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Acquired infection during neonatal and pediatric extracorporeal membrane oxygenation

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Katherine Cashen,[1] Ron Reeder,[2] Heidi J. Dalton,[3] Robert A. Berg,[4] Thomas P. Shanley,[5] Christopher J. L. Newth,[6] Murray M. Pollack,[7] David Wessel,[7] Joseph Carcillo,[8] Rick Harrison,[9] J. Michael Dean,[2] Robert Tamburro[10] and Kathleen L Meert[1]

Abstract

Introduction: Our objectives are to (1) describe the pathogens, site, timing and risk factors for acquired infection during neonatal and pediatric ECMO and (2) explore the association between acquired infection and mortality.

Methods: Secondary analysis of prospective data collected by the Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. Clinical factors associated with acquired infection were assessed with multivariable Cox regression. Factors associated with mortality were assessed with logistic regression.

Results: Of 481 patients, 247 (51.3%) were neonates and 400 (83.2%) received venoarterial ECMO. Eighty (16.6%) patients acquired one or more infections during ECMO; 60 (12.5%) patients had bacterial, 21 (4.4%) had fungal and 11 (2.3%) had viral infections. The site of infection included respiratory for 53 (11.0%) patients, bloodstream for 21 (4.4%), urine for 20 (4.2%) and other for 7 (1.5%). *Candida* species were most common. Median time to infection was 5.2 days (IQR 2.3, 9.6). On multivariable analysis, a greater number of procedures for ECMO cannula placement was independently associated with increased risk of acquired infection during ECMO (Hazard Ratio 2.13 (95% CI 1.22, 3.72), $p<0.01$) and receiving ECMO in a neonatal ICU compared to a pediatric or cardiac ICU was associated with decreased risk (Hazard Ratio pediatric ICU 4.25 (95% CI 2.20, 8.20), cardiac ICU 2.91 (95% CI 1.48, 5.71), neonatal ICU as reference, $p<0.001$). Acquired infection was not independently associated with mortality.

Conclusion: ECMO procedures and location may contribute to acquired infection risk; however, acquired infection did not predict mortality in this study.

Keywords

extracorporeal membrane oxygenation; infection; pediatrics; neonatal; mortality

[1]Division of Critical Care, Department of Pediatrics, Children's Hospital of Michigan/Wayne State University, Detroit, MI, USA
[2]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA
[3]Department of Pediatrics, Inova Fairfax Hospital, Falls Church, VA, USA
[4]Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[5]Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University Feinberg School of Medicine; Chicago, IL, USA
[6]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA
[7]Department of Pediatrics, Children's National Health System, Washington, DC, USA
[8]Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
[9]Department of Pediatrics, Mattel Children's Hospital UCLA, Los Angeles, CA, USA
[10]Trauma and Critical Illness Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

Corresponding author:
Kathleen L. Meert, Division of Pediatric Critical Care Medicine, Children's Hospital of Michigan, 3901 Beaubien, Detroit, MI 48201, USA.
Email: kmeert@med.wayne.edu

Introduction

Extracorporeal membrane oxygenation (ECMO) is an invasive treatment modality for patients with respiratory and cardiac failure refractory to maximal medical therapy. Patients treated with ECMO are at risk for acquired infection due to underlying patient characteristics and the extracorporeal circuit itself.[1–6] A study based on the Extracorporeal Life Support Organization (ELSO) registry reported an 11.7% prevalence of infection, with a rate of 15.4 infections per 1000 ECMO days.[1] Rates for pediatric and neonatal patients were 20.8 and 10.1 infections per 1,000 ECMO days, respectively. The most common organism identified was coagulase-negative staphylococcus followed by *Candida* and *Pseudomonas* species. A single-center, retrospective, Canadian study found an even higher rate of infection than the ELSO report; the authors speculated that under-reporting of presumed contaminants occurs in the ELSO registry.[7] Other single-center studies have found increased days of mechanical ventilation and increased mortality among ECMO patients with acquired infections.[6,8,9]

The high prevalence of infections on ECMO is multifactorial. Most patients on ECMO have several life-sustaining indwelling catheters. In cardiac patients, an open chest, transthoracic cannulation and increased bleeding and clot formation all contribute to an increased infection risk.[10] Other identified risk factors include the number of invasive procedures performed on ECMO.[11] Some centers support daily surveillance blood cultures or antibiotic prophylaxis although no studies have demonstrated improved outcomes with these approaches.[6,7,11–13] Most reports of acquired infection during ECMO are retrospective, single-center audits or are based on ELSO registry data.[1–11] Prospective, multicenter data are needed to gain more accurate and generalizable knowledge. The objectives of this project are to (1) describe the pathogens, site, timing and risk factors for acquired infection during neonatal and pediatric ECMO in the context of a prospective, multicenter study and (2) explore the association between acquired infection and mortality.

