ORIGINAL RESEARCH

Sepsis After Cardiac Surgery Early in Infancy and Adverse 4.5-Year Neurocognitive Outcomes

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***Background*—**We aimed to determine whether sepsis is associated with neurocognitive outcomes 4.5 years after congenital heart disease surgery in early infancy.

***Methods and Results*—**A secondary analysis from a prospective inception cohort included all children having congenital heart disease surgery done at ≤6 weeks of age with cardiopulmonary bypass at the Western Canadian referral center from 1996 to 2009. Follow-up at the referral center determined the primary outcomes at 4.5 years with full-scale, performance, and verbal intelligence quotients on the Wechsler Preschool and Primary Scale of Intelligence. Perioperative variables were collected prospectively, and confirmation of blood culture–positive sepsis was done retrospectively. Multiple linear regression models for neurocognitive outcomes and multiple Cox proportional hazards regression for mortality were determined. Sepsis occurred in 97 of 502 patients (19%) overall and in 76 of 396 survivors (19%) with 4.5-year follow-up. By 4.5 years, there were 91 (18%) deaths, and 396 of 411 survivors (96%) had follow-up completed. Extracorporeal membrane oxygenation was associated with worse scores on all neurocognitive outcomes on multivariable regression; the association between extracorporeal membrane oxygenation and full-scale intelligence quotient had a regression coefficient of −13.6 (95% CI −21.3 to −5.9; *P*=0.001). Sepsis perioperatively was associated with performance and verbal intelligence quotients, with a trend for full-scale intelligence quotient (*P*=0.058) on multivariable regression. The regression coefficient for sepsis was strongest for performance intelligence quotient (−5.31; 95% CI −9.84 to −0.78; *P*=0.022). Sepsis was not but extracorporeal membrane oxygenation was associated with mortality by 4.5 years.

***Conclusions*—**Perioperative sepsis and extracorporeal membrane oxygenation were associated with adverse neurocognitive outcomes on multivariable regression. Quality improvement to prevent sepsis has the potential to improve long-term neurocognitive outcomes in infants after surgery for congenital heart disease. **(*J Am Heart Assoc*. 2015;4:e001954 doi: 10.1161/JAHA.115.001954)**

Key Words: congenital • extracorporeal circulation • heart defects • infection • morbidity • risk factors

Severe sepsis has been recognized increasingly as a cause of adverse neurocognitive outcomes in adults.[1–4] A large recent cohort found that at 12 months after severe sepsis, approximately one-quarter of survivors had global cognition scores similar to those with mild Alzheimer's disease; this was true even for those aged ≤49 years.[4] Similar results in adults have been found by others.[1–3] In children, limited data suggest that similar adverse neurocognitive outcomes may occur[5–9]; however, the available pediatric studies have limitations, including small sample sizes, low rates of follow-up, short periods of follow-up, lack of detailed neurocognitive testing, and lack of critically ill control groups.[5–9]

Infants who have cardiac surgery for complex congenital heart disease (CHD) also can have adverse neurocognitive outcomes.[10,11] As survival has improved, a focus on these adverse outcomes and their potentially modifiable predictors has become more important. In this study, we aimed to determine whether sepsis may be a potentially modifiable variable independently associated with adverse neurocognitive outcomes after cardiac surgery for CHD early in infancy. The opportunity to examine this potential association in a large prospective cohort of infants would overcome many of the limitations of previous pediatric studies of outcomes after sepsis.

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Methods

An ongoing outcomes follow-up project with a prospective inception cohort in western Canada was started in 1996. As described previously, infants were identified at the time of complex cardiac surgery and were followed prospectively.[11] In this study, we included all infants aged ≤6 weeks who were admitted to the pediatric intensive care unit after surgery for complex CHD (defined as requiring cardiopulmonary bypass) at the Stollery Children's Hospital between September 1996 and February 2009. Demographic, preoperative, intraoperative, and postoperative variables that were previously agreed on were collected prospectively.[11]

