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Risk Factors for Mortality in Refractory Pediatric Septic Shock Supported with Extracorporeal Life Support

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Abstract

Risk factors for mortality in children with refractory pediatric septic shock who are supported with extracorporeal life support (ECLS) are largely unknown. Therefore, we performed univariable and multivariable analyses to determine risk factors for mortality among children (<19 years) who underwent an ECLS run between January 2012 and September 2014 at eight tertiary pediatric hospitals, and who had septic shock based on 2005 International Consensus Criteria. Of the 514 children treated with ECLS during the study period, 70 were identified with septic shock. The mortality rate was similar between those with (54.3%) and without septic shock (43.7%). Among

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those with septic shock, significant risk factors for mortality included cardiac failure or extracorporeal cardiopulmonary resuscitation (ECPR) as indication for ECLS cannulation compared with respiratory failure ($P = 0.003$), having a new neurologic event following cannulation ($P = 0.032$), acquiring a new infection following cannulation ($P = 0.005$), inability to normalize pH in the 48 hours following ECLS cannulation ($P = 0.010$), and requiring higher daily volume of platelet transfusions ($P = 0.005$). These findings can be used to help guide clinical decision making for children with septic shock that is refractory to medical management.

Keywords

sepsis; septic shock; extracorporeal membrane oxygenation; extracorporeal life support; child; critical care; clinical decision making

Extracorporeal life support (ECLS) is an advanced therapeutic modality intended to support the failing heart and/or lungs, as a bridge to transplant or recovery.¹ Generally, ECLS is indicated for patients with a reversible disease process who are failing maximal medical therapy and are at high risk for death.² Pediatric septic shock affects over 75,000 US children annually.³ It is reversible in most cases, but has 9–25% overall mortality, and nearly 50% mortality in certain patient populations.^{3,4} Early recognition and rapid treatment are critical to survival and prevent or at least mitigate the progression to multiple organ dysfunction syndrome (MODS).^{5–7}

Pediatric septic shock guidelines from both the Surviving Sepsis Campaign and the American College of Critical Care Medicine emphasize first-hour treatment aimed at controlling the underlying infection, improving oxygen delivery, and restoring normal perfusion.^{8,9} These goals can be achieved through utilization of antimicrobials, administration of intravenous fluid resuscitation, and initiation of vasoactive and inotropic support. If shock is refractory to maximal medical therapy, ECLS is recommended.

Pediatric septic shock was previously considered a contraindication to ECLS cannulation, but ECLS has been deployed for refractory sepsis with hospital survival ranging from about 50% nationally to 74% at a single institution.^{10–12} It remains unclear which children with septic shock are most likely to benefit from ECLS. Physician attitudes toward candidacy for various indications for ECLS use, including septic shock, remain significantly varied.¹³ Clearly, more data are needed to help inform decision making. Thus, the objective of the current study is to identify risk factors for mortality among children with septic shock who are supported with ECLS, utilizing the data collected in the Bleeding and Thrombosis during extracorporeal membrane oxygenation (BATE) study.¹⁴

Methods

Study Design and Data Source

This is a secondary analysis of data prospectively collected for the BATE study, an observational cohort investigation of bleeding and thrombosis associated with pediatric and neonatal ECLS runs. The dataset included all 514 patients less than 19 years old who underwent a first ECLS run in a neonatal, pediatric, or cardiac intensive care unit (ICU), at

the eight pediatric hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) between December 2012 and September 2014. Details of the BATE study methodology have been previously published.¹⁴ A waiver of informed consent was granted by the institutional review board for each clinical site and the Data Coordinating Center at the University of Utah.

Data were prospectively collected by trained research coordinators *via* direct observation, discussion with bedside clinicians, and concurrent review of medical records. Baseline variables included patient demographics; primary, secondary, and chronic diagnoses; baseline technology dependence; baseline clinical characteristics including vital signs, ventilator settings, and laboratory values, all of which were collected prior and closest to ECLS initiation; baseline infection status; baseline vasoactive inotropic scores (VIS)¹⁵; and indication for and mode of ECLS initiation. Indications for ECLS included respiratory failure, cardiac failure, and extracorporeal cardiopulmonary resuscitation (ECPR); mode of ECLS included venovenous (VV) and venoarterial (VA). After ECLS initiation, the following variables were collected daily, utilizing those values closest to 0700 on each day: ECLS parameters, ventilator settings, laboratory values, vital signs, and organ failure assessment. Definitions of individual organ failures, as defined by the BATE study, are displayed in Table 1, Supplemental Digital Content, <http://links.lww.com/ASAIO/A488>. Additional variables collected included vital status at discharge, and discharge functional and neurologic status, assessed by the Functional Status Scale (FSS),¹⁶ the Pediatric Cerebral Performance Category (PCPC),¹⁷ and the Pediatric Overall Performance Category (POPC).¹⁷