Methods

Design and Setting

The study was a secondary analysis of the Bleeding and Thrombosis during ECMO (BATE) study[14] that investigated the incidence of bleeding and thrombosis in neonatal and pediatric ECMO patients. The BATE study was conducted at eight children's hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. Trained research coordinators collected data prospectively from all patients treated with ECMO via direct observation, discussion with bedside clinicians and medical record review. The Institutional Review Boards for each hospital and the Data Coordinating Center at the University of Utah approved the study with waiver of parental permission.

Study Population

The BATE study included 514 neonatal (≤30 days of age) and pediatric patients receiving ECMO in a neonatal, pediatric or cardiac intensive care unit (ICU).[14] In this secondary analysis, only patients with at least 24 hours of ECMO were included (n=481) to allow sufficient time for infection acquired during ECMO to develop. For patients who received ECMO more than once, only the initial ECMO course was included in the analysis.

Outcomes

Outcomes included documented infection acquired during ECMO; pathogens; site of infection; time to infection; duration of ECMO, ICU and hospital stay; and mortality at hospital discharge. Acquired infection during ECMO was defined as a documented infection (positive bacterial, fungal or viral culture or polymerase chain reaction (PCR) test) after at least 24 hours of ECMO that was not reported prior to or during the first 24 hours of ECMO. If three or more organisms were identified in a culture, the culture was considered a contaminant and not an infection. Serial cultures or PCR tests demonstrating the same organism were considered as one infection. Site of infection was categorized as bloodstream, respiratory, urine or other. Time to infection was the number of days between ECMO initiation and the diagnosis of an acquired infection. If the day of diagnosis was missing from the dataset (n=10), time to infection was based on the following times, as described in culture reports, in order of preference and depending on availability: (1) date of sample collection, (2) date of initial growth or (3) date of final culture report.

Clinical Data

Data included demographics; history of prematurity; acute and chronic diagnoses; presence of immune compromise; cardiopulmonary bypass (CPB) in the 24 hours prior to ECMO initiation; Vasoactive Inotrope Score (VIS)[15,16] at the time of ECMO initiation; documented or suspected infection prior to or during the first 24 hours of ECMO; location of ECMO; indication for ECMO; mode of ECMO; cannulation site; method of ECMO

priming; configuration of the circuit bridge; number of procedures for ECMO cannula placement; patient-related thrombotic events during ECMO; circuit thrombosis during ECMO; daily volume of red cell transfusion during ECMO; laboratory blood test values recorded closest to 7 am on each ECMO day; and clinical site.

Demographics included age at ECMO initiation, sex, race and ethnicity. Prematurity was defined as <37 weeks gestational age at birth and collected for neonates only. Immune compromise included a diagnosis of cancer, hematologic disorders, transplant or Human Immunodeficiency Virus. The vasoactive inotropic score (VIS)[15,16] was calculated from the hourly dose of dopamine, dobutamine, epinephrine, milrinone, vasopressin and norepinephrine administered at the time of ECMO initiation. VIS scores were categorized as none (VIS=0), low (VIS >0 and <20) and high (VIS $\geq$20). Documented infection prior to or during the first 24 hours of ECMO was a positive bacterial, fungal or viral culture or PCR test for which the patient was being treated at the time of ECMO initiation or which was diagnosed during the first 24 hours of ECMO. Suspected infection prior to or during the first 24 hours of ECMO was an unproven infection treated with antibiotics, antifungals or antiviral agents at the time of ECMO initiation or during the first 24 hours of ECMO. Location of ECMO was neonatal, pediatric or cardiac ICU. Indication for ECMO was categorized as respiratory, cardiac or extracorporeal cardiopulmonary resuscitation (ECPR). Mode of ECMO was venoarterial (VA) or venovenous (VV). VV ECMO that was converted to VA was categorized as VA ECMO. Cannulation site was categorized as central or other site. Method of ECMO priming was categorized as blood or non-blood (clear) prime. Configuration of the circuit bridge was categorized as in-line with stopcocks, in-line, but clamped or not in-line. Number of procedures for ECMO cannula placement was the number of such procedures on each ECMO day and within the preceding 3 days. If two or more cannulas were placed at the same time, it was considered one procedure. Patient-related thrombotic events included intracranial infarction, limb ischemia, pulmonary embolus, intra-cardiac thrombus, aorto-pulmonary shunt thrombus or other sites of thrombosis. Circuit thrombosis was thrombosis that required replacement of a circuit component. Laboratory blood test values included platelet count, prothrombin time, partial thromboplastin time (PTT), international normalized ratio, fibrinogen, lactate, total bilirubin, lactate dehydrogenase and leukocyte count.

