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ORIGINAL ARTICLE

Bloodstream infections in pediatric ECLS: usefulness of daily blood culture monitoring and predictive value of biological markers. The British Columbia experience

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Abstract
Introduction The incidence of bloodstream infection (BSI) in extracorporeal life support (ECLS) is reported between 0.9 and 19.5%. In January 2006, the Extracorporeal Life Support Organization (ELSO) reported an overall incidence of 8.78% distributed as follows: respiratory: 6.5% (neonatal), 20.8% (pediatric); cardiac: 8.2% (neonatal) and 12.6% (pediatric).
Method At BC Children's Hospital (BCCH) daily surveillance blood cultures (BC) are performed and antibiotic prophylaxis is not routinely recommended. Positive BC (BC+) were reviewed, including resistance profiles, collection time of BC+, time to positivity and mortality. White blood cell count, absolute neutrophile count, immature/total ratio, platelet count, fibrinogen and lactate were analyzed 48, 24 and 0 h prior to BSI. A univariate linear regression analysis was performed.
Results From 1999 to 2005, 89 patients underwent ECLS. After exclusion, 84 patients were reviewed. The attack rate was 22.6% (19 BSI) and 13.1% after exclusion of coagulase-negative staphylococci ($n = 8$). BSI patients were significantly longer on ECLS (157 h) compared to the no-BSI group (127 h, 95% CI: 106–148). Six BSI patients died on ECLS (35%; 4 congenital diaphragmatic hernias, 1 hypoplastic left heart syndrome and 1 after a tetralogy repair). BCCH survival on ECLS was 71 and 58% at discharge, which is comparable to previous reports. No patient died primarily because of BSI. No BSI predictor was identified, although lactate may show a decreasing trend before BSI ($P = 0.102$).
Conclusion Compared with ELSO, the studied BSI incidence was higher with a comparable mortality. We speculate that our BSI rate is explained by underreporting of "contaminants" in the literature, the use of broad-spectrum antibiotic prophylaxis and a higher yield with daily monitoring BC. We support daily surveillance blood cultures as an alternative to antibiotic prophylaxis in the management of patients on ECLS.

Keywords ECLS · ECMO · ELSO · Bloodstream infection · Sepsis · Pediatric

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Introduction

Bloodstream infection (BSI) is a known complication of extracorporeal life support (ECLS). In 2005, the Extracorporeal Life Support Organization (ELSO) reported an incidence of 8.8% culture proven infections in 29.993 neonatal and pediatric patients since recording [1]. Several reviews have reported incidences between 0.9 and 19.5% [2–6]. Diagnosing sepsis clinically is challenging in patients on ECLS. We follow the somewhat controversial practice to perform daily blood cultures in those patients. We here review our institutional experience and describe the incidence, mortality, time of BSI onset, pathogens and

evaluate possible predictive hematological and biochemical markers of BSI in patients on ECLS. We also review the current literature on the topic.

Methods

This study is a retrospective chart review of all neonatal and pediatric patients who underwent ECLS, categorized according to the ELSO definitions [1], between 1999 and 2005 at the British Columbia Children's Hospital (BCCH). The following data were recovered: age, gender, underlying diagnosis, total hours on ECLS, time of ECLS when positive blood culture (BC+) was collected, time to positivity, organisms recovered and antimicrobial use in the 24 h before and after BSI. Cultures were drawn from the ECLS central venous catheters, through a 3-way stopcock, on the pre-membranous side. As per local policy, after local desinfection with an alcohol solution and after disposing of the initially drawn 2 ml, the actual blood for the culture was taken. This access port is kept routinely closed with a 2 ml syringe filled with sterile NaCl 0.9%, which is routinely replaced with a fresh syringe after each sampling/manipulation. BSI was defined by 1 or more BC+ while on ECLS or within 24 h of decannulation. A subsequent BC+ with an identical pathogen and susceptibility pattern within 7 days was counted as 1 BSI. Blood culture contamination was suspected when low-level pathogen were identified beyond 72 h in a single set of blood culture. Clinical correlation was also undertaken to rule out the possibility of this being a true BSI.

