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Original Article

Pathogens and outcomes in pediatric septic shock patients supported by extracorporeal membrane oxygenation

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Abstract *Background:* Refractory septic shock is the leading cause of mortality in children. There is limited evidence to support extracorporeal membrane oxygenation (ECMO) use in pediatric septic shock. We described the etiology and outcomes of septic patients in our institution and attempted to find predictive factors.
Methods: We retrospectively reviewed 55 pediatric patients with septic shock who required ECMO support in a tertiary medical center from 2008 to 2015. Septic shock was defined as culture proved or clinical suspected sepsis with hypotension or end-organ hypoperfusion. ECMO would be applied when pediatric advanced life support steps were performed thoroughly without clinical response. Patient's demographics, laboratory parameters before and after ECMO, and outcomes were analyzed.
Results: Among 55 children with ECMO support, 31% of them survived on discharge. For 25 immunocompromised patients, causal pathogens were found in 17 patients: 7 due to bacteremia, 9 with preexisting virus infections and one with invasive fungal infection. Among 30 previously healthy patients, causal pathogens were found in 18 patients: 10 due to bacteremia

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(the most common was *pneumococcus*), 7 with preexisting virus infections including influenza (n = 4), adenovirus (n = 2), RSV, and 1 patient had mixed virus and bacterial infections. Predictive factors associated with death were arterial blood gas pH, CO_2 and Glasgow Coma Scale ($p < 0.05$). SOFA score was a valuable predictive scoring system for outcome prediction ($p < 0.05$).

Conclusions: Pediatric patients with refractory septic shock had high mortality rate and ECMO could be used as a rescue modality, and SOFA score could be applied to predict outcomes.

Background

Severe sepsis or septic shock is one of the major causes of pediatric death. It accounted for about 8% pediatric intensive care unit (PICU) admission and the proportion varied across regions from 6.2 to 23.1%.[1] The overall mortality rate was 24%, ranging from 21% in North America and 40% in Africa.[1–3] Extracorporeal membrane oxygenation (ECMO) had first been introduced in cardiopulmonary support during surgery in 1970 by Thomas G. Baffes.[4] In 1976, Robert H. Bartlett reported the first case of neonatal ECMO survivors.[5] Since then, ECMO had become an important modality for the transition during the critical condition such as neonatal respiratory distress syndrome or cardiac surgery. However, sepsis or septic shock had been considered as a contraindication for ECMO before 1990. Previous concerns included secondary contamination of the circuit (later reports refuted this assumption),[6] disseminated intravascular coagulation or risk of hemorrhage, and poor prognosis.[7] After 1990, strict heparin management and improvement of circuit care lead to fewer complications. In the sequentially published guidelines,[8,9] for septic shock unresponsive to fluid resuscitation and inotropic agents, ECMO could be considered. In contrast, there were limited studies to analyze the outcomes and prognostic factors of these patients. We thus initiated this study to investigate the etiology and outcomes of septic patients in our institution and attempted to find predictive factors.

Patients and methods

We retrospectively reviewed 55 pediatric septic patients (age from 0 to 18 years old) with ECMO support in National Taiwan University Children's Hospital from 2008 to 2015. They fulfilled the definition of sepsis which included systemic infections with culture-proven microorganisms or systemic inflammatory response syndrome (SIRS) with highly clinical suspicion of sepsis. Refractory shock was defined as persistent hypotension with poor end-organ perfusion even under fluid resuscitation and the use of inotropic agents. Generally, we used 20 mL/kg of isotonic crystalloid solution for fluid challenge. pH < 7.2, PaO_2/FiO_2 < 200, serum lactate > 5 mM/L, inotropic equivalent >25 and ejection fraction <40% were parameters for poor perfusion. Traumatic, cardiogenic, post-cardiac surgery or acute myocarditis related ECMO supports were excluded.

Patient's demography, medical history, laboratory data during hospitalization, ECMO indication, mode, duration of ECMO support and discharge status were collected. For causal agents of sepsis, bacteria found in blood culture before or on the day of ECMO were considered as related pathogens. Viral or fungal infections were diagnosed based on isolation, serology titers or antigen tests. All pathogen isolation results were correlated with medical charts and clinical presentations.

The data collections and medical chart reviews were approved by the National Taiwan University Hospital's IRB (Institutional Review Board for Human Subject Research) with IRB number of 201701062RINC.