Statistical Analysis

Data were summarized using counts and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. The association of pre-ECMO and daily variables with acquired infection was assessed with Cox regression. Hazard ratios and the associated 95% confidence intervals are presented. Reported p-values are based on a null hypothesis of no effect against a two-sided alternative. Missing laboratory values were imputed, when possible, by carrying forward the last observation. Rates of missingness for lab values are based on post-imputation data. Imputation reduced the rate of missingness by no more than 12 percentage points for any lab value and did not substantively change the direction, magnitude, significance or interpretation of the modeled effects. Daily assessments were modeled as time-varying predictors. Variables associated with acquired infection ($p<0.10$) in univariable analysis with no more than 10% missing values were considered as potential predictors in multivariable analysis. The predictors for the final multivariable Cox model were chosen using bi-directional stepwise selection on the potential predictors with a significance criterion of $p<0.05$ to enter and stay in the model. No variables were forced into the multivariable model of acquired infection. Cox regression accounts for duration of ECMO naturally by assigning greater cumulative risk in the presence of longer exposure. Therefore, duration of ECMO was not explicitly included in models of acquired infection. The number of subjects with each acquired pathogen was presented as counts. An analogous strategy was used to build a multivariable model of in-hospital mortality. Mortality was modeled with logistic regression and acquired infection variables were forced into the multivariable model as the primary predictors of interest. Duration of ECMO was also forced into the model to ensure that relationships between infection and mortality are not confounded with duration of ECMO. Analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

Results

Of 481 ECMO patients included, 44 (9.1%) were preterm neonates, 203 (42.2%) full-term neonates, and 234 (48.6%) were pediatric patients (Table 1). Two hundred and eighty-three (58.8%) were male and 232 (48.2%) were white. One hundred and forty-eight (30.8%) had a suspected infection and 98 (20.4%) had a documented infection prior to or during the first 24 hours of ECMO. Two hundred and thirty (47.8%) received ECMO in a cardiac ICU, 151 (31.4%) in a neonatal ICU and 100 (20.8%) in a pediatric ICU. VA ECMO was used for 400 (83.2%) patients and baseline VIS was categorized as high in 186 (38.7%). The primary indication for ECMO was respiratory for 229 (47.6%), cardiac for 184 (38.3%) and ECPR for 68 (14.1%). Forty-one (8.5%) patients were immune compromised (Supplementary Table 1).

Eighty (16.6%) patients acquired one or more infections during ECMO (Table 2). Sixty (12.5%) patients

Table 1. Description of Cohort.

	Overall (N = 481)[1]
Age	
Pre-term neonate	44 (9.1%)
Full-term neonate	203 (42.2%)
Infant	114 (23.7%)
Child	77 (16.0%)
Adolescent	43 (8.9%)
Male	283 (58.8%)
Race	
White	232 (48.2%)
Black or African American	87 (18.1%)
Other	26 (5.4%)
Unknown/Not Reported	136 (28.3%)
Hispanic or Latino	82 (17.0%)
Infection prior to or during the first 24 hours of ECMO	
None	235 (48.9%)
Suspected	148 (30.8%)
Bacterial	49 (10.2%)
Viral	32 (6.7%)
Fungal	6 (1.2%)
Multiple	11 (2.3%)
Location of ECMO care	
PICU	100 (20.8%)
NICU	151 (31.4%)
CICU	230 (47.8%)
Mode of ECMO	
VA	400 (83.2%)
VV	81 (16.8%)
Baseline Vasoactive Inotropic Score[2]	
None	140 (29.1%)
Low	155 (32.2%)
High	186 (38.7%)
Primary ECMO indication	
Respiratory	229 (47.6%)
Cardiac	184 (38.3%)
ECPR	68 (14.1%)

ECMO: extracorporeal membrane oxygenation; PICU: pediatric intensive care unit; NICU: neonatal intensive care unit; CICU: cardiac intensive care unit; VA: venoarterial; VV: venovenous; ECPR: extracorporeal cardiopulmonary resuscitation.
[1]Data are expressed as counts and column percentages.
[2]None is Vasoactive Inotropic Score (VIS) =0, low is VIS >0 and <20 and high is VIS ≥20.