Exposure and Outcome Measures

The primary exposure was the presence of refractory septic shock before ECLS cannulation. Patients with septic shock were identified using 2005 International Consensus Criteria¹⁸ (Figure 1). We first identified 240 patients who were cannulated with VA ECLS and had a primary diagnosis of sepsis/ systemic inflammatory response syndrome (SIRS)/septic shock or had a known or suspected infection. Primary diagnoses of sepsis/SIRS/septic shock were determined by bedside clinicians and collected prospectively by trained research coordinators. Venovenous ECLS patients were excluded as it is unlikely that their primary indication for ECLS support was refractory septic shock. Known infections were defined as culture- or polymerase chain reaction (PCR)-proven bacterial, fungal, or viral infections diagnosed before ECLS cannulation. Suspected infections were laboratory-unproven infections treated with antibiotics, antifungals, or antivirals before ECLS cannulation. Of these patients, 78 met SIRS criteria¹⁸ before ECLS cannulation, and 70 had evidence of cardiovascular dysfunction, defined as 1) requiring vasoactive infusion, 2) having hypotension,¹⁹ or 3) having a metabolic acidosis with pH < 7.2 without concurrent hypercarbia before ECLS.

The primary outcome was in-hospital mortality. Additional patient outcomes included hospital and ICU length of stay (LOS), duration of ECLS, bleeding and thrombotic

complications associated with ECLS, and functional and neurologic status at discharge utilizing the FSS, PCPC, and POPC scales.

Statistical Analysis

Baseline characteristics, complications, and outcomes are summarized by pre-ECLS refractory septic shock status using counts and percentages for categorical variables and medians, first quartiles, and third quartiles for continuous variables (Tables 1 and 2). The relationship of pre-ECLS refractory septic shock with complications and outcomes was assessed using Fisher's exact test for nominal complications and outcomes, and the Wilcoxon rank-sum test for ordinal complications and outcomes (Table 2). The number of subjects with each reported pathogen is presented with counts in Table 2, Supplemental Digital Content, <http://links.lww.com/ASAIO/A488>.

Before modeling mortality among subjects with pre-ECLS septic shock, the distributions of potential predictors were examined. Variables with little to no variation, *e.g.*, diagnoses pertaining to 5 subjects, were excluded from modeling. Acute and chronic neurologic conditions had similar associations with mortality and were combined. All seven subjects with both pre-ECLS septic shock and ECPR died in the hospital, precluding maximum likelihood estimation for logistic regression. Therefore, Firth penalized likelihood was used to obtain model estimates despite the problem of separation.²⁰ Univariable logistic regression models identified variables associated with mortality (Table 3). Variables at least marginally associated with mortality ($P < 0.10$) that were assessed in at least 90% of the subjects with pre-ECLS septic shock were candidates for inclusion in a multivariable model. The multivariable model was derived using backward stepwise selection with a criterion of $P < 0.05$ to stay in the final model (Table 4). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

The BATE dataset contains 514 subjects, of which 70 met the International Consensus Conference definition for septic shock¹⁸ before ECLS cannulation (Figure 1). Demographic and clinical characteristics of children in the BATE cohort and those with refractory septic shock are displayed in Table 1. Among the 70 children with refractory septic shock, the most common acute diagnosis was respiratory failure (47.1%), while the most common acute diagnosis among those without refractory septic shock was congenital cardiovascular disease (40.3%). The most common chronic diagnoses were similar in both groups: congenital anomaly/chromosomal defect (21.4% and 23.2% in those with and without septic shock, respectively) and congenital heart disease (24.3% and 18.0%, respectively). Among septic children with a documented infection (30%), the most common pathogen was bacterial, and the most common source of infection was respiratory. Details of infectious pathogens among children with septic shock are displayed in Table 2, Supplemental Digital Content, <http://links.lww.com/ASAIO/A488>. The median hospital and ICU lengths of stay (LOS) before ECLS cannulation were relatively short both for children with and without septic shock: 1.1 days (interquartile range [IQR]: 0.4, 7.4) and 0.9 days (IQR: 0.3, 3.7), respectively, among

the children with septic shock, and 2.1 days (IQR: 0.4, 7.6) and 1.3 days (IQR: 0.3, 5.8), respectively, among the children without septic shock.