Chromosomal abnormalities were identified by routine karyotype and analysis for del22q11.2 in all infants and as clinically indicated up to age of follow-up. Sepsis was defined as a positive blood culture that was treated for at least 5 days with intravenous antibiotics. Potential skin contaminants in the blood culture (coagulase-negative staphylococci, *Aerococcus* spp, *Micrococcus* spp, *Corynebacterium* spp, *Propionibacterium* spp, viridians group streptococci, or *Bacillus* spp [not *B. anthracis*])[12] required 2 positive blood cultures or 1 positive blood culture associated with fever or hypothermia, abnormal white blood cell count, and increase in inotrope score on the day of the culture. The patients with potential skin contaminants in the blood culture were identified as those with a Gram-positive organism grown from the culture. All of these patients had their charts reviewed retrospectively to confirm the above criteria; sepsis was confirmed in 41 of 57 (72%) and ruled out in the others. Pragmatically, our definition of sepsis was meant to include children with clinical sepsis (ie, had an indication for the clinician to perform blood culture and to decide to treat with intravenous antibiotics for at least 5 days) with bacteremia and did not capture children that may have had clinical sepsis without proven bacteremia. We were able to review all required charts to confirm the criteria, and we cross-checked them with our hospital infection control nosocomial bacteremia database. Long-term follow-up was performed, with parental or guardian consent, during the respective follow-up visits at the tertiary site of origin. The follow-up study and database were approved by the institutional health research ethics board.

Neurocognitive Assessment

Outcomes assessments were completed at a mean of 55 months (SD 6; median 54 months, interquartile range 51 to 59 months) of age. Pediatric psychologists administered the Wechsler Preschool and Primary Scale of Intelligence, revised (38 children tested prior to 2002) and third edition (358 children tested from 2002 onward), to obtain the full-scale intelligence quotient (FSIQ), the performance intelligence quotient (PIQ), and the verbal intelligence quotient (VIQ) and administered the Beery-Buktenica Developmental Test of Visual Motor Integration (VMI), fifth edition; the results of the Adaptive Behavior Assessment System, second edition (ABAS-II) were obtained at the respective referral institutions.[13–16] The preschool version of ABAS-II is a parent/caregiver-completed questionnaire to provide comprehensive, norm-referenced assessment of adaptive skills for children aged 0 to 5 years. The General Adaptive Composite (GAC) score from the ABAS-II is used to assess adaptive function in children. All scores have a normative population mean of 100 and SD of 15, and higher scores indicate better performance; a score <70 is 2 SD below the mean and is expected in 2.27% of the normative population.

Statistics

Continuous variables are presented as mean (SD), and categorical variables are presented as counts (percentages). To screen for variables associated with the outcome variables, we used univariate regression models and included the following a priori specified variables from the respective perioperative time periods: demographic (gestational age, birth weight, socioeconomic status,[17] sex, chromosomal abnormality, and single ventricle anatomy), preoperative (5-minute Apgar score, year of surgery), intraoperative (cardiopulmonary bypass time, aortic cross-clamp time, and deep hypothermic circulatory arrest used), postoperative (day 1 highest lactate, day 1 inotrope score,[18] day 1 highest creatinine, day 1 highest base deficit, and the time for lactate to fall to ≤2 mmol/L), and all perioperative time periods (seizures, cardiopulmonary resuscitation, dialysis, sepsis, and extracorporeal membrane oxygenation [ECMO] anytime up to age 4 years). To screen for variables associated with neurocognitive outcomes, we used univariate regression models. Multiple linear regression models consisted of variables found approaching significance at $P \leq 0.10$ in the univariate analysis and after screening for multicollinearity; they are presented as regression coefficients with 95% CIs and 2-sided *P* values. The regression coefficient represents the average change in the outcome for each unit increase in the explanatory (predictor) variable. Multiple Cox proportional hazards regression analysis for mortality by 4.5 years included variables that were significant at $P \leq 0.10$ in the corresponding univariate analysis and after screening for multicollinearity, and they are presented as hazard ratios with 95% CIs and 2-sided *P* values. Low counts for some variables did not allow validation of the proportionality assumption in Cox models. Multicollinearity was assessed using Pearson correlation for continuous variables and, when at least 1 of the variables was binary, using Spearman correlation; pairs of variables with a correlation >0.7 were declared collinear, and only 1 was entered into the multiple model according to clinical and statistical significance.[19] Using