Table 2. Complications and Outcomes.

	Overall (N = 481)
Acquired infection[1]	80 (16.6%)
Pathogen type[1]	
Bacterial	60 (12.5%)
Fungal	21 (4.4%)
Viral	11 (2.3%)
Site of infection[1]	
Blood	21 (4.4%)
Respiratory	53 (11.0%)
Urine	20 (4.2%)
Other	7 (1.5%)
Time to infection (days)[2]	
Overall	5.2 [2.3, 9.6]
Blood	5.8 [4.0, 9.7]
Respiratory	5.7 [2.5, 10.9]
Urine	9.5 [2.5, 13.5]
Other	6.2 [3.9, 7.8]
Duration of ECMO (days)[2]	5.4 [3.0, 9.8]
Length of ICU Stay (days)[2]	29.2 [15.3, 53.4]
Length of Hospital Stay (days)[2]	37.6 [17.5, 69.9]
In-hospital mortality[1]	211 (43.9%)

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.
[1]Data are expressed as counts and column percentages.
[2]Data are expressed as medians and interquartile ranges.

had bacterial, 21 (4.4%) had fungal and 11 (2.3%) had viral infections. The site of infection included respiratory for 53 (11.0%) patients, bloodstream for 21 (4.4%), urine for 20 (4.2%) and other site for 7 (1.5%). The median time to infection was 5.2 days (IQR 2.3, 9.6) from ECMO initiation. Specific bacteria, fungi and viruses identified by culture or PCR are listed in Supplementary Table 2. The most commonly reported organisms were *Candida albicans, Staphylococcus aureus, Enterobacter cloacae, Pseudomonas aeruginosa, Escherichia coli and Staphylococcus epidermidis*. For the entire cohort, the median duration of ECMO was 5.4 days (IQR 3.0, 9.8), ICU stay was 29.2 days (IQR 15.3, 53.4) and hospital stay was 37.6 days (IQR 17.5, 69.9). Two hundred and eleven (43.9%) patients died during the hospitalization.

Univariable Cox models evaluating associations between clinical factors and acquired infection during ECMO are depicted in Table 3. Associated factors included age, diagnoses, primary indication for ECMO, number of procedures for ECMO cannula placement, location of ECMO, fibrinogen concentration and leukocyte count.

On multivariable analysis, the clinical factors independently associated with an increased risk of acquired infection during ECMO included a greater number of procedures for ECMO cannula placement (Table 4). Clinical factors independently associated with decreased risk of acquired infection included receiving ECMO in a neonatal ICU.

Univariable logistic models evaluating associations between clinical factors and in-hospital mortality are depicted in Table 5. Associated factors included age, diagnoses, CPB in the 24 hours prior to ECMO, primary indication for ECMO, mode of ECMO, location of ECMO, bloodstream infection during ECMO and average daily red cell volume transfused.

Table 3. Univariable Cox Models of Acquired Infection.