There were no significant differences between children with and without septic shock with respect to hospital and ICU LOS, duration of ECLS, or thrombotic or bleeding ECLS complications (Table 2). Functional status at hospital discharge among survivors was significantly worse in children with septic shock, with 20.0% categorized as moderately or severely abnormal, compared to only 14.9% among those without septic shock ($P = 0.018$). Similarly, children with refractory septic shock had significantly worse neurologic and functional outcomes at discharge compared to children without septic shock based on PCPC and POPC scores ($P = 0.009$ and $P = 0.017$, respectively). In-hospital mortality was similar between groups: 54.3% (38 patients) in those with refractory septic shock and 43.7% (194 patients) in those without septic shock ($P = 0.121$).

In univariable analysis (Table 3), the pre-ECLS variables significantly associated with in-hospital mortality among children with septic shock ($P < 0.05$) included primary indication for ECLS cannulation (respiratory *versus* cardiac *versus* ECPR) and baseline lactate level. The following postcannulation variables were significantly associated with in-hospital mortality: having a new neurologic event, having an acquired infection while on ECLS support, inability to clear lactate (lowest lactate concentration in 48 hours post-ECLS initiation), inability to normalize pH, and average daily platelet transfusion volume. Variables with marginal association with in-hospital mortality ($P < 0.1$) that were included in multivariable modeling included an acute diagnosis of meconium aspiration syndrome ($P = 0.070$), underlying neurologic condition ($P = 0.083$), baseline blood infection ($P = 0.068$), and baseline hepatic dysfunction ($P = 0.059$).

Several of these variables remained significantly associated with in-hospital mortality after multivariable modeling (Table 4). Compared with respiratory failure as the indication for ECLS, cannulation for cardiac failure and *via* ECPR were both significantly associated with increased mortality ($P = 0.003$). Of note, all seven patients with septic shock that were cannulated *via* ECPR died. Two acquired conditions, having either a new neurologic event or a new acquired infection following ECLS cannulation, were both significantly associated with in-hospital mortality (odds ratio [OR]: 6.37; 95% confidence interval [CI]: 1.31–45.79 and OR: 20.74; 95% CI: 3.19–262.51, respectively). Within the first 48 hours following ECLS cannulation, for each 0.1 increase in the highest achieved pH, the odds of in-hospital mortality decreased by 76% (OR: 0.24; 95% CI: 0.07–0.66). Finally, the average daily platelet transfusion volume was significantly associated with mortality, with the odds of death increasing by 11% for every 1 ml/kg of platelets transfused (OR: 1.11; 95% CI: 1.04–1.22).

Discussion

In this study, the mortality rate for children with refractory septic shock who were supported with ECLS was 54.3%, similar to those in the BATE cohort that did not have refractory septic shock (43.7%). However, survivors with refractory septic shock had significantly worse functional and neurologic outcomes at hospital discharge, as evidenced by worse FSS,

PCPC, and POPC scores compared to children without septic shock. Risk factors for mortality among septic children were related to 1) pre-ECLS cannulation clinical conditions, specifically cardiac failure and cardiac arrest with need for ECPR, and 2) post-ECLS cannulation clinical status, including having a new neurologic event or acquired infection following cannulation, inability to achieve adequate tissue oxygenation with the additional support of the ECLS circuit, as measured by arterial pH, and need for larger volume platelet transfusions. The association between platelet transfusion volume and mortality has also been shown in the entire BATE cohort and appears even stronger in those with septic shock.

Functional status before illness was not available in the BATE dataset; however, our results indicate that children with septic shock who are treated with ECLS have worse FSS, PCPC, and POPC scores at discharge compared to those without septic shock. This is consistent with previous reports that suggest nearly 20% of severe sepsis survivors have a new functional disability at discharge.^{4,21} This may be particularly relevant for children with underlying chronic illness who may not return to their baseline level of health and functional status if they survive their septic shock, and whose quality of life may be severely impacted.⁴ As the success of ECLS support becomes more common in complex patients, it is becoming more difficult to define what constitutes a true contraindication to ECLS cannulation. Every child with a potential need for ECLS support should be considered individually. However, understanding the risk for both mortality and poor functional outcome may help guide physicians and family members when considering the risk-benefit profile of this invasive therapy.