variance inflation factor as a regression diagnostic measure did not change the findings for collinearity.[19] The statistical modeling is exploratory, investigating the effect of prespecified clinically and biologically important variables (sepsis and ECMO) while controlling for other potentially predictive confounding variables (those found significant on univariate analyses). We hypothesized that sepsis and ECMO would be associated with outcomes on multivariable analyses based on previous studies.[1–9,20,21] Statistical analyses were performed using SAS version 9.3 (SAS Institute). The primary outcomes for this study were the intelligence quotient (FSIQ, PIQ, VIQ) outcomes in survivors. Secondary outcomes were VMI and GAC outcomes in survivors.

Results

Description of the Cohort

There were 502 consecutive infants enrolled in the inception cohort at the time of cardiac surgery at age ≤6 weeks. Demographics included 315 (63%) male patients, 160 (32%) with single ventricle anatomy, 49 (10%) having ECMO at any time up to age 4.5 years, and 45 (9%) with chromosomal abnormality. Perioperative sepsis occurred in 97 patients (19%) overall and in 76 of 396 survivors (19%) with 4.5-year follow-up. By 4.5 years of age, there were 91 deaths (18%), and 396 of 411 survivors (96%) had neurocognitive follow-up completed (Figure). Regarding mortality, 31 (6.2%) and 86 (17%) patients had died at 30 days and 2 years, respectively. There was no evidence of collinearity between sepsis and ECMO at any time (correlation 0.03, *P*=0.48). The mean neurocognitive outcomes in survivors at 4.5 years of age included FSIQ 90.6 (SD 18.6), VIQ 90.8 (SD18.6), PIQ 91.4 (SD 19.2), VMI 89.7 (SD 16.7), and GAC 89.6 (SD 18.1).

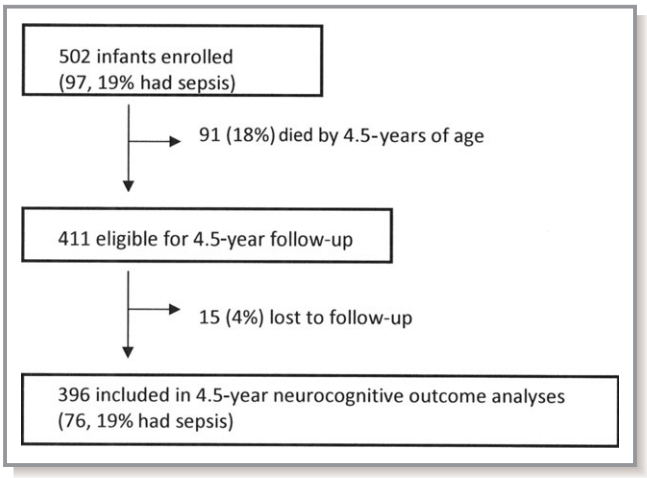

Figure. Flow diagram of the inception cohort and analyses for mortality and neurocognitive outcomes.

Scores <70 on both FSIQ and GAC occurred in 43 patients (10.9%); therefore, the neurocognitive outcomes shifted to the left of the normative population, with more than expected having scores >2 SD below the mean. Other descriptive and outcome variables of the cohort are given in Table 1.

On multiple Cox proportional hazards regression analysis, sepsis was not and ECMO was associated with mortality by 4.5 years (hazard ratio 1.9; 95% CI 1.17 to 3.18; *P*=0.01) (Table 2).

Associations With Neurocognitive Outcomes

Mean FSIQ, PIQ, and VIQ scores at 4.5 years of age for the 76 sepsis survivors were 84.8 (SD 17.5), 84.8 (SD 17.6), and 85.8 (SD 17.7), respectively; these scores are statistically significantly lower than the respective scores in the rest of the cohort (92 [SD 18.6], *P*=0.002; 93 [SD 19.3], *P*=0.001; and 92 [SD 18.6], *P*=0.009).