	Acquired infection		
	Hazard ratio[1] (95% CI)	p-value	% Missing[2]
Prior patient-related thrombotic event	1.45 (0.66, 3.18)	0.354	0%
Circuit clot or change-out	0.99 (0.43, 2.30)	0.985	0%
Central cannulation	1.62 (0.92, 2.86)	0.095	0%
Number of ECMO cannulation procedures	2.17 (1.23, 3.80)	0.007	0%
Platelets (10^3/microliter)	1.00 (1.00, 1.01)	0.214	0%
Prothrombin time (seconds)	0.98 (0.90, 1.06)	0.544	10%
Partial thromboplastin time (seconds)	0.99 (0.99, 1.00)	0.115	8%
International normalized ratio	0.92 (0.48, 1.74)	0.788	10%
Fibrinogen (10 mg/dL)	1.02 (1.00, 1.04)	0.018	2%
Lactate (mmol/L)	1.03 (0.96, 1.11)	0.383	4%
Total bilirubin (mg/dL)	0.96 (0.91, 1.02)	0.161	21%
Lactate dehydrogenase (IU/L)	1.00 (1.00, 1.00)	0.344	85%
Leukocytes (10^3/microliter)	1.04 (1.01, 1.07)	0.014	0%
Clinical site		0.294	0%
A	1.86 (0.91, 3.80)		
B	Reference		
C	1.47 (0.53, 4.08)		
D	0.60 (0.22, 1.65)		
E	1.26 (0.51, 3.07)		
F	0.54 (0.16, 1.89)		
G	1.39 (0.46, 4.18)		
H	1.49 (0.73, 3.02)		
Age		0.002	0%
Pre-term neonate	0.49 (0.15, 1.64)		
Full-term neonate	Reference		
Infant	2.90 (1.58, 5.33)		
Child	2.14 (1.09, 4.22)		
Adolescent	1.83 (0.85, 3.93)		
Sex		0.210	0%
Male	Reference		
Female	1.35 (0.84, 2.16)		
Race		0.202	34%
Black or African American	0.57 (0.27, 1.23)		
White	Reference		
Other	0.41 (0.10, 1.71)		
Ethnicity		0.952	0%
Hispanic or Latino	1.04 (0.55, 1.98)		
Not Hispanic or Latino	Reference		
Unknown or Not Reported	1.10 (0.61, 1.98)		
Immunocompromised	1.44 (0.69, 3.02)	0.330	0%
Acute diagnoses			
Airway abnormality	1.11 (0.27, 4.54)	0.884	0%
Cardiac Arrest	2.35 (1.11, 4.95)	0.025	0%
Cardiovascular disease (acquired)	1.38 (0.70, 2.70)	0.352	0%
Cardiovascular disease (arrhythmia)	0.60 (0.08, 4.37)	0.618	0%
Cardiovascular disease (congenital)	1.39 (0.82, 2.37)	0.221	0%
Hypoxic/anoxic injury	0.57 (0.08, 4.09)	0.572	0%
Gastrointestinal disorder	1.89 (0.76, 4.70)	0.171	0%
Pertussis or Sepsis	1.41 (0.80, 2.46)	0.233	0%
Pneumonia or bronchiolitis	2.15 (1.06, 4.34)	0.033	0%
Shock (non-septic)	-	0.985	0%
Respiratory distress/failure	1.66 (1.04, 2.67)	0.035	0%

(Continued)

Table 3. (Continued)

	Acquired infection		
	Hazard ratio[1] (95% CI)	p-value	% Missing[2]
Neurologic condition	1.10 (0.27, 4.51)	0.892	0%
Meconium aspiration syndrome	0.24 (0.06, 0.98)	0.047	0%
Congenital diaphragmatic hernia	0.32 (0.14, 0.75)	0.009	0%
Persistent pulmonary hypertension of the newborn	0.42 (0.19, 0.92)	0.029	0%
Chronic diagnoses			
Chronic lung disease	2.03 (0.88, 4.71)	0.098	0%
Congenital anomaly or chromosomal defect	0.42 (0.22, 0.78)	0.006	0%
Neurologic condition	0.64 (0.20, 2.03)	0.444	0%
Cardiovascular disease (congenital)	0.84 (0.43, 1.65)	0.620	0%
Infection prior to ECMO		0.053	0%
None	Reference		
Suspected	0.80 (0.45, 1.42)		
Documented	1.71 (0.97, 3.03)		
Cardiopulmonary bypass in the 24 hours prior to ECMO initiation	1.42 (0.80, 2.53)	0.234	0%
Baseline Vasoactive Inotropic Score[3]		0.514	0%
None	Reference		
Low	0.78 (0.44, 1.37)		
High	0.72 (0.40, 1.30)		
Primary ECMO indication		0.037	0%
Respiratory	Reference		
Cardiac	1.76 (1.02, 3.03)		
ECPR	2.21 (1.08, 4.51)		
Location of ECMO care		<0.001	0%
PICU	4.22 (2.19, 8.15)		
NICU	Reference		
CICU	2.98 (1.52, 5.83)		
Mode of ECMO		0.051	0%
VA	Reference		
VV	1.68 (1.00, 2.84)		
Configuration of circuit bridge		0.991	0%
In-line with stopcocks	Reference		
In-line, but clamped	1.00 (0.58, 1.72)		
Not in-line	1.04 (0.53, 2.04)		
Method for priming the circuit		0.615	0%
Non-blood (clear)	1.27 (0.50, 3.18)		
Blood product	Reference		
Average daily red cell transfusion volume (10 mL/kg)	1.00 (0.91, 1.10)	0.945	0%

ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; PICU: pediatric intensive care unit; NICU: neonatal intensive care unit; CICU: cardiac intensive care unit; VA: venoarterial; VV: venovenous.
[1]Results are based on univariable model(s).
[2]The percentage of missing values is calculated out of the records with a non-missing value for timing and event type variables associated with the particular outcome.
[3]None is Vasoactive Inotropic Score (VIS) =0, low is VIS >0 and <20 and high is VIS ≥20.