ECMO indication

According to 2012 Surviving sepsis campaign,[9] ECMO could be a rescue modality for refractory septic shock. There was no worldwide consensus for definite parameters or clinical conditions that ECMO should be initiated. In our hospital, ECMO will be considered when PALS (Pediatric advanced life support) steps are performed thoroughly without clinical response, such as the development of adult respiratory distress syndrome (ARDS) or failure to maintain adequate end-organ perfusion even under the use of high-dose inotropic agents. Prematurity with gestational age less than 34 weeks, body weight less than 2 kg, irreversible pulmonary or cardiovascular disease, obvious intracranial hemorrhage, severe hypoxic-ischemic encephalopathy or malignant end stage disease are contraindicated.

Data analysis

All analyses were performed with commercially available statistical software (SPSS v22.0). Patients were categorized into two groups, survivors and nonsurvivors. Continuous data were analyzed with Mann–Whitney test or *t*-test, and categorical data were compared with the chi-square test. The receiver operating characteristic curve analysis was applied to determine the best cut-off-point for each parameter which was significant in univariate analysis, and then multiple logistic regressions were applied to perform multivariate analysis for predicting the most significant factors associated with mortality. p Value less than 0.05 by two-tailed test was considered statistical significance in both tests.

Results

Demographic data

Between 2008 and 2015, 55 pediatric patients, who received ECMO support due to refractory septic shock, were collected from our database. Patients' characteristics and basic data were listed in Table 1. The mean age was 7.2 years (SD = 6.16) with 29 male (52.7%) and 26 female (47.3%). Venoarterial ECMO (VA-ECMO) was applied to 48 (87.3%) patients. The average ECMO support days and hospital length of stay were 16.75 (SD: 22.73) and 47.24 (SD: 41.7) days, respectively. Among all the children, 25 (45.5%) of them were immunocompromised person. There were 17 (31%) survived to discharge and 35 (69%) expired. The mean age of survival group and non-survival group were 8.1 and 6.8 years ($p = 0.47$). Male patients had the trend of mortality ($p = 0.083$). The initial hemodynamics showed no difference in these two groups except Glasgow coma scale (GCS). Survivors had better levels of consciousness than fatal group (12.9 points vs. 7 points, $p < 0.001$). After 24 h ECMO support, systemic perfusion parameters such as systolic blood pressure (111.7 mmHg vs. 93.55 mmHg, $p = 0.012$) and mean arterial pressure (87 mmHg vs. 74.8 mmHg, $p = 0.03$) were lower in the fatal group. Conversely, central venous pressure was higher in this group (9 cmH_2O vs. 11.76 cmH_20, $p = 0.009$). Among the 17 survivors, there were 6 children had neurological sequelae: 3 patients had epilepsy, one suffered from sensorineural hearing loss, one had developmental delay and one person had right hemiplegia.

Laboratory data and blood gas analysis

There was no difference between survival and non-survival groups in complete blood count. The white blood cell count (10,516/μL vs. 12,767/μL, $p = 0.49$), hematocrit (30.2% vs. 33.53%, $p = 0.12$) and platelet count ($108*10^3$/μL vs. $130*10^3$/μL, $p = 0.42$) all revealed no statistical significance (Table 2). Other biochemistry results also showed no obvious impact.

In the survival group, blood gas showed less acidosis (7.33 vs. 7.21, $p = 0.008$) and less CO2 retention (41.57 mmHg vs. 56.68 mmHg, $p = 0.026$) compared with the non-survival group. After ECMO support for 24 h, there was no statistical difference between these two groups.

For parameters which were significant in univariate analysis, the receiver operating characteristic curve analysis was applied to determine the best cut-off-point for multivariate analysis. Table 3 shows factors associated with mortality by subsequent multiple logistic regressions. Both $PaCO_2$ and GSC level reveal significance ($p = 0.031$ and 0.005, respectively).

SOFA scores

Table 4 shows the SOFA (sequential organ failure assessment) scores from initiation of ECMO to day 9 in our patients. Before day 7, significant difference ($p < 0.05$) was found between survivors and nonsurvivors but there was no statistical significance after 1 week of ECMO support ($p = 0.1$ on day 8, $p = 0.145$ on day 9).

Table 1 Demographic data and clinical characteristics between survivors and nonsurvivors.

