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Infection and White Matter Injury in Infants with Congenital Heart Disease

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Abstract

More than 60 percent of newborns with severe congenital heart disease develop perioperative brain injuries. Known risk factors include: preoperative hypoxemia, cardiopulmonary bypass characteristics, and postoperative hypotension. Infection is an established risk factor for white matter injury in premature newborns. In this study, we examined term infants with congenital heart disease requiring surgical repair to determine whether infection is associated with white matter injury. Acquired infection was specified by site (bloodstream, pneumonia, or surgical site infection) according to strict definitions. Infection was present in 23/127. Pre and post-operative imaging was evaluated for acquired injury by a pediatric neuroradiologist. Overall, there was no difference in newly acquired postoperative white matter injury in infants with infection (30 percent), compared to those without (31 percent). When stratified by anatomy, infants with transposition of the great arteries and bloodstream infection had an estimated doubling of risk of white matter injury that was not significant, whereas those with single ventricle anatomy had no apparent added risk. When considering only infants without stroke, the estimated association was higher, and became significant after adjusting for duration of inotrope therapy. In this study, nosocomial infection was not associated with white matter injury. Nonetheless, when controlling for risk factors, there was an association between bloodstream infection and white matter injury in selected sub-populations. Infection prevention may have the potential to mitigate long-term neurologic impairment as a consequence of white matter injury, which underscores the importance of attention to infection control for these patients.

Keywords (MeSH)

Heart defects, congenital; Sepsis; Magnetic resonance imaging; Leukomalacia, periventricular; Pneumonia, ventilator acquired

Introduction

Severe congenital heart disease occurs in approximately 6–8 of 1000 live births in North America(1, 2). While most forms of congenital heart disease are amenable to corrective surgical repair, survivors often have gross and fine motor delay, and may be left with behavior difficulties and functional limitations in socialization, communication, and daily living skills that persist into late childhood(3–11). Historically, efforts to improve neurodevelopmental outcomes in newborns with congenital heart disease have focused on the surgical procedure itself, and specifically on the type and duration of cardiopulmonary bypass, lowest flow, and base deficit during bypass, which are known to be major risk factors for adverse neurodevelopmental outcome(8, 11–13). However, increasing recognition that neurobehavioral abnormalities and brain injury may exist prior to the operative procedure has lead to the examination of pre- and postoperative risk factors(14, 15). Non-operative risk factors for adverse outcome or brain injury in this population include perioperative instability (e.g. hypoxemia, hypotension, acidosis, or preoperative need for balloon atrial septostomy), and cardiac lesion (i.e. hypoplastic left heart syndrome) (4, 15–19).

Focal, non-cystic white matter injury, which is a characteristic pattern of brain injury in preterm newborns(20, 21), is now also recognized as the predominant pattern of injury in newborns with congenital heart disease. More than 50 percent of infants with congenital heart disease show some degree of white matter injury when imaged using magnetic resonance imaging or examined at autopsy in the postoperative period (15, 19, 22–24). The reasons why infants with congenital heart disease are susceptible to this classic “preterm” pattern of injury are not known, and may, in part, be related to the relative immaturity of the brain of newborns with congenital heart disease (reviewed in(25)).

Infection is an established risk factor for white matter injury in the preterm population(26–31). The mechanism of white matter injury in the setting of infection is unclear, and current hypotheses have centered on direct injury due to inflammation, versus injury occurring as a consequence of hypoxia-ischemia during septic shock. Chau *et al.* recently found that both postnatal bloodstream infection and episodes of hypotension requiring treatment were risk factors for white matter injury, whereas chorioamnionitis confirmed by histopathology was not(26). These findings suggest that the pathogenesis of white matter injury may be multifactorial, with contributions to the underlying pathogenesis from both inflammation and hemodynamic shock. Acquired infection is also common in newborns with congenital heart disease, whose critical illness results in prolonged need for mechanical ventilation, intravenous therapy, and intensive care. Whether infection is also associated with white matter injury in infants with congenital heart disease, over and above established risk factors relating to impaired oxygen delivery, is not known.