The Bactec System (Becton Dickinson Diagnostics, Sparks, MD, USA) was used to incubate blood cultures. Our local protocol does not recommend routine endotracheal aspirates, urine cultures or skin/wound swabs. Survival was defined as survival to discharge or transfer. To evaluate the predictability of BSI, white blood cell count (WBC), absolute neutrophil count (ANC), immature/total neutrophil ratio (I/T), platelet count, fibrinogen and lactate levels were retrieved 48 and 24 h before and at the collection time of BC+. Daily monitoring aerobic and anaerobic blood cultures are performed while on ECLS. Prophylactic antibiotic coverage is not routinely used at our center. We did not discriminate between ECLS types.

We used descriptive statistics for the BCCH versus ELSO comparison (using a 95% confidence interval) and performed a univariate linear regression analysis to test each biological markers as predictors of BSI (SPSS 11.5, SPSS Inc., Chicago, IL, USA).

Results

In the 90 patients who underwent ECLS, we identified 33 BSI. We excluded patients as follows:

- One adult (>18 years)
- Four patients with 5 BSI before ECLS initiation (3 coagulase-negative staphylococci (CoNS), 2 *S. aureus*)
- One patient with 1 BC+ collected after decision to withdraw intensive care (*E. cloacae*). We identified 84 patients at risk for developing BSI.

From the remaining 27 BC+, we excluded 8 contaminants (defined as above): 4 *Propionibacterium acnes*, 1 *Micrococcus* spp., 1 *Enterobacter aerogenes*, 1 *Sphingomonas* spp. and 1 *Pseudomonas* spp.

The final analysis included 17 patients with 19 BSI (Table 1). The overall attack rate was 22.6% versus the ELSO average of 8.78% (Table 2). A total of 50% of patients had a BSI after 120 h on ECLS (range 15–480). We identified a peak in 2003 with 6 BSI in 5 patients out of 13 patients on ECLS. In 2004, the rate decreased to 4 BSI in 12 patients without any change of practice. While using the same ECLS treatment regimen, there was a maximum of 3 BSI/year in the years 1999–2002 and 2005.

By excluding all coagulase-negative staphylococci (CoNS, $n = 8$), the attack rate dropped to 13.1%. By excluding one-time CoNS isolates only ($n = 5$), the attack rate was 16.6%. Three patients had more than 1 BC+ for CoNS. Table 2 summarizes the BSI and compares these results (with and without CoNS) to the ELSO data.

The mean ECLS run times in patients without BSI (no-BSI) were significantly shorter (127 h; 95% CI: 106–148 h), compared to 157 h (95% CI: 105–208 h) in the BSI group (Table 2). The mean run times in the BSI group were not significantly longer than the ELSO average.

Out of 17 patients with bloodstream infections (BSI), 6 died (35%). These patients were: four neonates with congenital diaphragmatic hernias, one neonate with a hypoplastic left heart syndrome and one child after an attempted tetralogy of Fallot repair (Table 1). All deaths were attributed to the primary condition and not BSI.

Survival on ECLS at BCCH was 71% (60 of 84) and 58% (49 of 84) until discharge or transfer (Table 2). To evaluate the predictability of a BSI, we performed a univariate regression analysis and showed no significant trend 48 and 24 h prior to BSI using the following parameters: WBC ($P = 0.737$), ANC ($P = 0.626$), I/T ratio ($P = 0.792$), platelet count ($P = 0.827$), fibrinogen ($P = 0.605$) and lactate ($P = 0.102$).

Discussion

Our data present our experience with daily blood culture monitoring in providing early targeted therapy of BSI. This is an alternative to prophylactic broad-spectrum antibiotics, which is in use in many other centers.