Characteristics	All	Survivors	Nonsurvivors	p Value
Number	55	17	38	
Mean age	7.2 ± 6.19	8.1 ± 6.28	6.8 ± 6.15	0.47
Neonate (<1 m/o)	4	1	3	
Children (1 m/o–12 y/o)	35	10	25	
Adolescent (>12 y/o)	16	6	10	
Male gender	29 (52.7%)	6 (35.3%)	23 (60.5%)	0.083
Initial hemodynamics				
GSC	8.77 ± 5.5	12.9 ± 3.97	7.03 ± 5.13	<0.001
SBP (mmHg)	95 ± 34.16	99.88 ± 28.25	93.03 ± 36.51	0.51
MAP (mmHg)	70.17 ± 23.05	75.54 ± 23.62	67.84 ± 22.73	0.27
CVP (cm)	12.65 ± 5.38	10.47 ± 5.46	13.71 ± 5.09	0.054
Post-ECMO 24hrs status				
SBP(mmHg)	99.7 ± 24.56	111.7 ± 22.7	93.55 ± 23.46	0.012
MAP (mmHg)	78.93 ± 18.98	87 ± 16.96	74.8 ± 18.87	0.03
CVP(cm)	10.82 ± 3.98	9 ± 2.92	11.76 ± 4.17	0.009
ECMO days (day)	9 (0–103)	14 (2–83)	7 (0–103)	0.09
Hospitalization stays (day)	36 (0–162)	65 (22–115)	21 (0–162)	0.005
VA mode	48 (87.3%)	14 (82.4%)	34 (89.5%)	0.664
Immunocompromised	25 (45.5%)	6 (35.3%)	19 (50%)	0.311
Neurologic sequelae	NA	6 (35.3%)	NA	NA
CPR before ECMO	17 (31%)	2 (12%)	15 (88%)	0.04

Glasgow coma scale denotes Glasgow coma scale, SBP: systolic blood pressure, MAP: mean arterial pressure, CVP: central venous pressure, ECMO: extracorporeal membrane oxygenation, VA: venoarterial, NA: non-applicable.
Data were expressed as number (%), mean ± SD or median (range).

Table 2 Laboratory data between survivors and nonsurvivors.

Characteristics	All	Survivors	Nonsurvivors	p Value
Number	55	17	38	
WBC (μL)	12,060 ± 10,577	10,516 ± 7746	12,767 ± 11,679	0.49
Hct (%)	32.5 ± 7.2	30.2 ± 9.1	33.53 ± 6.04	0.12
Plt (μL)	124 K ± 91 K	108 K ± 65 K	130 K ± 101 K	0.42
PT (s)	1.63 ± 0.74	1.26 ± 0.26	1.79 ± 0.83	0.003
Pre-ECMO ABG				
pH	7.24 ± 0.19	7.33 ± 0.09	7.21 ± 0.22	0.008
CO_2	52.2 ± 31.77	41.57 ± 11.7	56.68 ± 36.34	0.03
HCO_3^-	21.3 ± 9.19	21.38 ± 6.84	21.24 ± 10.1	0.96
BE	−5.3 ± 10	−3.81 ± 7.68	−5.87 ± 10.85	0.50
Post-ECMO 24hrs ABG				
pH	7.41 ± 0.12	7.41 ± 0.09	7.41 ± 0.13	0.96
CO_2	37.7 ± 11.54	36.87 ± 9.62	38.24 ± 12.53	0.70
HCO_3^-	23.8 ± 6.36	24.19 ± 4.54	23.63 ± 7.17	0.74
BE	0.06 ± 6.88	0.03 ± 4.83	0.08 ± 7.74	0.98

WBC: white blood cell count, Hct: hematocrit, Plt: platelet, PT: prothrombin time, ECMO: extracorporeal membrane oxygenation, ABG: arterial blood gas, BE: base excess. Data were expressed as mean ± SD.

Table 3 Multivariate analysis of factors associated with mortality.

	Odds ratio	95% confidence interval	p Value
Pre-ECMO value			
pH ≦ 7.2	0.774	0.054—11.098	0.85
$PaCO_2$ ≧ 56.9	35.97	1.375—940.98	0.031
GCS ≦ 9	31.787	2.872—351.763	0.005
Post-ECMO 24 h			
SOFA score ≦ 15	0.953	0.086—10.603	0.969
SBP ≦ 95 mmHg	0.793	0.02—31.472	0.902
MAP ≦ 82 mmHg	4.655	0.156—139.025	0.375
CVP ≦ 12.5 cm	0.125	0.007—2.151	0.152

SOFA: sequential organ failure assessment, ECMO: extracorporeal membrane oxygenation, GCS: Glasgow coma scale, SBP: systolic blood pressure, MAP: mean arterial pressure, CVP: central venous pressure.