We analyzed infants enrolled in a cohort study examining magnetic resonance imaging predictors of neurodevelopmental outcome in term newborns with congenital heart disease in order to examine the hypothesis that infection is an independent risk factor for white matter injury in this population.

Methods

The study subjects were infants greater than 36 weeks gestation at birth who were admitted to the intensive care units at the University of California, San Francisco Medical Center and the Children’s and Women’s Health Centre of British Columbia within the first month of life requiring surgery for congenital heart disease. Neonates with a diagnosis of congenital

infection were excluded. The University of California, San Francisco and University of British Columbia Committees on Human Research approved the study protocol.

Clinical Data Collection

From August 2001 to March 2009, 127 of the enrolled newborns were examined with magnetic resonance imaging preoperatively, and 108 (85 percent) had repeat studies postoperatively. Clinical data were prospectively collected from the medical records by a team of trained neonatal research nurses, and reviewed by a pediatric intensivist who was blinded to the neuroimaging findings. Perinatal variables included gestational age at birth and birth weight. Perioperative clinical variables included cardiac lesion (transposition of the great arteries, single ventricle anatomy or “other”); lowest oxygen saturation (SaO₂) bypass type; blood pressure on the first postoperative day; days intubated; and days of inotrope therapy. The lowest SaO₂ was recorded from pulse oximetry and extracted from the bedside patient record for each 24-hour period.

Data for infections (blood stream infection, pneumonia, and surgical site infection) were extracted from clinical charts and microbiology reports, and reviewed by a specialist in pediatric infectious diseases according to the following definitions: 1) Blood stream infection was diagnosed when blood cultures grew pathogenic species, or *Staphylococcus epidermidis* in the setting of a central venous catheter, and clinical signs or symptoms suggesting infection (temperature instability, low (less than 4,000 cells/mm³) or elevated (greater than 12,000 cells/mm³) white blood cell count, greater than 10 percent band forms, or stated clinical suspicion by treating physician); 2) pneumonia (viral or bacterial) was diagnosed if an infiltrate was identified on chest X-Ray and “clinical signs of respiratory symptoms were documented”; 3) surgical site infection was diagnosed in children who had clinical signs of cellulitis (erythema with purulent discharge or wound dehiscence) within 30 days of operation, and received antibiotic therapy. None of the infants had meningitis. With the exception of the patient diagnosed with RSV pneumonia, in order to further enhance our certainty of a clinically significant infection, we only considered infections that were treated with antibiotic therapy for at least 5 days.

Magnetic Resonance Imaging

Preoperatively, MR studies were performed as soon as the baby could be transported safely from the cardiac intensive care unit to the imaging suite. Postoperative studies were performed after temporary pacemaker wires were removed. If necessary, infants were sedated according to institution guidelines.

Magnetic resonance were acquired at the University of California, San Francisco using a 1.5 Tesla scanner (General Electric Signa) and a specialized, high-sensitivity neonatal head coil, built into the MR compatible incubator (General Electric or Lammers Medical Technologies). Image sequences included: (1) T1-weighted sagittal spin echo images (4-mm thickness) using a repetition time (TR) of 500ms, echo time (TE) of 11 ms, 1 excitation, and 192×256 acquisition matrix; (2) dual-echo T2-weighted spin echo (4-mm thickness) with a TR of 3000ms, TE of 60 and 120ms, and 192×256 acquisition matrix; and (3) coronal volumetric 3-dimensional gradient echo images with radiofrequency spoiling, spoiled gradient recalled images (1.5mm thickness) with a TR of 36ms, a TE of 9ms, a flip angle of 35°, and 1 excitation. At the University of British Columbia, magnetic resonance imaging studies were carried out without pharmacological sedation on a Siemens 1.5 Tesla Avanto using VB 13A software and included comparable imaging to that obtained at the University of California, San Francisco (TR/TE/FOV/Slice thickness/Gap): (1) 3D coronal volumetric T1-weighted images (36/9.2/200 mm/1mm/0); (2) axial fast spin echo T2-weighted images (4610/107/160mm/4 mm/0.2mm). Average diffusivity (D_{av}) maps were generated from

diffusion tensor imaging acquired with a multirepetition, single-shot echo planar sequence with 12 gradient directions (4900/104/160mm/3mm/0), $b=0, 600$ and 700s/mm^2 , and an in-plane resolution of 1.3 mm.