Univariate and multivariable predictors of the FSIQ, VIQ, and PIQ outcomes are given in Tables 3 and 4, respectively. Chromosomal abnormality was associated with worse scores on all of these outcomes on multivariable analyses. ECMO anytime in the first 4 years was also strongly associated with worse scores on all of these outcomes on multivariable analyses; for FSIQ, the regression coefficient was −13.6 (95% CI −21.3 to −5.9; *P*=0.001). Sepsis perioperatively was associated with PIQ and VIQ, with a trend toward significance for FSIQ (*P*=0.058) on multivariable analyses. The regression coefficient for sepsis was strongest for PIQ (−5.31; 95% CI −9.84 to −0.78; *P*=0.022). Other variables associated with 2 IQ outcomes on multivariable analyses included socioeconomic status, single ventricle anatomy, and sex. Post hoc exploration for an interaction between sepsis and single ventricle anatomy found that interaction terms were not statistically significant.

Univariate and multivariable predictors of the secondary outcomes of VMI and GAC are given in Tables 5 and 6. The results are similar to the IQ outcomes. Chromosomal abnormality was again a predictor of worse outcome in multivariable analyses. ECMO anytime in the first 4.5 years was also strongly associated with worse scores on multivariable analyses, with regression coefficients of −13.4 (95% CI −20.1 to −6.7; *P*<0.001) and −12.7 (95% CI −20.3 to −5.0; *P*=0.001) for VMI and GAC, respectively. Sepsis was not associated with these outcomes on multivariable analyses. Other predictors on multivariable analysis for GAC included birth weight and sex and for VMI included birth weight and single ventricle anatomy.

Sensitivity Analysis

Post hoc, we explored whether excluding children who had ECMO at any time in the first 4.5 years would change the

Table 1. Description of the Cohort of 502 Patients Having Cardiac Surgery in Early Infancy

Descriptive Variable	Result
Demographic variables	
Gestational age, week, mean (SD)	38.8 (1.9)
Birth weight, g, mean (SD)	3290 (613)
Sex, male, n (%)	315 (62.7)
Chromosomal abnormality, n (%)	45 (9)
Single ventricle, n (%)	160 (31.9)
Socioeconomic status, mean (SD)	43.6 (13.2)
Preoperative variables	
Apgar at 5 min, mean (SD)	8.3 (1.2)
Year of surgery, mean (SD); median [IQR]	2003.3 (3.5); 2003 [2000–2006]
Sepsis, n (%)	29 (5.8); Gram-negative bacilli 12, Gram-positive cocci/bacilli 17
Intraoperative variables (during first surgery)	
Cardiopulmonary bypass time, min, mean (SD)	116.1 (55.6)
Aortic cross-clamp time, min, mean (SD)	54.3 (25.0)
Deep hypothermic circulatory arrest used, n (%)	374 (74.5)
Postoperative day 1 variables	
Highest lactate, mmol/L, mean (SD)	6.4 (3.9)
Time for lactate to reduce to ≤2 mmol/L, h, mean (SD)	12.7 (12.8)
Highest modified inotrope score, mean (SD)	14.9 (16.2)
Lowest base deficit, mean (SD)	−1.4 (3.8)
Postoperative sepsis (day 1+), n (%)	75 (14.9%); Gram-negative bacilli 32, Gram-positive cocci/bacilli 40, *Candida* spp 3
Perioperative (during first hospitalization) variables, n (%)	
Sepsis*	97 (19)
Seizures	47 (9.4)
Cardiopulmonary resuscitation	38 (7.6)
Anytime up to 4.5 year visit, n (%)	
Extracorporeal membrane oxygenation	49 (9.8)
Outcomes†	
Follow-up testing age, months, mean (SD); median [IQR]	55 (6); 54 [51 to 59]
Death by 30 days, n (%)	31 (6.2)
Death by 2 years, n (%)	86 (17.1)
Death by 4 years, n (%)	91 (18.1)
FSIQ (n=396), mean (SD)	90.6 (18.6); score <70 in 54 (13.6%)
PIQ (n=396), mean (SD)	91.4 (19.2); score <70 in 48 (12.1%)
VIQ (n=396), mean (SD)	90.8 (18.6); score <70 in 50 (12.6%)
GAC (n=396), mean (SD)	89.6 (18.1); score <70 in 64 (16.2%)
VMI (n=396), mean (SD)	89.7 (16.7); score <70 in 47 (11.9%)
Intellectual disability (score <70 on both FSIQ and GAC) (n=396), n (%)	43 (10.9)

