytosis treated with extracorporeal membrane oxygenation. *Pediatr Surg Int* 2005; 21: 692-694

33. Assy J, Seguela PE, Guillet E, et al: Severe Neonatal Pertussis Treated by Leukodepletion and Early Extra Corporeal Membrane Oxygenation. *Pediatr Infect Dis J* 2015; 34: 1029-1030

34. Liko J, Koenig WJ, Cieslak PR. Suffer the Infants: A Severe Case of Pertussis in Oregon, 2012. *Public Health Rep* 2015; 130: 435-439

**Figure 1: ROC for Multivariable Risk Model I for Survival of Pertussis Patients on ECMO**

PLACE FIGURE HERE

Area under the Receiver Operator Curve (ROC) = 0.81

**Figure 2: Probability of Survival Related to Duration of ECMO in Pertussis patients**

PLACE FIGURE HERE

Vertical lines are at 5, 15 and 35 days

Footnote: Missing data for 6 patients

**Table 1: Defining the Study Group**

| Categories | Number | Proportion of survivors |
|---|---|---|
| All Pertussis in database | 275 | 80/275 (29%) |
| Adults in database* | 7 | 2/7 (28%) |
| Neonate and Pediatric prior to 2002* | 60 | 18/60 (30%) |
| Multiple runs* | 6 | 3/6 (50%) |
| Children > 1 year of age* | 2 | 2/4 (50%) |
| | | |
| Neonate and Pediatric Final Study Group | 200 | 56/200 (28%) |

* Removed from final analysis

Table 2

**Table 2: Risk factors of interest and their relationship with survival in pertussis patients on ECMO: Univariate Analysis**

| Pre-ECMO Parameter | Number with missing data Survivors: non-survivors | Mean (SD), or number (%) for survivors n = 56 | Mean (SD), or number (%) for non-survivors n = 144 | OR (95% CI) | P value |
|---|---|---|---|---|---|
| Age (per month) | | 1.9 (1.2) | 1.4 (0.9) | 1.65 (1.17, 2.32) | 0.004 |
| pH (per 0.1 units) | 2 : 7 | 71.8 (1.2) | 71.2 (1.7) | 1.29 (1.05, 1.59) | 0.015 |
| P/F ratio (per 10-unit increase) | 3 : 16 | 8.6 (7.3) | 6.2 (5.2) | 1.06 (1.007, 1.12) | 0.03 |
| OI (per 10-unit increase) | 54 : 22 | 3.6 (2.1) | 5.4 (3.4) | 0.78 (0.65, 0.93) | 0.006 |
| Intubation time* | 0 : 4 | 66 (40.5, 111.5)* | 36 (20, 64)* | 2.20 (1.40, 3.45) | 0.001 |
| Inhaled Nitric Oxide use | | 44 (78.6) | 109 (75.7) | 1.18 (0.56, 2.48) | 0.67 |
| Inotrope Use | | 43 (76.8) | 132 (91.7) | 0.30 (0.13, 0.71) | 0.006 |
| Pre-ECMO arrest | | 6 (10.7) | 29 (20.1) | 0.48 (0.19, 1.22) | 0.12 |
| VA ECMO<br>VV ECMO<br>VV-VA ECMO | 3 : 3 | 45 (84.9)<br>6 (11.3)<br>2 (3.8) | 115 (81.6)<br>8 (5.7)<br>18 (12.8) | <br>1.92 (0.63, 5.83)[a]<br>0.28 (0.06, 1.27)[b] | <br>0.25<br>0.10 |
| Co-Infection pre ECMO | | 17 (30.4) | 27 (18.8) | 1.89 (0.93, 3.83) | 0.08 |
| | | | | | |
| **On-ECMO Parameter** | | | | **OR (95% CI)** | **P value** |
| Co-Infection on ECMO | | 8 (14.3) | 44 (30.6) | 0.38 (0.17, 0.87) | 0.02 |
| Renal Complication | | 38 (67.9) | 115 (79.9) | 0.53 (0.27, 1.06) | 0.08 |
| Neurologic Complication | | 17 (30.4) | 62 (43.1) | 0.58 (0.30, 1.11) | 0.10 |
| Any Complication (Renal, Neurologic, Infectious) | | 40 (71.4) | 130 (90.3) | 0.27 (0.12, 0.60) | 0.001 |

SD: standard deviation, OR: Odds Ratio, CI: confidence interval

*Log transformation used, median and interquartile range presented

[a] VV vs VA EMCO, [b] VV-VA vs VA ECMO

**Table 3: Multivariable regression analysis identifying factors independently associated with survival**

| **Multiple Model I** (both Pre-ECMO and On-ECMO variables) | | | |
|---|---|---|---|
| **Variable** | **OR** | **95% CI** | **P value** |
| Pre-ECMO Age (months) | 1.43 | 1.03, 1.98 | 0.034 |
| Pre-ECMO P/F ratio (per 10 unit increase) | 1.10 | 1.03, 1.17 | 0.003 |
| Pre-ECMO Intubation time* | 2.10 | 1.37, 3.22 | 0.001 |
| Pre-ECMO Inotrope use | 0.33 | 0.11, 0.99 | 0.047 |
| Any complication on ECMO (Infection, renal or neurologic) | 0.21 | 0.08, 0.56 | 0.002 |
| | | | |
| **Multiple Model II** (only Pre-ECMO variables) | | | |
| **Variable** | **OR** | **95% CI** | **P value** |
| Pre-ECMO Age (months) | 1.47 | 1.07, 2.04 | 0.019 |
| Pre-ECMO P/F ratio (per 10 unit increase) | 1.09 | 1.02, 1.16 | 0.005 |
| Pre-ECMO Intubation time* | 2.11 | 1.38, 3.23 | 0.001 |
| Pre-ECMO Inotrope use | 0.31 | 0.11, 0.88 | 0.028 |