A neuroradiologist blinded to all clinical information beyond corrected gestational age and cardiac anatomic diagnosis scored each magnetic resonance imaging scan for acquired focal, multifocal, or global changes, as reported previously(32). Acquired focal and multifocal lesions included focal infarct, germinal matrix and intraventricular hemorrhage, and white matter injury. Focal infarct referred to discrete areas of cortical and/or white matter reduced intensity on Dav maps, or focal hyperintensity on T2-weighted images. Single white matter lesions measuring less than 3mm were classified as white matter injury, while larger lesions were considered stroke(32, 33). White matter injury was considered “minimal” if there were three or fewer areas of T1 signal abnormality, each less than two millimeters. Injury was considered “moderate” if there were more than three areas of T1 signal abnormality or if these areas measured more than two millimeters but less than five percent of the hemisphere was involved. “Severe” injury was defined as involvement of more than five percent of the hemisphere (20). The presence of newly acquired injury on the postoperative study was noted.

Statistical Analysis

Statistical analysis was performed using Stata 10.0 software (Stata Corp., College Station, Texas). Differences between clinical predictors were assessed using two-tailed student's *t*-test and Wilcoxon rank sum for continuous variables and chi-square, or Fisher exact for categorical variables. We performed stratified analysis by heart lesion and presence of stroke to look at the relative risk of white matter injury in these subpopulations. We also performed multivariable logistic regression analysis to look at the adjusted odds of white matter injury. We included in the initial model any potential confounders associated with both the predictor (infection) and the outcome (white matter injury) at significance of *p* less than or equal to 0.1.

Results

During the study period, 135 newborns were enrolled. Of these, 8 were excluded from the study for the following reasons: never imaged (4 infants), congenital *cytomegalovirus* infection (1 infant), gestational age less than 36 weeks (1 infant), and no surgery (1 infant). Of the remaining infants 127, 89 (70 percent) constituted the University of California, San Francisco cohort.

Infection

The clinical characteristics of study subjects appear in Table 1. Infection was common, with 23 of 127 infants (18 percent) sustaining at least one of bloodstream infection, pneumonia, or surgical site infection during the admission, and prior to the second scan. The clinical and imaging characteristics of the 23 newborns with infection appear in Table 2. Bloodstream infection was most common (13 infants)(Table 3). Organisms cultured from the blood included: *Staphylococcus epidermidis* (4 cases), *Escherichia coli*, *Enterobacter cloacae*, and *Bacillus* species (2 cases each), *Staphylococcus aureus*, *Enterococcus*, and *Klebsiella* (1 case each). Of the 23 children with infection, surgical site infection was present in 8 (6 percent) and pneumonia in 7 (6 percent) infants. Five infants (5 percent) had recurrent infections.

Infection and White Matter Injury

The preoperative magnetic resonance imaging was performed at a median age of 5 days of life (range 1, 43 days). One hundred and eight children were also imaged postoperatively, at a median of 21 days of life (range 9, 65 days), which was a median of 10 days after the operation day (range 4, 61 days postoperative). Infection occurred prior to the first magnetic resonance imaging in 4 children (3 percent, 2 with bloodstream infection), whereas the remainder of infections occurred after the time of the first magnetic resonance imaging but prior to the second scan.

Thirty of 127 infants (24 percent) had white matter injury on the preoperative magnetic resonance imaging. None of these newborns were diagnosed with nosocomial infection prior to the time of imaging, and therefore, we considered only new white matter injury acquired on the second magnetic resonance imaging for the remainder of the analysis. Newborns with white matter injury on the first scan were not at increased risk for developing infection (p greater than 0.6).