The mortality rate among children with septic shock supported with ECLS varies widely in the literature, with rates ranging from 26% to 69% at single institutions,^{10,11,22} and rates of approximately 50% from larger, multicenter studies,^{4,12,23} consistent with the findings of the current study (54% mortality). These mortality rates in the 50% range suggest that pursuing ECLS therapy in the child with refractory septic shock may not be a “futile” endeavor, as has been previously suggested.²⁴ While the mortality rate for children with septic shock supported by ECLS is higher than the 25% overall mortality reported for children with septic shock admitted to a pediatric intensive care unit (PICU),⁴ those children placed on ECLS likely have a higher severity of illness as evidenced by failure of conventional therapy and need for ECLS as a rescue. Thus, these children presumably represent a group with a high likelihood of death without escalation of support to ECLS.

The results of the current study suggest one pre-ECLS factor that could help aid clinical decision making with respect to understanding the potential survival benefit of ECLS support in pediatric septic shock: cardiac arrest before ECLS cannulation. Not surprisingly, all septic children in our cohort who suffered a cardiac arrest and were cannulated for ECLS *via* ECPR died. The risk of death following cardiac arrest is increased in both adults and children with septic shock compared to those without septic shock at the time of arrest.²⁵ This increased risk is related to both difficulty in achieving return of spontaneous circulation, as well as postarrest complications and ongoing MODS, exacerbated by the underlying septic shock and postcardiac arrest physiology.²⁵ In contrast to our findings, other investigators have reported that children with septic shock who suffer cardiac arrest are more likely to survive when rescued with ECLS support.²³ Given these conflicting data,

further investigation is needed to determine factors associated with improved outcomes among children with septic shock who arrest before cannulation. However, we suggest consideration of cardiac arrest in a child with septic shock as a possible contraindication for ECLS support, and full disclosure to families of the possibility of death.

Pediatric in-hospital death associated with septic shock is most commonly due to refractory septic shock, followed by persistent MODS after shock recovery.²⁶ Therefore, ECLS may be useful as a rescue from refractory septic shock and a bridge to organ recovery, provided that organ recovery is achievable *via* the improved perfusion and oxygen delivery of an ECLS circuit, or by the additional time it may provide for other modalities such as antibiotics to be optimized. Our study demonstrates that children with persistent acidosis during the first 48 hours of cannulation have increased odds of death. It is possible that these children represent the subset of patients with such profound shock that they have progressed to mitochondrial dysfunction with impaired oxygen consumption,^{27,28} despite providing adequate oxygen delivery *via* ECLS. It is not surprising that failure to restore adequate cellular metabolism is associated with worse outcome, although it remains unclear why some children are adequately supported and others not, and if ECLS support can be strategically optimized to provide timely and adequate oxygen delivery to restore perfusion before irreversible organ injury has occurred.

A recent multicenter investigation comparing children in the PICU with severe septic shock supported with conventional therapy to those supported with VA ECLS, found no significant difference in survival to hospital discharge between groups, with survival rates of 40% and 50%, respectively.²³ Interestingly, among those supported with VA ECLS, survival was 82% in those with high-flow VA ECLS, defined as flow rates ≥ 150 ml/kg/min, *vs.* 43% in those with standard flow. All survivors in the high-flow group had central (*i.e.*, atrio-aortic) ECLS cannulation. Similarly, MacLaren *et al.*¹⁰ have reported impressive survival rates at their center when central cannulation and high-flow rates are utilized to support pediatric septic shock. It is possible that increasing flow rates and maximizing circulatory support and therefore oxygen delivery allows for superior reversal of the shock state and eventual recovery. The potential benefit of high-flow VA ECLS could not be assessed in our cohort given median daily flow rates of 93.2 ml/kg/min (IQR: 70.4, 116.9) and only eight patients with flow rates ≥ 150 ml/kg/min. Flow rate was not significantly correlated with mortality on univariate analysis (Table 3) and thus was not selected for the multivariable model. It should also be noted that in both of the studies showing benefit of high flow rates, median time from ICU admission to ECLS cannulation was quite short, at 7 and 7.8 hours, compared to over 24 hours in our study. Thus, the survival benefit in these investigations of VA ECLS may also be related to more rapid escalation to ECLS support with improved oxygen delivery before irreversible oxygen consumption failure, differences in thresholds to initiate ECLS, or other center-specific practices, rather than solely related to central cannulation with high flow rates.