* Log transformation used

Table 4

**Table 4: Univariate and Multivariate Analysis: Expanded Pertussis Dataset (n=73)**

| Pre-ECMO parameter | Mean (SD) or number (%) for survivors n=23 | Mean (SD) or number (%) for non-survivors n=50 | Odds Ratio (95% CI) | P value |
|---|---|---|---|---|
| **Univariate Analysis** | | | | |
| Highest WBC count (per 10,000) | 7.8 (3.5) | 7.7 (2.6) | 1.01 (0.85, 1.20) | 0.88 |
| Pulmonary Hypertension | 18 (78.3) | 49 (98.0) | 0.07 (0.01,0.67) | 0.02 |
| Leukodepletion received | 9 (39.1) | 9 (18.0) | 2.93 (0.97, 8.84) | 0.06 |
| | | | | |
| **Multivariate Analysis** | | | | |
| Pulmonary Hypertension | 18 (78.3) | 49 (98.0) | 0.06 (0.01, 0.55) | 0.01 |
| Leukodepletion received | 9 (39.1) | 9 (18.0) | 3.36 (1.13, 11.68) | 0.03 |

SD: standard deviation, CI: confidence interval, WBC: white blood cell count

Figure 1

Click here to download Figure Figure 1 ROC Curve .tif

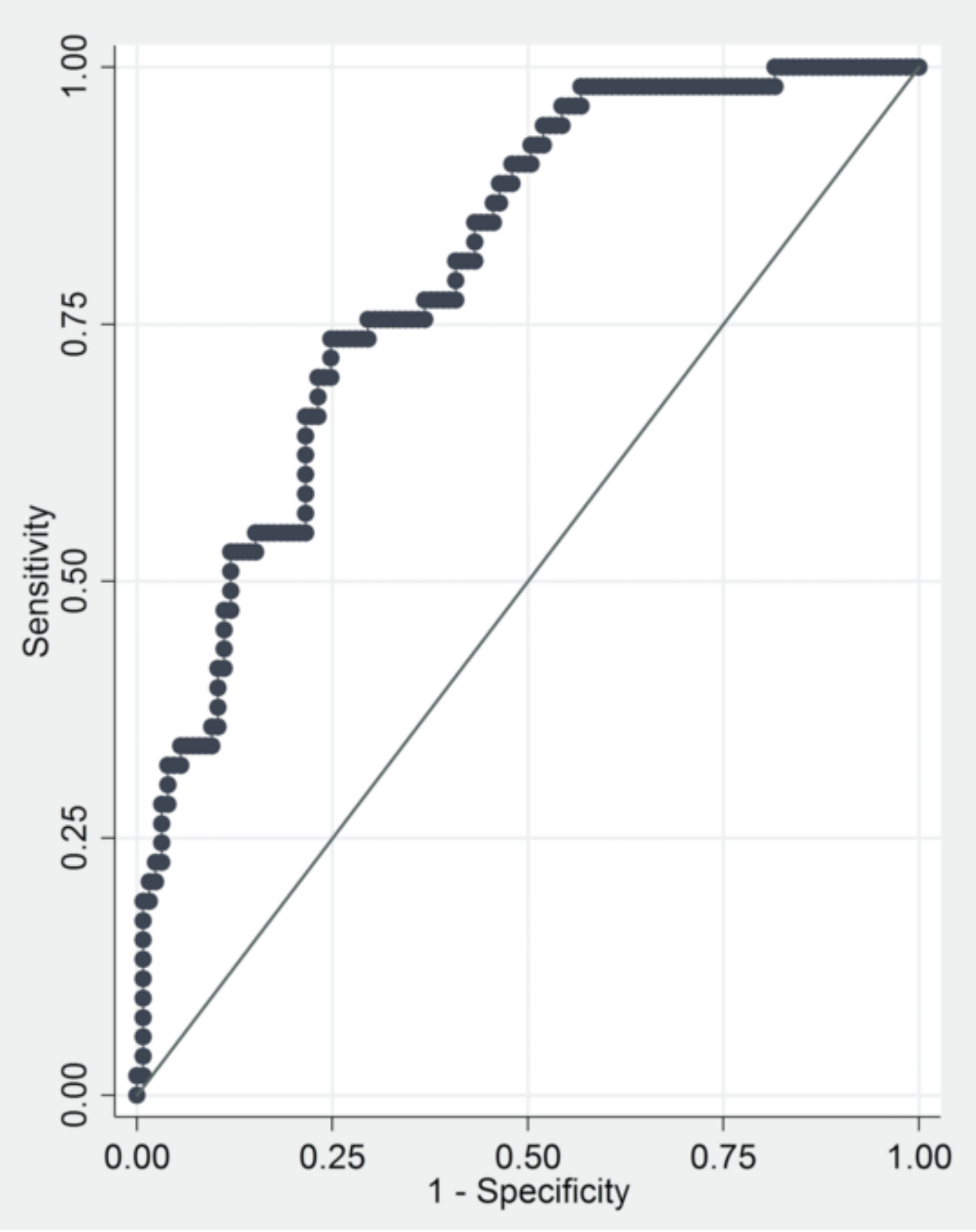

Figure 2

Click here to download Figure Figure 2 ECMO Duration .tif