Of the 108 infants reimaged postoperatively, new white matter injury (not seen on the first scan) was present in 33 (31 percent). There was no difference in the timing of magnetic resonance imaging (postoperative day, or day of life) in newborns with and without injury (p equal to 0.7). Overall, there was no significant difference in the frequency of newly acquired postoperative white matter injury in infants with infection (30 percent), compared to those without (31 percent). When restricting the analysis to bloodstream infection, there was also no significant association with white matter injury (relative risk 1.3; 95 percent confidence interval 0.6 – 2.9, p equal to 0.5). Pneumonia (relative risk 0.9; 95 percent confidence interval 0.3 – 3.1, p equal to 0.9), and surgical site infection (relative risk 0.8; 95 percent confidence interval 0.2 – 2.7, p equal to 0.7) were also not associated with white matter injury.

Infection and White Matter Injury: Subgroup Analyses

Given the hypothesized association of infection with white matter injury, we examined the infants without stroke to avoid the potential overlapping impact of infection on both stroke and white matter injury. When analyzing only the 73 newborns without stroke, the estimated association between infection and white matter injury was higher, though the results were not significant for bloodstream infection (relative risk 1.9; 95 percent confidence interval 0.8 – 4.2, p equal to 0.1), pneumonia (relative risk 1.6; 0.5 – 5.1, p equal to 0.4), and surgical site infection (relative risk 1.0; 95 percent confidence interval 0.3 – 3.4, p equal to 1.0).

Because postoperative hypotension is an independent risk factor for white matter injury (23, 34) and postoperative hemodynamics vary by cardiac diagnosis and procedure, we performed subgroup analyses by cardiac anatomy. When considering cardiac anatomy, white matter injury was more common in the 29 infants with single ventricle anatomy (41 percent) as compared to the 64 with transposition of the great arteries (25 percent). While the overall association between infection and white matter injury among newborns with single ventricle anatomy and transposition of the great arteries was the same (relative risk 1.2; 95 percent confidence interval 0.4 – 3.7 vs. relative risk 1.1; 95 percent confidence interval 0.4 – 2.8), infants with transposition of the great arteries and bloodstream infection had an estimated risk of white matter injury that was twice as high as those with single ventricle anatomy and bloodstream infection (relative risk 2.2; 95 percent confidence interval 0.8 – 6.5 vs. relative risk 0.8; 95 percent confidence interval 0.2 – 2.5), though the difference was not significant. When considering only those without stroke, the risk of white matter injury in newborns with bloodstream infection was higher and significant for those with transposition of the great arteries (relative risk 3.2; 95 percent confidence interval 1.0 –

9.8, p equal to 0.04), but not single ventricle anatomy (relative risk 1.3; 95 percent confidence interval 0.4 – 4.0, p equal to 0.6) (Table 4).

Adjusted Analysis

Of the possible confounding covariates listed Table 1, only duration of inotrope therapy was associated with white matter injury. Again, there was no overall association between infection and white matter injury. However, the risk of bloodstream infection among the 64 newborns with transposition of the great arteries, after adjusting for days inotropes and mean postoperative blood pressure, persisted and was higher (odds ratio 7.3; 95 percent confidence interval 0.9 – 61.0, p equal to 0.06), especially when considering the only 42 newborns without strokes (odds ratio 182.3; 95 percent confidence interval 1.8 – greater than 100, p equal to 0.003).

Discussion

In this cohort of newborns with congenital heart disease admitted to one of two university hospitals for surgery, nosocomial infection was present in almost 20 percent of the population. Overall, infection had no effect on white matter injury. Bloodstream infection was associated with a trend toward higher frequency of white matter injury in those infants with transposition of the great arteries, but not those with single ventricle anatomy. After adjusting for markers of illness severity, and when considering only the children without stroke, the effect was stronger and significant. Because the pneumonias, bloodstream, and surgical site infections that we identified were hospital acquired, nearly all were potentially preventable.