Our study has several limitations. First, because this is a secondary analysis of a prospectively collected dataset, our investigation of factors associated with mortality was limited to the data available in this dataset. Thus, we are not able to evaluate the effect of clinically relevant variables that were not included. Similarly, we were not able to balance

the groups with respect to underlying diagnoses. For example, the septic shock cohort had a much higher proportion of patients with acute respiratory failure, while the nonseptic shock cohort had higher rates of congenital heart disease. These diagnoses also affect mortality risk, and differences in patient mix should be considered when interpreting the finding of similar mortality in septic and nonseptic groups. Second, the definition of septic shock used in our investigation was based on the 2005 International Consensus Criteria.¹⁸ The primary diagnoses of “SIRS/ sepsis/septic shock” and “known or suspected infections” was left to the discretion of individual sites, and thus, some children may have been inappropriately included or excluded due to the use of the diagnostic categories included in the BATE dataset. Because the 2005 definition lists “known or suspected infection” as a criterion for septic shock, some children included in the refractory septic shock cohort had culture-negative sepsis, a well-documented finding in the pediatric septic shock literature.^{29,30} Similarly, given the high frequency of infections among critically ill children, there are some children in the nonseptic shock cohort that also had a known or suspected infection, but did not meet additional criteria for septic shock. Third, this dataset cannot address the issue of selection bias; thresholds to initiate ECLS support vary by institution and individual, thus some clinicians may have chosen to provide ECLS for septic patients who did not need it, and some may have excluded septic patients who were unlikely to survive. Finally, although our cohort is one of the largest evaluated for ECLS use in pediatric septic shock, it is still relatively small. Further investigation of ECLS use in pediatric septic shock is warranted, with particular attention to the timing of ECLS initiation, the site of VA ECLS cannulation (central *versus* peripheral) and ECLS flow rate. Our cohort did not have adequate patients with central cannulation (n = 7) or flow rates ≥ 150 ml/ kg/min (n = 8) to evaluate these factors.

Conclusions

Children with septic shock who are supported with ECLS have similar mortality to children placed on ECLS for other indications, but worse functional status and neurologic outcome at hospital discharge. Specific risk factors for mortality in this population include ECPR, and, following cannulation, new infectious and neurologic complications, inability of the ECLS circuit to adequately restore oxygen utilization and reverse the shock state, and need for larger volume platelet transfusions. Further research is needed to evaluate the safety, efficacy, and impact of early VA ECLS initiation with central cannulation and high flow rates in improving survival of pediatric septic shock.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BATE: Bleeding and Thrombosis During ECMO
SIRS: Systemic Inflammatory Response Syndrome

Figure 1.

Patient identification for inclusion in the septic shock cohort, based on the international consensus conference criteria for pediatric septic shock from Goldstein *et al.*¹⁸ Cut off values for systemic inflammatory response syndrome (SIRS) criteria and hypotension were also based on those suggested by Goldstein *et al.*^{18,19} VV ECMO, venovenous extracorporeal membrane oxygenation.

Table 1.
Baseline Characteristics of the BATE Cohort, Including Those with and Without Refractory Septic Shock

	Refractory Septic Shock		
	No (N = 444) (%)	Yes (N = 70) (%)	Overall (N = 514) (%)
Preterm neonate	44 (9.9)	6 (8.6)	50 (9.7)
Male	270 (60.8)	32 (45.7)	302 (58.8)
Race			
White	216 (48.6)	38 (54.3)	254 (49.4)
Black or African American	75 (16.9)	16 (22.9)	91 (17.7)
Other	22 (5.0)	4 (5.7)	26 (5.1)
Unknown/not reported	131 (29.5)	12 (17.1)	143 (27.8)
Acute diagnoses			
Cardiovascular disease (congenital)	179 (40.3)	14 (20.0)	193 (37.5)
Respiratory distress/failure	137 (30.9)	33 (47.1)	170 (33.1)
Persistent pulmonary hypertension of the newborn	72 (16.2)	18 (25.7)	90 (17.5)
Cardiovascular disease (acquired)	52 (11.7)	13 (18.6)	65 (12.6)
Congenital diaphragmatic hernia	50 (11.3)	6 (8.6)	56 (10.9)
Cardiac arrest	41 (9.2)	8 (11.4)	49 (9.5)
Meconium aspiration syndrome	40 (9.0)	7 (10.0)	47 (9.1)
Immune dysfunction	31 (7.0)	6 (8.6)	37 (7.2)
Gastrointestinal disorder	19 (4.3)	4 (5.7)	23 (4.5)
Pneumonia or bronchiolitis	20 (4.5)	4 (5.7)	24 (4.7)
Cardiovascular disease (arrhythmia)	18 (4.1)	0 (0.0)	18 (3.5)
Hypoxic/anoxic injury	11 (2.5)	6 (8.6)	17 (3.3)
Neurologic condition	11 (2.5)	6 (8.6)	17 (3.3)
Shock (nonseptic)	10 (2.3)	4 (5.7)	14 (2.7)
Airway abnormality	10 (2.3)	2 (2.9)	12 (2.3)
Chronic diagnoses			
Congenital anomaly or chromosomal defect	103 (23.2)	15 (21.4)	118 (23.0)
Cardiovascular disease (congenital)	80 (18.0)	17 (24.3)	97 (18.9)
Neurologic condition	19 (4.3)	8 (11.4)	27 (5.3)