ECMO indicates extracorporeal membrane oxygenation; FSIQ, full-scale intelligence quotient; GAC, General Adaptive Composite; IQR, interquartile range; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient; VMI, Beery-Buktenica Developmental Test of Visual Motor Integration.

*Perioperative sepsis occurred in 97 patients, 29 preoperatively, 75 postoperatively, and 7 both pre- and postoperatively.

†In the sepsis subgroup, 12 of 97 (12%) had ECMO and 11 of 97 (11%) had chromosomal abnormalities. Of the 76 sepsis survivors, 5 (7%) had ECMO and 7 (9%) had chromosomal abnormality.

results for the primary outcomes. We hypothesized that ECMO could mask other predictors that may be important in determining outcomes. There was no evidence of collinearity between sepsis and ECMO (correlation 0.03, P=0.48). Excluding children who had ECMO did not significantly change the results for any of the primary outcomes (data not shown). Sepsis remained a predictor of VIQ and PIQ, and the trend for FSIQ remained (P=0.079) on multivariable analyses. The only new association on multivariable analysis was between socioeconomic status and PIQ (regression coefficient 0.14; 95% CI 0.01 to 0.28; P=0.039).

Discussion

This study had several important findings. First, perioperative sepsis, defined as a positive blood culture not due to a contaminated specimen and treated with intravenous antibiotics for at least 5 days, was associated with adverse long-term VIQ and PIQ (and with a trend to adverse FSIQ; P=0.058) outcomes on multivariable analyses. Second, ECMO at any time in the first 4.5 years of life was associated with adverse outcomes on all FSIQ, VIQ, PIQ, VMI, and GAC scores on multivariable analyses. Third, these associations on multivariable analyses were found after controlling for other

Table 2. Univariate and Multiple Cox Proportional Hazards Regressions for Death at 4.5 Years in 502 Patients Having Cardiac Surgery in Early Infancy

Variable	HR (95% CI) for 4-Year Mortality			
	Univariate	*P* Value	Multivariable	*P* Value
Seizures perioperatively	2.25 (1.14 to 4.45)	0.019		
Birth weight, 100 g	0.95 (0.92 to 0.99)	0.006	0.95 (0.92 to 0.98)	0.003
CPR perioperatively	1.77 (1.12 to 2.82)	0.015		
ECMO anytime	1.69 (1.07 to 2.66)	0.025	1.93 (1.17 to 3.18)	0.010
CPB time, 5 min	1.02 (1.00 to 1.03)	0.029	1.02 (1.00 to 1.03)	0.014
Birth gestation, week	0.91 (0.82 to 1.00)	0.055		
Sepsis perioperatively	0.82 (0.49 to 1.36)	0.433	0.64 (0.37 to 1.11)	0.111

CPB indicates cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio.

prespecified contributors to adverse outcomes, including severity of illness (eg, lactate, inotrope score), demographics (eg, birth weight, sex, socioeconomic status, chromosomal abnormality, single ventricle anatomy), and other perioperative events (eg, deep hypothermic circulatory arrest, cardiopulmonary resuscitation, seizures). In fact, several of these variables were also associated with some of the adverse neurocognitive outcomes on multivariable analyses, including birth weight, socioeconomic status, single ventricle anatomy, and chromosomal abnormality. Of particular importance, sepsis was the only consistently identified, potentially modifiable variable associated with the neurocognitive outcomes on

Table 3. Univariate Linear Regressions for Full-Scale Intelligence Quotient, Performance Intelligence Quotient, and Verbal Intelligence Quotient at 4.5 Years of Age in 396 Survivors of Cardiac Surgery in Early Infancy