Causal pathogens

Table 5 describes the pathogens isolated from our patients. For 25 immunocompromised patients, causal pathogens were found in 17 (68%) patients: 7 of them were due to bacteremia, 9 had preexisting virus infection and 1 patient had invasive fungal infection. Among 30 previously healthy patients, causal pathogens were found in 18 patients: 10 had ECMO support due to bacteremia (the most common strain was *Streptococcus pneumoniae*), 7 had preexisting virus infections including influenza (n = 4), adenovirus (n = 2), RSV (n = 1), and 1 patient had mixed virus and bacterial infections (secondary pneumococcal bacteremia after influenza infection).

Discussion

In Extracorporeal Life Support Organization (ELSO) Registry Report, the survival rate in pediatric patients received

Table 4 SOFA score.

Characteristics	All	Survivors	Nonsurvivors	p Value
Number	55	17	38	
SOFA score day 0	12.97 ± 4.06	11.14 ± 3.68	14.04 ± 3.96	0.032
SOFA score day 1	16.74 ± 4.48	14.12 ± 4.21	18.13 ± 4.02	0.003
SOFA score day 2	16.72 ± 4.6	14.31 ± 3.77	18.39 ± 4.44	0.005
SOFA score day 3	15.73 ± 4.95	13.40 ± 4.12	17.32 ± 4.91	0.016
SOFA score day 4	16.35 ± 5.47	12.67 ± 4.48	18.68 ± 4.79	0.002
SOFA score day 5	15.27 ± 5.64	12.00 ± 4.37	17.44 ± 5.41	0.007
SOFA score day 6	15.53 ± 5.91	11.55 ± 4.46	17.84 ± 5.48	0.003
SOFA score day 7	15.93 ± 6.4	12.18 ± 5.23	18.50 ± 5.97	0.009
SOFA score day 8	14.53 ± 5.65	12.50 ± 5.54	16.78 ± 5.14	0.100
SOFA score day 9	10.74 ± 5.08	9.27 ± 4.69	12.75 ± 5.18	0.145

SOFA: sequential organ failure assessment. Data were expressed as mean ± SD.

Table 5 Casual Pathogens in immunocompromised patients and previously healthy patients.

	Immunocompromised (N = 25)	N	Previously healthy (N = 30)	N
Pathogens		17		19
Gram positive	*Staphylococcus aureus*	1	*Streptococcus pneumoniae*	4
	Staphylococcus haemolyticus	1	*Group A Streptococcus*	2
			Group B Streptococcus	1
			Staphylococcus aureus	1
			Listeria monocytogenes	1
Gram negative	*Stenotrophomonas maltophiliae*	2	*Pseudomonas aeroginosa*	1
	Escherichia coli	2	*Escherichia coli*	1
	Klebsiella pneumoniae	1		
Virus	CMV	3	Influenza A	3
	RSV	2	Influenza B	2
	Influenza A	1	Adenovirus	2
	Influenza B	1	RSV	1
	Parainfluenza-3	1		
	EBV	1		
Antigen test	Aspergillus	1		

CMV: cytomegalovirus, RSV: respiratory syncytial virus, EBV: Epstein—Barr virus.

ECMO support was around 60—70% in these years.[10] From the Pediatric Health Information System (PHIS) database in the US, for the septic children, overall survival rate after ECMO use was about 42—52.2%.[11] The proportion varied among small studied or single institution experience (47—74%).[12—14]

The survival rates are also different in neonates, children and adults. Initially, neonates with refractory septic shock had benefits on ECMO support. Higher survival rates, which ranged from 64% to 80%,[10,15,16] were reported. In recent years, the mortality rate showed no significant change. The possible explanation is the improvement of neonatal respiratory care, which may be attributed to introduction of gentle ventilation, inhaled nitric oxide and high frequency oscillatory ventilator. Fewer neonates will progress to cardiopulmonary failure, resulting from septic shock or persistent pulmonary hypertension of newborn (PPHN) secondary to sepsis.[10] Hence, neonates who needed ECMO support accounted for only small numbers in our hospital and the mortality rate was high due to disease severity. As for children elder than 30 days old, the overall survival rate was around 55%.[17—20] The reason is unclear now. The disease diversity in this age group varies. There are no randomized control trials or disease-matched studies to guide the clinical indication for ECMO use in this population. In our institution, immunocompromised hosts (such as immunodeficiency, solid organ transplantation or malignancy) consisted of nearly half of cases (45.5%). The mortality rate is supposed to be higher than previously healthy patients. However, compared with adult data (mortality rate ranging from 63% to 71%) with propensity score matching, the mortality rate is still lower in the pediatric group.[21]