	Refractory Septic Shock			Overall (N = 514) (%)
	No (N = 444) (%)	Yes (N = 70) (%)		
Immune dysfunction	15 (3.4)	2 (2.9)		17 (3.3)
Chronic lung disease	15 (3.4)	2 (2.9)		17 (3.3)
Infection				
None	275 (61.9)	0 (0.0)		275 (53.5)
Suspected	110 (24.8)	49 (70.0)		159 (30.9)
Documented				
Bacterial	28 (6.3)	12 (17.1)		40 (7.8)
Viral	22 (5.0)	6 (8.6)		28 (5.4)
Fungal	3 (0.7)	2 (2.9)		5 (1.0)
Multiple	6 (1.4)	1 (1.4)		7 (1.4)
System of documented infection				
Blood	18 (4.1)	9 (12.9)		27 (5.3)
Respiratory	41 (9.2)	16 (22.9)		57 (11.1)
Other	3 (0.7)	0 (0.0)		3 (0.6)
Home technology dependence (nonneonates only; N = 247)				
Feeding tube	43 (20.4)	5 (13.9)		48 (19.4)
Supplemental oxygen	29 (13.7)	2 (5.6)		31 (12.6)
Ventilation	5 (2.4)	2 (5.6)		7 (2.8)
Chronic vascular access	14 (6.6)	2 (5.6)		16 (6.5)
PRISM III Score	8.0 [3.0, 12.0]	12.5 [7.0, 17.0]		9.0 [4.0, 13.0]
Organ failure				
Cardiovascular	419 (94.4)	69 (98.6)		488 (94.9)
Hepatic	104 (23.4)	33 (47.1)		137 (26.7)
Stage 2+ AKI	57 (12.8)	24 (34.3)		81 (15.8)
Neurologic	35 (7.9)	8 (11.4)		43 (8.4)
Clinical site				
A	58 (13.1)	9 (12.9)		67 (13.0)
B	100 (22.5)	4 (5.7)		104 (20.2)
C	25 (5.6)	12 (17.1)		37 (7.2)
D	47 (10.6)	16 (22.9)		63 (12.3)

	Refractory Septic Shock			Overall (N = 514) (%)
	No (N = 444) (%)	Yes (N = 70) (%)		
E	54 (12.2)	6 (8.6)		60 (11.7)
F	57 (12.8)	10 (14.3)		67 (13.0)
G	23 (5.2)	5 (7.1)		28 (5.4)
H	80 (18.0)	8 (11.4)		88 (17.1)
Hospital LOS before ECMO (days)	2.1 [0.4, 7.6]	1.1 [0.4, 7.4]		2.0 [0.4, 7.5]
ICU LOS before ECMO (days)	1.3 [0.3, 5.8]	0.9 [0.3, 3.7]		1.2 [0.3, 5.5]

AKI, acute kidney injury; BATE, Bleeding and Thrombosis during ECMO; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; PRISM, pediatric risk of mortality.