Variable	FSIQ		PIQ		VIQ	
	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Chromosomal abnormality	−21.16 (−27.40 to −14.92)	<0.001	−21.09 (−27.54 to −14.63)	<0.001	−20.02 (−26.27 to −13.77)	<0.001
ECMO	−17.39 (−25.63 to −9.15)	<0.001	−17.18 (−25.69 to −8.67)	<0.001	−12.48 (−20.77 to −4.19)	0.003
Birth gestation, week	1.96 (0.99 to 2.94)	<0.001	1.04 (0.02 to 2.06)	0.046	1.74 (0.76 to 2.71)	0.001
Birth weight, 100 g	0.49 (0.18 to 0.80)	0.002	0.36 (0.04 to 0.69)	0.026	0.37 (0.06 to 0.68)	0.019
Socioeconomic status	0.22 (0.08 to 0.35)	0.002	0.16 (0.02 to 0.31)	0.024	0.25 (0.12 to 0.39)	<0.001
Sepsis perioperatively	−7.18 (−11.81 to −2.56)	0.002	−8.14 (−12.90 to −3.38)	0.001	−6.18 (−10.81 to −1.56)	0.009
Single ventricle anatomy	−5.18 (−9.36 to −0.99)	0.015	−7.37 (−11.66 to −3.09)	0.001	—	—
Postoperative day 1 highest lactate, mmol/L	−0.76 (−1.38 to −0.14)	0.016	−0.64 (−1.28 to 0.00)	0.051	−0.63 (−1.24 to −0.01)	0.047
Postoperative day 1 inotrope score	−0.18 (−0.33 to −0.03)	0.017	−0.17 (−0.33 to −0.02)	0.026	−0.15 (−0.30 to −0.00)	0.046
Seizures perioperatively	−7.53 (−13.82 to −1.24)	0.019	−7.44 (−13.93 to −0.95)	0.025	−7.41 (−13.68 to −1.15)	0.021
Postoperative time for lactate to reduce to ≤2 mmol/L, h	−0.18 (−0.34 to −0.02)	0.030	—	—	−0.18 (−0.34 to −0.02)	0.032
Use of deep hypothermic circulatory arrest	−4.14 (−8.15 to −0.13)	0.043	−5.03 (−9.16 to −0.91)	0.017	—	—
Sex, female	3.57 (−0.24 to 7.38)	0.066	—	—	4.13 (0.34 to 7.92)	0.033
Aortic cross-clamp time, min	—	—	0.07 (−0.00 to 0.15)	0.055	—	—
Year of initial surgery	—	—	0.49 (−0.06 to 1.04)	0.079	—	—

ECMO indicates extracorporeal membrane oxygenation; FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient.

Table 4. Multivariable Linear Regressions for Full-Scale Intelligence Quotient, Performance Intelligence Quotient, and Verbal Intelligence Quotient at 4.5 Years of Age in 396 Survivors of Cardiac Surgery in Early Infancy

	FSIQ		PIQ		VIQ	
R^2 of the Model	21%		17%		17%	
Variable	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Chromosomal abnormality	−20.29 (−26.29 to −14.29)	<0.001	−20.96 (−27.18 to −14.74)	<0.001	−19.99 (−26.06 to −13.93)	<0.001
ECMO	−13.60 (−21.28 to −5.93)	0.001	−13.48 (−21.46 to −5.49)	0.001	−9.01 (−16.87 to −1.14)	0.025
Birth weight, 100 g	0.39 (0.11 to 0.68)	0.007	—	—	—	—
Socioeconomic status	0.19 (0.06 to 0.32)	0.005	0.13 (−0.01 to 0.26)	0.067	0.21 (0.08 to 0.34)	0.002
Sepsis perioperatively	−4.20 (−8.55 to 0.15)	0.058	−5.31 (−9.84 to −0.78)	0.022	−4.46 (−8.82 to −0.09)	0.045
Single ventricle anatomy	−5.20 (−9.07 to −1.34)	0.008	−7.26 (−11.37 to −3.31)	<0.001	—	—
Sex, female	4.50 (1.01 to 7.99)	0.012	—	—	4.31 (0.75 to 7.86)	0.018
Year of initial surgery	—	—	0.50 (−0.30 to 1.01)	0.051	—	—
Postoperative time for lactate to reduce to ≤2 mmol/L, h	—	—	—	—	−0.15 (−0.30 to −0.00)	0.048