Newborns with congenital heart disease may be critically ill with unstable hemodynamics before, during and following surgical repair. Multiple risk factors for stroke or white matter injury have been identified in this population, including cyanosis, invasive catheterization, hypotension and cardiac arrest(1, 23, 34, 35). Each type of congenital heart disease may have variable exposure to specific risk factors such as intracardiac shunting. Given the complex interplay between infection, inflammation and adverse hemodynamics, perhaps it is not surprising that we were not able to uncover a strong association between infection and brain injury in this heterogeneous sample of newborns with congenital heart disease. Nevertheless, these results suggest that the association between bloodstream infection and white matter injury in children with congenital heart disease is not as clear as for preterm children(26, 27, 29). The larger effect in children with transposition of the great arteries when compared with those with single ventricle anatomy may be related to differences in perioperative hemodynamic stability. The Norwood operation for palliation of single ventricle anatomy is associated with higher risk of mortality and hospital length of stay compared with the arterial switch procedure for correction of transposed great arteries (36, 37). For children with single ventricle anatomy, the presence of multiple potential risk factors for brain injury over a more prolonged admission may make an effect of infection more difficult to detect. The increased association after excluding those newborns with strokes highlights the fact that multiple potential risk factors, including infection, may have overlapping effects on the brain.

The reasons why children with congenital heart disease are susceptible to white matter injury, a pattern of injury more typically associated with premature birth is not known, but may be related to the fact that children with congenital heart disease appear to have delayed brain growth and maturation, making their brains resemble those of younger gestation children(16, 17). Brain immaturity is the substrate upon which other insults such as hypotension and hypoxemia provide the proximate injury mechanism. Furthermore, like their preterm counterparts, children with congenital heart disease often have prolonged

hospitalizations, extending the period of risk for multiple potential factors including nosocomial infection and hemodynamic instability. White matter injury in preterm newborns appears to be related to damage to pre-oligodendroglial cells, which are important for myelination. These oligodendrocyte precursors are extremely vulnerable to glutamate-receptor mediated injury and cell death following exposure to free radicals, reactive oxygen and nitrogen species, as well as inflammatory cytokines (reviewed in(38)). The causative “upstream mechanisms” – i.e., the events leading to production of these harmful factors -- are poorly understood, and may include ischemia, and/or infection/inflammation (reviewed in (39)). There is increasing evidence from clinical studies in preterm newborns that nosocomial infection is an important risk factor for white matter injury (26, 27, 29). It is not known whether the injury is a direct result of inflammation to the central nervous system or whether it is due to ischemia suffered as a result of impaired cerebral blood flow during periods of hypotension.

We acknowledge several limitations of this study. Although this is the largest reported cohort of newborns with congenital heart disease studied with pre- and post-operative imaging, the relatively small numbers of infants with infection requires our conclusions to be viewed with caution. Moreover, the cohort includes patients with multiple forms of congenital heart disease including transposition of the great arteries and single ventricle anatomy. In this critically ill population, there may be multiple causes for brain injury, and small cohort size may have limited the ability to find an association between our variables of interest. Finally, the optimal timing for detecting white matter injury in this cohort has not been determined; it is therefore possible that we missed white matter injury in some affected newborns who were imaged too early or too late to see changes related to infection, which would further restrict our ability to observe an effect.

Conclusions

The strong association of infection with white matter injury in premature newborns, combined with observations of delayed brain development in term newborns with congenital heart disease, provides clear rationale for the present study. However, heterogeneity inherent in the congenital heart disease population, along with multiple interacting risk factors may have obfuscated a relationship between infection and brain injury in this population. The fact remains that newborns with congenital heart disease suffer acquired brain injury at unacceptably high rates. In this study, we have provided a first measurement of the association of nosocomial infection with brain injury in infants with congenital heart disease. Interventions to reduce nosocomial infection may decrease brain injury, but a larger sample in more uniform populations will be necessary to definitively prove this concept. An alternative possibility is that previously identified risk factors for brain injury that directly impair brain oxygen delivery are relatively more potent, and thus more important, determinants of brain injury in newborns with congenital heart disease.