Table 2.
Complications and Outcomes Among Those with and Without Refractory Septic Shock Before ECMO Cannulation

	Refractory Septic Shock at Baseline			<i>p</i>
	No (N = 444) (%)	Yes (N = 70) (%)		
Length of hospital stay (days)	37.2 [16.8, 68.6]	28.3 [12.1, 66.4]		0.079 *
Length of ICU stay (days)	28.5 [14.2, 50.7]	23.1 [11.6, 54.0]		0.294 *
Duration of ECMO (days)	5.0 [2.7, 9.2]	5.5 [2.8, 9.4]		0.448 *
Thrombotic event	164 (36.9)	29 (41.4)		0.508 †
Bleeding event	310 (69.8)	51 (72.9)		0.674 †
Functional status at hospital discharge				0.018 *
Good	84 (18.9)	5 (7.1)		
Mildly abnormal	99 (22.3)	13 (18.6)		
Moderately abnormal	56 (12.6)	11 (15.7)		
Severely abnormal	10 (2.3)	3 (4.3)		
Very severely abnormal	0 (0)	0 (0)		
Not applicable (dead)	194 (43.7)	38 (54.3)		
PCPC score at hospital discharge				0.009 *
1: normal	135 (30.4)	10 (14.3)		
2: mild disability	85 (19.1)	12 (17.1)		
3: moderate disability	22 (5.0)	5 (7.1)		
4: severe disability	8 (1.8)	5 (7.1)		
5: coma/vegetative state	0 (0)	0 (0)		
6: brain death	194 (43.7)	38 (54.3)		
POPC score at hospital discharge				0.017 *
1: good	47 (10.6)	5 (7.1)		
2: mild disability	119 (26.8)	9 (12.9)		
3: moderate disability	67 (15.1)	11 (15.7)		
4: severe disability	17 (3.8)	7 (10.0)		
5: coma/vegetative state	0 (0)	0 (0)		
6: brain death	194 (43.7)	38 (54.3)		

	<u>Refractory Septic Shock at Baseline</u>		<i>p</i>
	No (N = 444) (%)	Yes (N = 70) (%)	
In-hospital mortality	194 (43.7)	38 (54.3)	0.121 [‡]

* Wilcoxon rank-sum test.

[‡] Fisher's exact test.

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PCPC, Pediatric Cerebral Performance Category; POPC, Pediatric Overall Performance Category.

Table 3.
Univariable Models of In-Hospital Mortality in Children with Refractory Septic Shock Supported by ECMO

	Overall (N = 70) (%)	In-Hospital Mortality		
		Odds Ratio (95% CI)	p	% Missing
Preterm neonate	6 (8.6)	3.45 (0.64–34.99)	0.228	0
Sex			0.448	0
Male	32 (45.7)	1.44 (0.57–3.73)		
Female	38 (54.3)	Reference		
Race			0.663	17
White	38 (54.3)	Reference		
Black or African American	16 (22.9)	1.14 (0.36–3.68)		
Other	4 (5.7)	0.39 (0.04–2.61)		
Acute diagnoses				
Cardiovascular disease (congenital)	14 (20.0)	1.14 (0.36–3.70)	0.832	0
Respiratory distress/failure	33 (47.1)	1.02 (0.40–2.59)	0.969	0
Persistent pulmonary hypertension of the newborn	18 (25.7)	0.60 (0.20–1.71)	0.349	0
Cardiovascular disease (acquired)	13 (18.6)	1.39 (0.43–4.84)	0.596	0
Congenital diaphragmatic hernia	6 (8.6)	1.59 (0.33–9.67)	0.601	0
Cardiac arrest	8 (11.4)	2.44 (0.57–14.10)	0.282	0
Meconium aspiration syndrome	7 (10.0)	0.16 (0.02–0.84)	0.070	0
Immune dysfunction	6 (8.6)	1.59 (0.33–9.67)	0.601	0
Gastrointestinal disorder	4 (5.7)	0.84 (0.12–5.71)	0.861	0
Pneumonia or bronchiolitis	4 (5.7)	0.84 (0.12–5.71)	0.861	0
Hypoxic/anoxic injury	6 (8.6)	0.83 (0.16–4.20)	0.829	0
Chronic diagnoses				
Congenital anomaly or chromosomal defect	15 (21.4)	1.31 (0.43–4.22)	0.645	0
Cardiovascular disease (congenital)	17 (24.3)	0.93 (0.32–2.75)	0.894	0
Neurologic condition	8 (11.4)	0.28 (0.05–1.19)	0.124	0
Combined acute/chronic diagnoses				
Neurologic condition	13 (18.6)	0.32 (0.09–1.07)	0.083	0
Baseline blood infection	9 (12.9)	5.85 (1.21–57.34)	0.068	0