R^2 indicates the variability in the outcomes scores accounted for by the model. ECMO indicates extracorporeal membrane oxygenation; FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient.

multivariable analyses. The only other potentially modifiable variables associated with neurocognitive outcomes on multivariable analyses reflected early postoperative severity of illness: Postoperative time for lactate to fall ≤2 mmol/L and postoperative day 1 inotrope score were associated with adverse VIQ and GAC, respectively.

These findings are important in the context of previous literature. The finding of the association between sepsis and adverse neurocognitive outcomes on multivariable analyses is consistent with the adult literature[1–4] and strengthens the existing pediatric literature[5–9] by using a large sample size in a prospective inception cohort (n=396 survivors), a high rate of follow-up (96% of survivors followed to 4.5 years of age), a detailed neurocognitive assessment done with validated standardized testing,[13–16] and adjustment for many potentially confounding variables. That sepsis is a potentially

Table 5. Univariate Linear Regressions for General Adaptive Composite of the Adaptive Behavioral Assessment System and Visual Motor Integration at 4 Years of Age in 396 Survivors of Cardiac Surgery in Early Infancy

	General Adaptive Composite		Visual Motor Integration	
Variable	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Chromosomal abnormality	−19.45 (−25.54 to −13.35)	<0.001	−18.37 (−23.97 to −12.77)	<0.001
ECMO anytime	−14.92 (−22.97 to −6.88)	<0.001	−16.83 (−24.18 to −9.48)	<0.001
Birth gestation, week	1.37 (0.41 to 2.33)	0.005	1.45 (0.57 to 2.33)	0.001
Sex, female	5.14 (1.46 to 8.82)	0.006	3.59 (0.18 to 7.00)	0.039
Birth weight, 100 g	0.40 (0.10 to 0.70)	0.009	0.58 (0.31 to 0.86)	<0.001
Postoperative day 1 inotrope score	−0.18 (−0.32 to −0.03)	0.016	−0.14 (−0.27 to −0.01)	0.04
Postoperative time for lactate to reduce to ≤2 mmol/L, h	−0.19 (−0.35 to −0.03)	0.018	−0.20 (−0.34 to −0.06)	0.007
Seizures perioperatively	−6.59 (−12.71 to −0.48)	0.035	−4.98 (−10.63 to 0.67)	0.084
Sepsis perioperatively	−3.98 (−8.51 to 0.55)	0.085	−5.50 (−9.65 to −1.34)	0.01
Single ventricle anatomy	—	—	−8.92 (−12.59 to −5.25)	<0.001
Deep hypothermic circulatory arrest used	—	—	−5.70 (−9.27 to −2.14)	0.002
Postoperative day 1 highest lactate, mmol/L	—	—	−0.73 (−1.28 to −0.17)	0.01

ECMO indicates extracorporeal membrane oxygenation.

Table 6. Multivariable Linear Regressions for General Adaptive Composite and Visual Motor Integration at 4 Years of Age in 396 Survivors of Cardiac Surgery in Early Infancy

	General Adaptive Composite		Visual Motor Integration	
R^2 of the Model	17%		25%	
Variable	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Chromosomal abnormality	−18.56 (−24.51 to −12.61)	<0.001	−17.68 (−22.90 to −12.45)	<0.001
ECMO anytime	−12.66 (−20.27 to −5.04)	0.001	−13.38 (−20.05 to −6.71)	<0.001
Birth weight, 100 g	0.28 (−0.01 to 0.56)	0.056	0.48 (0.23 to 0.73)	<0.001
Sepsis perioperatively	−2.68 (−6.89 to 1.54)	0.212	−2.92 (−6.64 to 0.80)	0.124
Sex, female	6.13 (2.67 to 9.58)	0.001	5.09 (2.07 to 8.11)	0.001
Postoperative day 1 inotrope score	−0.14 (−0.28 to −0.01)	0.038	—	—
Single ventricle anatomy	—	—	−9.04 (−12.40 to −5.68)	<0.001