Certainly, comorbidity and pre-existing diseases make an impact on the survival rate. Blood gas analysis before ECMO use also predicts outcome. In our patients, nonsurvivors had lower initial pH compared with survivors. According to Zabrocki and Stewart,[22,23] uncorrectable acidosis was an independent predictor of mortality. In Boston Children's Hospital's experience, Mehta and his colleagues also found that using pH 7.2 or lower as a cutoff for the pre-ECMO blood gas value allowed identification of outcome with a sensitivity of 84%, specificity of 76%, and an overall outcome prediction of 79%.[24] Besides, pH lower than 7.2 also indicated poor neurologic outcomes or CNS complications.[25] Usually, lower pH is associated with persistent CO_2 retention. After multiple logistic regression analysis, elevation of CO_2 was an independent risk factor of mortality in our patients, too. It may be explained that compromised respiratory status was the leading presentation before ECMO use. To summarize, there are dysregulated host responses in septic patients. Excess proinflammatory cytokines, such as TNFα and IL-6,[26] will lead to hypotension, increased endothelial permeability and serial reactions in septic shock. Low pH is the result of decompensated and prolonged hypoperfusion. It also implied severe sepsis and low- or no-flow status in central nervous system. Therefore, poor consciousness level or no recovery of hemodynamics within one day was more likely to occur in nonsurvivors (Table 1). As a consequence, death, brain infarction or other complications developed.

There are many other factors or parameters reported for outcome prediction. However, the result of sepsis is multiple organ failure. These parameters imply different degree of damage to end organs. For systemic evaluations of patients' outcomes in ICU, some scoring systems had been developed to access disease severity. Commonly used models in children include pediatric risk of mortality (PRISM) III, Pediatric Logistic Organ Dysfunction (PELOD) scoring system, pediatric Index of Mortality2 (PIM2) and sequential organ failure assessment (SOFA) score. The sequential organ failure assessment (SOFA) score has been suggested as the initial evaluation tool for infection or sepsis.[27] In pediatric patients, SOFA score is also a useful tool to predict outcome and disease severity in critical care.[28] For a predictive indicator, it has higher sensitivity (96%) and specificity (96%) after 72 h ICU care compared with PELOD.[29] For immunocompromised hosts such as

pediatric oncology patients, the sequential monitoring SOFA score also correlated closely with outcome.[30] Our study demonstrated that SOFA score could be applied to as long as 1 week. To the best of our knowledge, it is the first single center study to evaluate the validity of scoring system in pediatric ECMO use.

Successful treatment of bacterial or fungal sepsis in children with ECMO support had been previously reported.[31–33] Before 1990, gram-negative organisms were the major cause of sepsis. Since then, there are more invasive procedures and hospital-acquired infections, gram-positive organisms and fungal infections have become the emerging pathogens in adult sepsis.[34,35] In this population, virus related sepsis or ICU admission had seldom been discussed.[36,37] Unlike adults, viral infections play an important role in pediatric sepsis. It composed 30% of the identified microorganisms in our patients with ECMO support during septic shock whether immunocompromised or not. Some nationwide studies demonstrated the same findings, which range from 12.7% to 21%.[1,3] In the post-vaccination era, the proportion of bacterial infections decreased. Viral infections with poor vaccine protection emerge.[3] In our study, we observed the similar trend. In children, the respiratory tract is still the most common route for community acquired infections. Respiratory syncytial virus (RSV), influenza or adenovirus will cause respiratory distress which may lead to ARDS or multiple organ failure. ECMO is the last resort for these patients.[38,39]

There are some limitations in this study. First, it is a single center study. Second, the disease diversity varied in our patients. The results of predictors and scoring systems should be interpreted case by case. Further study should aim to specific disease entity with much more cases, like enterovirus infections or acute myocarditis, for more precisely clinical guide and management. Moreover, we didn't provide the proportion of complications during ECMO support. Because nearly one quarter of patients were transferred from other hospitals, previous status and the effect of transportation may influence the interpretations.

Conclusion

Septic shock is no longer a contraindication to ECMO. In our experience, patients who had poor initial consciousness level, metabolic acidosis or CO_2 retention, no recovery of hemodynamics within one day and higher SOFA scores tended to be fatal. Initial GCS and CO_2 are the two independent predictive factors.

Conflicts of interest

All the authors have no conflicts of interest to disclose.

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