On multivariable analysis, acquired bloodstream, respiratory, urinary or other sites of infection were not independently associated with mortality (Table 6). Clinical factors independently associated with increased mortality included congenital diaphragmatic hernia, immune compromised status; cardiac failure or ECPR as primary indication for ECMO; increased average daily red cell volume transfused; and increased duration of ECMO. Clinical factors independently associated with decreased mortality included a diagnosis of meconium aspiration syndrome.

Discussion

Our findings demonstrate a high rate (16.6%) of acquired infection during neonatal and pediatric

Table 4. Multivariable Model of Acquired Infection.

	Acquired infection	
	Hazard ratio[1] (95% CI)	p-value
Location of ECMO care		<0.001
PICU	4.25 (2.20, 8.20)	
NICU	Reference	
CICU	2.91 (1.48, 5.71)	
Number of ECMO cannulation procedures	2.13 (1.22, 3.72)	0.008

ECMO: extracorporeal membrane oxygenation; PICU: pediatric intensive care unit; NICU: neonatal intensive care unit; CICU: cardiac intensive care unit.
[1]Results are based on a multivariable model(s), adjusting for each of the predictors in this table.

ECMO. Our observed rate is consistent with other reports of acquired infection in these age groups (3-16%) and lower than rates reported during ECMO in adults (21%).[1,11,17] Our findings provide important information about the causative organisms, sites, timing, risk factors and outcomes of acquired infection during neonatal and pediatric ECMO in the current era.

The most common organisms identified in our study were *Candida albicans, Staphylococcus aureus, Enterobacter cloacae, Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus epidermidis.* Prior reports suggest *Candida* species are the most common pathogens in pediatric ECMO patients.[1,11] ECMO patients may be at high risk for invasive candidiasis due to the frequent use of broad spectrum antibiotics, steroids, invasive catheters and parenteral nutrition.[1,11]

Table 5. Univariable Logistic Models of In-hospital Mortality.

	In-hospital mortality (N = 481)		
	Odds ratio[1] (95% CI)	p-value	% Missing[2]
Duration of ECMO (days)	1.02 (0.99, 1.04)	0.134	0%
Bloodstream infection	2.67 (1.06, 6.74)	0.038	0%
Respiratory infection	1.16 (0.66, 2.06)	0.608	0%
Urine infection	1.05 (0.43, 2.58)	0.917	0%
Other site of infection	0.96 (0.21, 4.33)	0.957	0%
Clinical Site		0.679	0%
A	1.02 (0.54, 1.93)		
B	Reference		
C	0.85 (0.38, 1.88)		
D	1.31 (0.69, 2.47)		
E	0.78 (0.39, 1.58)		
F	1.40 (0.74, 2.62)		
G	1.33 (0.55, 3.20)		
H	1.40 (0.77, 2.55)		
Age		0.007	0%
Pre-term neonate	3.18 (1.62, 6.27)		
Full-term neonate	Reference		
Infant	1.82 (1.14, 2.90)		
Child	1.44 (0.84, 2.45)		
Adolescent	1.58 (0.81, 3.08)		
Sex		0.439	0%
Male	Reference		
Female	1.16 (0.80, 1.67)		
Race		0.775	28%
Black or African American	1.04 (0.63, 1.71)		
White	Reference		
Other	1.34 (0.60, 3.02)		
Ethnicity		0.970	0%
Hispanic or Latino	0.95 (0.58, 1.55)		
Not Hispanic or Latino	Reference		
Unknown or Not Reported	1.02 (0.63, 1.63)		
Immunocompromised	1.91 (1.00, 3.66)	0.051	0%
Acute diagnoses			
Airway abnormality	0.73 (0.21, 2.51)	0.613	0%

(Continued)

Table 5. (Continued)