In order to improve developmental outcomes in this population, each of the risk factors for brain injury must be addressed individually. The infections that we identified in this study were hospital acquired, and therefore many may have been preventable. The suggestion that infection prevention has the potential to mitigate long-term neurologic impairment as a consequence of white matter injury underscores the importance of vigilant attention to infection control practices for pediatric patients undergoing cardiac surgery.

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Table 1

Clinical characteristics for 127 infants with congenital heart disease with and without nosocomial infection

	Infection N = 23	No Infection N = 104	P
<i>Clinical Characteristics</i>			
Admitting hospital, UCSF:UBC	19:4	70:34	0.1
Male	8 (35%)	73 (70%)	0.001
Gestational Age at Birth, wks	39.0 ($\pm$ 1.3)	39.1 ($\pm$ 1.4)	0.9
Birth Weight, g	3240 ($\pm$ 496)	3378 ($\pm$ 543)	0.3
SNAPPE Score	19 ($\pm$ 11)	12 ($\pm$ 7)	0.01
Lowest SaO ₂ (%)	72 ($\pm$ 15)	67 ($\pm$ 17)	0.2
<i>Operative Characteristics</i>			
Bypass Type			
Full flow	13 (56%)	56 (54%)	0.4
RCP	8 (35%)	21 (20%)	
DHCA	0	9 (9%)	
Low Flow	0	8 (8%)	
Other	2 (9%)	10 (10%)	
Lowest Flow	124 (80, 670)	163 (0, 700)	0.7
CPB Base Excess	-0.9 ($\pm$ 4.7)	-1.5 ($\pm$ 4.8)	0.6
<i>Postoperative Characteristics</i>			
Postoperative Day 1			
MBP	44 ($\pm$ 11)	43 ($\pm$ 6)	0.6
DBP	37 ($\pm$ 8)	36 ($\pm$ 7)	0.3
Total Days			
Inotropes	8 (3, 74)	5 (0, 33)	0.004
Mechanical Ventilation	9 (2, 106)	5 (1, 67)	0.001

Values are listed as N (%), mean ($\pm$ standard deviation) or median (range). **UCSF** University of California, San Francisco; **UCB** University of British Columbia; **SaO₂** oxygen saturation; **RCP** regional cerebral perfusion; **DHCA** deep hypothermic circulatory arrest; **MBP** mean arterial blood pressure; **DBP** diastolic arterial blood pressure.