R^2 indicates the variability in the outcomes scores accounted for by the model. ECMO indicates extracorporeal membrane oxygenation.

modifiable predictor of adverse outcomes is supported by literature on the prevention of sepsis in the critical care environment.[22,23] This is also important because sepsis is increasingly common in the pediatric intensive care unit.[24–26] The finding of the association between ECMO and adverse neurocognitive outcomes on multivariable analyses has been suspected before but, to our knowledge, has not been confirmed in a large cohort, adjusting for potential confounders.[20,21] A recent review found that neurocognitive outcomes after ECMO in children has been examined in only a few small studies, often without detailed neurocognitive assessment and/or comparison to control groups with similar demographics and surgery.[20]

This study has limitations. First, it is an observational study, and we cannot claim a cause-and-effect relationship between predictors and outcomes. Unmeasured confounding variables may account for the associations we found. Second, our definition of sepsis requiring a positive blood culture may have missed many cases of nonbacteremic sepsis. In addition, we cannot confirm that all of our patients had the systemic inflammatory response syndrome, part of the definition of sepsis, because we did not record temperature, respiratory rate, heart rate, or white blood cell count for all of the included children. Third, although patients were enrolled and had variables recorded prospectively, the confirmation of blood culture results was done retrospectively. Fourth, the rates of perioperative blood culture–positive sepsis were high.[27] Hospital-acquired infection rates in pediatric patients undergoing surgical correction of CHD has been reported to be ≈16%, with bloodstream infection rates of 5% to 10%.[27] Fifth, a small number of the children at the beginning of the study were tested with an earlier edition of the Wechsler Preschool and Primary Scale of Intelligence test for neurocognitive outcomes. Data collection for this study extended for over 11 years, during which time the intelligence test was revised. The option of continuing with the outdated test was rejected based on the principle of using the up-to-date version. With no difference between the means (SDs) of the 2 editions within the normative population and within a previously published cohort from our group, we proceeded to include all children in the cohort.[28] Sixth, sepsis was not associated with ECMO; it is possible that the severity of the underlying CHD and residual cardiac lesions, postoperative complications including cardiac arrest and low cardiac output, and our definition of sepsis not capturing many children with clinical sepsis (ie, without bacteremia) may have confounded any impact of sepsis on need for ECMO. Finally, because this study explored the predictors of outcome in a large cohort of children, all of whom had surgery in early infancy for CHD, we cannot comment on outcomes or predictors of outcomes in children with CHD who did not have surgery in early infancy.

Nevertheless, the multivariate analyses done controlled for prespecified potential predictors of outcome identified in previous studies,[11] and the criteria used to confirm blood culture results were prespecified and objective, modified from the Centers for Disease Control and Prevention definitions.[12] Furthermore, we included a group of infants at high risk for sepsis, having complex surgery for CHD at age ≤6 weeks, requiring many days of pre- and postoperative intensive care, and often having central venous lines and intubation for much of that time.[27] Importantly, the high rate of sepsis suggests that known systems and interventions to prevent nosocomial infections have the potential to improve long-term neurocognitive outcomes in these children.[22,23] The association of sepsis with adverse neurocognitive outcomes may be an underestimate, given that many cases of nonbacteremic sepsis likely occurred.

Our statistical approach was to use multivariable analyses to explore for predictors of outcome while adjusting for

clinically (sepsis and ECMO) and statistically (on univariate analysis) important potentially confounding variables. In a large prospective inception cohort of patients having complex cardiac surgery early in infancy, we found that perioperative sepsis was associated with adverse neurocognitive outcomes on multivariable analyses. Having received ECMO at any time in the first 4 years of life was also found to be strongly associated with adverse neurocognitive outcomes on multivariable analyses. Nosocomial perioperative sepsis is a potentially modifiable variable, and these data highlight the importance of infection control practices in intensive care.

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Disclosures

None.

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