	In-hospital mortality (N = 481)		
	Odds ratio[1] (95% CI)	p-value	% Missing[2]
Cardiac Arrest	1.53 (0.82, 2.87)	0.185	0%
Cardiovascular disease (acquired)	1.38 (0.81, 2.34)	0.236	0%
Cardiovascular disease (arrhythmia)	1.29 (0.50, 3.31)	0.594	0%
Cardiovascular disease (congenital)	1.65 (1.13, 2.40)	0.009	0%
Hypoxic/anoxic injury	0.52 (0.18, 1.51)	0.229	0%
Gastrointestinal disorder	1.75 (0.72, 4.23)	0.215	0%
Pertussis or Sepsis	0.81 (0.50, 1.30)	0.372	0%
Pneumonia or bronchiolitis	0.63 (0.26, 1.49)	0.290	0%
Shock (non-septic)	0.79 (0.26, 2.47)	0.691	0%
Respiratory distress/failure	1.08 (0.74, 1.57)	0.707	0%
Neurologic condition	0.38 (0.12, 1.19)	0.097	0%
Meconium aspiration syndrome	0.08 (0.02, 0.25)	<.001	0%
Congenital diaphragmatic hernia	2.09 (1.18, 3.71)	0.012	0%
Persistent pulmonary hypertension of the newborn	0.44 (0.27, 0.73)	0.001	0%
Chronic diagnoses			
Chronic lung disease	1.46 (0.55, 3.85)	0.445	0%
Congenital anomaly or chromosomal defect	1.63 (1.06, 2.49)	0.024	0%
Neurologic condition	0.74 (0.33, 1.65)	0.463	0%
Cardiovascular disease (congenital)	0.92 (0.58, 1.46)	0.727	0%
Infection prior to ECMO		0.067	0%
None	Reference		
Suspected	0.65 (0.43, 0.99)		
Documented	1.15 (0.69, 1.91)		
Cardiopulmonary bypass in the 24 hours prior to ECMO initiation	1.63 (1.09, 2.44)	0.017	0%
Baseline Vasoactive Inotropic Score[3]		0.282	0%
None	Reference		
Low	0.71 (0.45, 1.13)		
High	0.94 (0.61, 1.46)		
Primary ECMO indication		<.001	0%
Respiratory	Reference		
Cardiac	1.74 (1.17, 2.59)		
ECPR	3.48 (1.97, 6.14)		
Location of ECMO care		0.002	0%
PICU	1.46 (0.87, 2.47)		
NICU	Reference		
CICU	2.17 (1.41, 3.32)		
Mode of ECMO		0.005	0%
VA	Reference		
VV	0.48 (0.29, 0.80)		
Configuration of circuit bridge		0.226	0%
In-line with stopcocks	Reference		
In-line, but clamped	0.75 (0.48, 1.15)		
Not in-line	0.70 (0.42, 1.15)		
Method for priming the circuit		0.878	0%
Non-blood (clear)	1.07 (0.45, 2.53)		
Blood product	Reference		
Average daily red cell transfusion volume (10 mL/kg)	1.15 (1.07, 1.23)	<.001	1%

ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; PICU: pediatric intensive care unit; NICU: neonatal intensive care unit; CICU: cardiac intensive care unit; VA: venoarterial; VV: venovenous.

[1]Results are based on univariable model(s).

[2]The percentage of missing values is calculated out of the records with a non-missing value for the outcome of the associated model.

[3]None is Vasoactive Inotropic Score (VIS) =0, low is VIS >0 and <20 and high is VIS ≥20.

Table 6. Multivariable Logistic Model of In-hospital Mortality.

	In-hospital mortality (N = 481)	
	Odds ratio[1] (95% CI)	p-value
Infection		
Blood	1.86 (0.68, 5.12)	0.230
Respiratory	1.08 (0.56, 2.10)	0.818
Urine	0.82 (0.29, 2.30)	0.708
Other	0.72 (0.13, 4.00)	0.709
Duration of ECMO (weeks)	1.25 (1.02, 1.54)	0.035
Primary ECMO indication		0.001
Respiratory	Reference	
Cardiac	1.67 (1.00, 2.78)	
ECPR	3.46 (1.78, 6.72)	
Congenital diaphragmatic hernia	2.40 (1.21, 4.74)	0.012
Meconium aspiration syndrome	0.13 (0.04, 0.45)	0.001
Immunocompromised	2.71 (1.28, 5.74)	0.009
Average daily red cell transfusion volume (10 mL/kg)	1.15 (1.07, 1.24)	<0.001

ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation.
[1]Results are based on a multivariable model(s), adjusting for each of the predictors in this table.

Staphylococcus aureus and coagulase negative staphylococci were the most common causes of bloodstream infection in our study. Bloodstream infections from Gram positive bacteria have shown a decreasing trend over time, based on ELSO registry data;[1,11,17] however, coagulase-negative staphylococci have been the most frequent cause of infections reported during ECMO in neonates.[1] *Enterobacter* and *Pseudomonas* have also been frequently reported during ECMO, particularly in relation to ventilator-associated pneumonia.[5,11,18]