Table 1 Details of the 17 patients with 19 bloodstream infections

Age	Sex	Cat.	Death	Diagnosis	ECLS run time (h)	BSI at h of ECLS	BC+ incubation time	Pathogens	>1 BC+	Antibiotics before BSI	Antibiotics after BSI
6 h	M	NR	Yes	CDH	179	101	48	*Acinetobacter*			Vanc/Cefot
19 h	M	NR	Yes	CDH	215	196	22	*B. fragilis*			Vanc/Cefot
						208	29	*C. albicans*			Ampho B
72 h	F	NR	Yes	CDH	286	301	13, 25	*S. viridans*	2	Vanc/Gent	Vanc/Cefot
127 h	M	NR	Yes	CDH	152	94	16	CoNS		Clox/Gent	Linez/Clox
						118	24	*S. aureus*		Clox/Gent	Linez/Clox
134 h	M	NC		Coarct, ASD, PDA	52	15	30	CoNS			Vanc
34 h	M	NC		TAPVR, PPHN	198	68	48	CoNS		Amp/Gent	Vanc/Cefot
166 h	M	NC	Yes	HLHS, Norwood	132	56	17	*Burkholderia cepacia*		Clox/Gent	Mero
3 months	M	PR		HMPV pneumonia/ BPD/influenza	227	223	8	*E. cloacae*		Vanc/Cefot	Mero
5 months	M	PR		RSV, BPD	227	125	17	*P. aeruginosa*			Cefot/Vanc/ Tobra
3 months	M	PR		Pneumonia	335	61	30, 28, 31, 34	CoNS	4	Cefur/Vanc	Cefo/Vanc
35 months	M	PR		ARDS	504	480	27	CoNS			Vanc/Clox
16 years	M	PC		Myocarditis	273	261	24, 30	CoNS	2	Vanc/Gent	Pip/Vanc
17 years	M	PC		Acute heart transplant rejection	133	81	22, 25	CoNS	2	Cefur	Cefur/Gent
6 months	M	PC		TOF, RVOT obstruction	129	120	11	*Acinetobacter*		Vanc/Cefot	Cefot/Gent
4 years	F	PC		Cardiomyopathy	302	112	20	CoNS			Vanc
7 months	M	PC	Yes	TOF	172	156	9	*Enterobacter*		Vanc	Vanc/Cefot/ Gent
6 months	F	PC		TOF, pulmonary hemorrhage	259	219	11	*E. faecalis*		Clox/Cefot/ Gent	Vanc/Cefot/ Gent

M Male, *F* female, *NR* neonatal respiratory, *NC* neonatal cardiac, *PR* pediatric respiratory, *PC* pediatric cardiac, *CDH* congenital diaphragmatic hernia, *Coarct* coarctation, *TAPVR* total anomalous pulmonary vein return, *PPHN* persistent pulmonary hypertension of the newborn, *TOF* tetralogy of Fallot, *PDA* persistent ductus arteriosus, *ASD* atrium septum defect, *RVOT* right ventricular ouflow tract obstruction, *HMPV* human meta-pneumovirus, *BPD* bronchopulmonary dysplasia, *ARDS* acute respiratory distress syndrome, *BSI at h of ECLS* collection time of BC+ on ECLS, *BC+ incubation time* incubation time of positive blood culture, *>1 BC+* more than 1 BC+, *CoNS* coagulase-negative staphylococci, *>1 BC+* number of BC+ if more than 1, *Amp* ampicillin, *Cefaz* cefazolin, *Cefot* cefotaxim, *Cefur* cefuroxim, *Clox* cloxacillin, *Gent* gentamicin, *Vanc* vancomycin, *Ampho B* amphotericin B, *Mero* meropenem

Table 2 BCCH versus ELSO comparison of attack rates, ECLS run times (with and without BSI) and overall survival on ECLS and at discharge/transfer

	BCCH patients	BSI		BSI-CoNS		ELSO BSI	ECLS mean run times (h)					Survival (%)			
							BCCH				ELSO (h)	On ECLS		To discharge/transfer	
		n	%	*n*	%	%	No BSI	95% CI	BSI	95% CI		BCCH	ELSO	BCCH	ELSO
NR	25	6	24	5	20	6.4	119	95–142	173	95–251	191.6	80	85	68	76
NC	17	3	17.6	1	5.9	8.2	155	94–217	47	15–78	145.7	40	58	40	38
PR	12	4	33.3	2	16.6	20.4	126	67–185	223	42–403	237.5	67	64	67	56
PC	30	6	20	3	10	12.6	104	83–125	159	103–214	157.2	68	59	68	43
Total	84	19	22.6	11	13.1	8.78	127	106–148	157	106–209	182.1	71	76	58	65