	Overall (N = 70) (%)	In-Hospital Mortality		
		Odds Ratio (95% CI)	p	% Missing
Baseline hepatic dysfunction	33 (47.1)	2.55 (0.99–6.80)	0.059	0
Baseline stage 2+ AKI	24 (34.3)	2.22 (0.82–6.37)	0.130	4
Baseline neurologic dysfunction	8 (11.4)	0.49 (0.11–2.02)	0.358	0
ICU LOS before ECMO (days)	0.9 [0.3, 3.7]	1.00 (0.99–1.04)	0.687	0
Primary ECMO indication			0.009	0
Respiratory	39 (55.7)	Reference		
Cardiac	24 (34.3)	4.10 (1.45–12.56)		
ECPR	7 (10.0)	26.38 (2.86–3,517.11)		
Baseline vasoactive inotropic score			0.638	0
None	5 (7.1)	0.52 (0.08–2.92)		
Low	15 (21.4)	0.64 (0.20–2.00)		
High	50 (71.4)	Reference		
Baseline lactate (mmol/L)	6.9 [3.9, 10.1]	1.13 (1.03–1.27)	0.022	13
Baseline pH in arterial blood	7.19 [7.07, 7.29]	0.13 (0.01–1.90)	0.162	6
Baseline leukocytes (10 ³ /μl)	14.7 [6.6, 25.9]	1.00 (0.97–1.04)	0.942	4
Baseline chloride (mmol/L)	104.0 [98.0, 109.0]	1.00 (0.94–1.07)	0.973	6
Baseline thrombocytopenia (platelets < 80,000/μl)	10 (14.3)	2.07 (0.55–9.24)	0.318	4
Cannulation site			0.698	0
Central	7 (10)	1.2 (0.27–5.80)		
Groin	7 (10)	2.05 (0.45–12.18)		
Neck	56 (80.0)	Reference		
New neurologic event	36 (51.4)	2.77 (1.08–7.39)	0.040	0
New renal dysfunction	21 (30.0)	1.17 (0.43–3.26)	0.769	0
New hepatic dysfunction	10 (14.3)	2.01 (0.54–8.92)	0.337	0
Thrombotic event	29 (41.4)	0.53 (0.20–1.36)	0.196	0
Bleeding event	51 (72.9)	0.83 (0.29–2.34)	0.731	0
Acquired infection	16 (22.9)	4.46 (1.34–18.86)	0.027	0
Lowest lactate in 48 hours post-ECMO initiation (mmol/L)	1.9 [1.3, 5.1]	1.26 (1.06–1.65)	0.027	3
Lactate 2.2 mmol/L within 48 hours post-ECMO	38 (54.3)	0.48 (0.18–1.24)	0.142	3
Highest pH within 48 hours post-ECMO initiation (odds ratio is for a 0.1 increase)	7.42 [7.36, 7.49]	0.54 (0.30–0.90)	0.030	0

	In-Hospital Mortality		
	Overall (N = 70) (%)	Odds Ratio (95% CI)	p % Missing
Estimated PRBC transfusion in first 24 hours post-ECMO initiation (dl/kg)	1.0 [0.4, 1.4]	0.99 (0.56–1.77)	0.966 0
Average daily platelet transfusion volume (ml/kg)	11.6 [7.3, 19.4]	1.10 (1.04–1.18)	0.004 0
Mean daily ECMO flow rate (ml/kg/min)	93.2 [70.4, 116.9]	1.01 (1.00–1.02)	0.242 0
Duration of ECMO (days)	5.5 [2.8, 9.4]	0.98 (0.93–1.02)	0.385 0

AKI, acute kidney injury; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; LOS, length of stay; PRBC, packed red blood cell.

Table 4.

Multivariable Model of In-Hospital Mortality Among Children with Refractory Septic Shock Supported with ECMO

	In-Hospital Mortality	
	Odds Ratio (95% CI)	<i>p</i>
Primary ECMO indication		0.003
Respiratory	Reference	
Cardiac	11.27 (2.38–86.03)	
ECPR	1,296.98 (26.06, -)	
New neurologic event	6.37 (1.31–45.79)	0.032
Acquired infection	20.74 (3.19–262.51)	0.005
Highest pH within 48 hours post-ECMO initiation (odds ratio is for a 0.1 increase)	0.24 (0.07–0.66)	0.010
Average daily platelet transfusion volume (ml/kg)	1.11 (1.04–1.22)	0.005

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.