The most common site of acquired infection in our study was the respiratory tract, occurring in 11% of our cohort. Previous studies have reported respiratory tract infection in 1-5% of neonatal and pediatric ECMO patients.[4,6] Variability across institutions in the methods of obtaining and reporting respiratory cultures is problematic in multicenter observational studies[19] and may, partly, explain differences in reported prevalence rates. Bloodstream infection occurred in 4.4% of our cohort whereas previous reports suggested a prevalence of bloodstream infection in the neonatal and pediatric population of 6-18%.[11] Urinary tract infections occurred in 4.2% of our cohort. We found no prior multicenter pediatric reports detailing urinary tract infection during ECMO and adult comparisons are suboptimal.[11,18]

The timing of acquired infection during ECMO has not been well described in neonatal and pediatric patients. Until recently, the ELSO registry did not record timing or site of infection, limiting prior reports.[1] Acquired infection has been associated with longer ECMO duration,[1,2,4,8,10,13,20] but no multicenter reports have described the timing of acquired infection in the current era. One single-center study reported bloodstream infection occurring at a median of 16.2 days of ECMO in a retrospective neonatal cohort from 1989-1998.[9] In comparison, we found that acquired infection occurred at a median of 5.2 days and that the median ECMO duration was 5.4 days for our entire cohort. Unlike the previous neonatal study,[9] our cohort includes older patients and a shorter duration of ECMO, suggesting differences in patient population and associated diagnoses, as well as treatment era.

Proclivity to acquired infection during ECMO is multifactorial, with patient-related factors, invasive therapies and the effects of therapies on the patient's immune system all contributing.[21-23] On univariable analysis, pre-ECMO diagnoses of pneumonia/bronchiolitis, respiratory distress/failure or cardiac arrest and ECPR as the primary indication for ECMO were associated with increased acquired infection risk. During ECPR, ECMO is initiated rapidly in an emergent situation. Increased acquired infection risk with ECPR may be related to less sterile cannulation technique and preparation of the circuit, as well as impaired patient immune response after cardiac arrest.[24] Invasive procedures, such as placing additional cannulas during ECMO, increase infection risk, likely due to violation of the skin's protective barrier and increased contact of the bloodstream with external devices. The neonatal age group, location of care in a neonatal ICU and neonatal diagnoses of meconium aspiration syndrome, congenital diaphragmatic hernia and persistent pulmonary

hypertension of the newborn are inter-related factors associated with decreased infection risk. Laboratory values, such as blood leukocyte count and fibrinogen, were also associated with infection risk; these laboratory values may be markers of infection or the immune state rather than causative factors. On multivariable analysis, only the location of ECMO and the number of procedures for ECMO cannula placement were associated with acquired infection risk.

In our study, acquired infection during ECMO was not an independent risk factor for in-hospital mortality. This finding differs from previous reports[1-3,11,17] and may be related to the high number of respiratory tract infections in our cohort. Respiratory cultures are primarily obtained by aspirating the endotracheal tube in neonatal and pediatric ECMO patients. Although positive tracheal aspirate cultures meet our definition of documented infection, the clinical significance of these cultures is unclear.[19] To account for this, each site of infection was considered separately in multivariable modeling; however, possibly due to the small number of infections at each site, we did not find independent associations with mortality. Interestingly, immune compromised patients had increased risk of mortality, but did not have a statistically significant increased risk of acquired infection in this study.

Strengths of this study include the multicenter design, daily prospective collection of data from all neonatal and pediatric patients treated with ECMO during the study period and the collection of detailed culture reports and the site and timing of infections. Limitations include the lack of implementation of standardized ECMO protocols across all clinical sites. Thus, prophylactic use of antibiotics, frequency and timing of cultures, treatment of documented and suspected infections and other aspects of care were not uniform. Data on antibiotic use was not collected in the BATE study. Differentiation of true infection from contaminant was also not entirely possible; this may have contributed specifically to the increased frequency of respiratory tract infections since tracheal aspirates are typically not sterile. Although many variables were evaluated, potential unmeasured confounders could exist. Importantly, this is an observational study and the associations observed do not infer causation.

Conclusions

Neonatal and pediatric ECMO patients have a high rate of acquired infection. *Candida* species were most commonly identified. The respiratory tract was the most common site of infection, followed by bloodstream, urine and other sites. The number of procedures for ECMO cannula placement and the location of ECMO were important contributors to acquired infection risk. Acquired infection was not independently associated with mortality in this study. Implications for future practice include careful attention to aspects of care that may increase susceptibility to *Candida* species and avoidance of invasive procedures during ECMO, if at all possible. Clinicians should be aware that acquired infection during ECMO often occurs earlier than previously reported.

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ORCID iDs

Kathleen L Meert https://orcid.org/0000-0002-4903-3503
Katherine Cashen https://orcid.org/0000-0002-8854-5085

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