BCCH British Columbia Children's Hospital, *BSI* bloodstream infections, *BSI-CoNS* BSI with CoNS excluded, *ELSO* Extracorporeal Life Support Organisation, *ECLS* extracorporeal life support, *No BSI* patients without BSI, *95% CI* 95% confidence interval. *NR* neonatal respiratory, *NC* neonatal cardiac, *PR* pediatric respiratory, *PC* pediatric cardiac

Table 3 Summary of the current literature, compared to our data

Reference	Center(s)	Type	Years	Patients	BC+ numbers	CoNS number	BSI rate (%)	50% BC+ at	Antibiotic prophylaxis	Daily BC	Survival (%)
Meyer [2]	E	RR	87–93	5123 NR/NC	217		4.2				82.1
Elerian [3]	4	RR	90–94	177 NR	13	5	7.3	9 days	Y	Most	70
Steiner [4]	1	RR	89–98	202 NR/NC	7	5	3.4	390 h	Y	Y	75
O'Neill [5]	1	RR	94–97	141 all	24	6	17	169 h	Y	Y	64
Brown [6]	1	IS	99–04	215 all	42	20	19.5			Y	58
BCCH	1	RR	99–05	84 all	19	8	22.6	120 h		Y	58

E ELSO Database, *RR* retrospective review, *IS* interventional study, *BC+* positive blood culture, *CoNS* coagulase-negative staphylococci, *BSI* bloodstream infection (CoNS included), *50% BC+* median time to BC+, *Y* yes, *Survival* survival to discharge

Daily surveillance blood cultures while on ECLS have been a controversial topic, and one previous report has considered this practice not helpful [2]. Between 1987 and 1993, the ELSO reported a bacteremia incidence of 4.2% (217/5123 newborns) with a higher mortality in the infected group (35 vs. 17%, $P < 0.001$) and a significantly longer ECLS by 85 h. Survival to discharge was 82.1%. In our cohort, no patient died primarily of a BSI. Table 3 summarizes the recent literature.

Elerian et al. [3] reported a BSI incidence of 0.9% ($n = 13$) in 177 neonatal respiratory (NR) patients (1990–1994). Daily blood cultures were performed and patients were on antibiotic prophylaxis. The pathogens reported were: 5 CoNS, 4 Methicillin Resistant *Staphylococcus aureus*, 2 *Bacillus* spp., 1 *Pseudomonas* spp., and 1 *S. pneumoniae*. The median ECLS duration until BSI in the late onset sepsis group (>72 h on ECLS) was 9 days. This comparatively late median might be due to the exclusion of the early onset group. They concluded that when sepsis was not suspected, the use of daily blood cultures was expensive (122,615 $ spent in 177 patients for a yield of 13 BC+) and therefore deemed not useful while on antibiotic prophylaxis. However, would they have used the number of patients rather than the number of blood cultures ($n = 1{,}370$) as the denominator, the attack rate would have been 7.3% in the late onset group only. The overall survival was 70%. This study did not address the long-term impact of broad-spectrum antibiotic prophylaxis on the local bacterial resistance profile. It is arguable that the rising antibiotic resistance linked to the use of prophylactic antibiotics might lead to superior cost compared with surveillance cultures. In our study, the study sample size prevents us from clearly answering this point.

Steiner et al. [4] showed a BSI incidence of 3.4% (7/202 neonates). CoNS (5 of 7) were the most common pathogen. Their most significant predictor for BSI was duration of ECLS: 391 versus 141 h in the no-BSI group ($P = 0.02$). 50% of BSI appeared after 390 h on ECLS. Further risk factors for BSI were: umbilical arterial catheters and more frequent screening BC. The overall survival was 75%. We share the findings regarding the unusefullness of the WBC and I/T ratio as predictors of BSI.

O'Neill et al. [5] reported a BSI incidence of 17% (24/141) in 75 neonatal and 66 pediatric patients. Patients with nosocomial infections were significantly longer on ECLS (median: 169 h) compared to the no-BSI group (median 146 h). Our BSI patients were on support for a median of 120 h (range 15–480) versus the no-BSI patients' median of 111 h (range 4–449). The median ECLS time for no-BSI patients in their study was longer than in our BSI group, partly because patients who were supported <48 h or more than once, were excluded. Importantly, CoNS, *Bacillus sp.* and corynebacteria were consistently regarded as contaminants if not present in more than one set of blood cultures, and therefore were excluded from further analysis. Their overall survival was 64%.

In a single-center interventional prospective evaluation, Brown et al. [6] described an overall attack rate of 19.5% (42/215). CoNS were identified in 20 BSI (47.6%), which is comparable to our percentage (42%). The main purpose of their study was to evaluate a multidisciplinary interventional approach to decrease BSI from an era 1 (1999–2001) to an era 2 (2002–2004). The overall decrease of sepsis from 23 to 14% was not statistically significant in a univariate regression model ($P = 0.08$). However, they might have been underpowered. Similarly to our policy, they did not use prophylactic antibiotics and further use was at the discretion of the attending physician. The most significant risk for sepsis identified, was ECLS duration ($P < 0.01$). Further risk identified was an open versus a closed chest ($P = 0.007$ in the multivariate regression). Their overall survival is identical to ours, 58%. The only risk factors for mortality was ECLS duration ($P = 0.003$), whereas sepsis was not significant ($P = 0.53$).

The overall BCCH survival (71% survived ECLS and 58% survived to discharge or transfer) is comparable to the ELSO database (76% survived ECLS, 65% survived to discharge/transfer) (Table 2). Reported center-specific survival rates vary between 58 and 70% [3–6] (Table 3), whereas the ELSO survival to discharge or transfer is 65% [1] (Table 2).

The definition of contaminant in blood cultures differs greatly among published reports and this lack of common definition underlines the potential heterogeneity of the ELSO data. We speculate that the incidence reported by ELSO may be artificially lowered, as some organisms such as CoNS, are frequently considered as contaminants and therefore not reported by many centers [7, 8]. CoNS may be pathogenic and has been associated with persistent thrombocytopenia and bacteremia in neonates [9]. Henceforth, we hypothesize, that the true incidence of BSI may be higher than previously reported.

In this study, we have attempted to find biological predictors for BSI. We could not see any significant trends within the WBC, ANC or I/T ratio, which confirms previous data [4]. Thrombocytopenia, being a complication of ECLS itself, was not useful as a marker of impending or persisting infection. Fibrinogen, previously not studied in this setting was a similarly poor predictor. The role of lactate is unclear, as there might have been a trend towards decreasing levels before the onset of BSI ($P = 0.102$). A larger and prospective assessment is needed to clarify this point. Furthermore, no data are yet available on pro-calcitonin, C-reactive protein or interleukins and their role in diagnosing BSI while on ECLS.

Limitations of our review are the retrospective data collection, population size and the single center aspect.

Conclusion

The attack rate of BSI in ECLS is 22.6% in our center, compared to the ELSO incidence of 8.78%, despite shorter ECLS run times. We explain this difference by:

- BSI underreporting to ELSO, due to inconsistency of the definition of "contaminant"
- The widespread use of broad spectrum antimicrobial prophylaxis in other published studies
- A higher yield for BC+ due to daily blood cultures monitoring.

WBC, ANC, I/T ratio, platelet count and fibrinogen are poor predictors for BSI, while the role of lactate has to be further investigated.

Our findings suggest that with similar mortality, daily blood culture monitoring is an alternative to prophylactic antibiotics. It promotes a more judicious use of antibiotics and may decrease the emergence of multiresistant organisms. Further evaluation regarding the impact of prophylactic antibiotic usage on local antimicrobial flora, length of stay, survival and costs is needed.

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