Table 2

Characteristics of 23 infants with congenital heart disease and infection

	General Characteristics	Infection Between MRI	MRI Findings
<i>Transposition of the great arteries</i>			
1	Female 41 weeks 3980g UCSF	Bloodstream infection (<i>staphylococcus epidermidis</i> ; vancomycin & ceftazidime 1 week)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Small focus L peritrigonal white matter injury (WMI = 1)
2	Female 36 weeks 2719g UCSF	Bloodstream infection (<i>Klebsiella oxytoca</i> ; ceftazidime 10 days)	<i>MRI 1</i> : Developmental venous anomaly, with thrombosis and hemorrhage (WMI = 0) <i>MRI 2</i> : Developmental venous anomaly, with thrombosis and hemorrhage, focal ischemia R frontal white matter (WMI 1)
3	Male 40 weeks 3580g UCSF	Bloodstream infection (<i>Escherichia coli</i> ; gentamicin 10 days)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Two small foci of deep R frontal white matter (WMI = 1)
4	Male 38 weeks 2789g UBC	Bloodstream infection (<i>Enterobacter cloacae</i> ; meropenem 6 weeks)	<i>MRI 1</i> : R frontal white matter injury (WMI = 1) <i>MRI 2</i> : No new injury (WMI = 0)
5	Male 40 weeks 2830g UCSF	Bloodstream infection (<i>Bacillus species</i>) Surgical site infection (culture negative; vancomycin & ceftriaxone 14 days) Pneumonia (vancomycin and ceftriaxone 7 days)*	<i>MRI 1</i> : Single focus L periventricular white matter injury (WMI = 1) <i>MRI 2</i> : Normal (WMI = 0)
6	Female 39 weeks 3115g UBC	Bloodstream infection & surgical site infections (<i>Enterobacter cloacae</i> ; meropenem 6 weeks)	<i>MRI 1</i> : R MCA stroke (WMI = 0) <i>MRI 2</i> : resolving R MCA stroke (WMI = 0)
7	Female 39 weeks 3360g UCSF	Surgical site infection (culture negative; vancomycin and ceftazamide >5 days)	<i>MRI 1</i> : Hemorrhagic infarct lentiform nucleus (WMI = 0) <i>MRI 2</i> : No new injury (WMI = 0)
8	Female 39 weeks 3340g UBC	Surgical site infection (coagulase negative <i>staphylococcus</i> ; cloxacillin 5 days, cephalexin 5 days)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : R occipital lobe bleed (WMI = 0)
9	Female 39 weeks 3170g UCSF	Pneumonia (<i>parainfluenza virus</i>)	<i>MRI 1</i> : L PCA stroke (WMI = 0) <i>MRI 2</i> : resolving L PCA stroke (WMI = 0)
10	Male 41 weeks 4180g UCSF	Urinary tract infection (<i>Escherichia coli</i> and <i>staphylococcus</i> ; vancomycin, gentamicin & ceftriaxone 7 days) Pneumonia (culture negative; vancomycin & ceftriaxone 7 days) Foot cellulitis (culture negative; vancomycin & ceftriaxone 7 days)*	<i>MRI 1</i> : Scattered foci of reduced diffusion consistent with embolic injury (WMI = 0) <i>MRI 2</i> : New scattered foci of reduced diffusion consistent with embolic injury (WMI = 0)
<i>Single Ventricle Anatomy</i>			
11	Male 37 weeks 3020g UCSF	Bloodstream infection (<i>Escherichia coli</i> ; cefotaxime 6 weeks)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : R MCA and watershed distribution strokes (WMI = 0)
12	Female 41 weeks 3900g UCSF	Bloodstream infection (<i>staphylococcus epidermidis</i> ; vancomycin & ceftazidime 7 days)	<i>MRI 1</i> : R frontal and corpus callosum white matter injury (WMI = 2) <i>MRI 2</i> : three new foci of white matter injury (WMI = 2)

	General Characteristics	Infection Between MRI	MRI Findings
13	Female 39 weeks 3300g UCSF	Bloodstream infection (<i>staphylococcus epidermidis</i> ; <i>vancomycin</i> 6 days)	<i>MRI 1</i> : multiple areas of R parietal white matter injury; intraventricular hemorrhage (WMI = 3) <i>MRI 2</i> : L PCA stroke (WMI = 0)
14	Female 39 weeks 3550g UCSF	Bloodstream infection (<i>enterococcus faecalis</i> ; <i>vancomycin</i> & <i>piperacillin/tazobactam</i> → <i>ampicillin</i> & <i>gentamicin</i> 4 weeks)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Normal (WMI = 0)
15	Male 39 weeks 3670g UCSF	Bloodstream infection (<i>bacillus species</i> ; <i>gentamicin</i> , <i>vancomycin</i> , <i>piperacillin/tazobactam</i> 6 days)	<i>MRI 1</i> : L MCA stroke; R parietal white matter injury (WMI = 1) <i>MRI 2</i> : resolving injury (WMI = 0)
16	Female 38 weeks 2740g UCSF	Bloodstream infection (<i>staphylococcus epidermidis</i> ; <i>vancomycin</i> 10 days) Pneumonia (<i>klebsiella pneumoniae</i> ; <i>piperacillin/tazobactam</i> unclear duration) Surgical site infection (<i>vancomycin</i> >10 days)*	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Normal (WMI = 0)
17	Female 38 weeks 3220g UCSF	Surgical site infection (<i>Escherichia coli</i> ; <i>vancomycin</i> & <i>cefotaxime</i> → <i>clindamycin</i> & <i>cephalexin</i> 3 weeks)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Multiple white matter lesions R hemisphere & splenium of corpus callosum (WMI = 2)
18	Male 37 weeks 2950g UCSF	Surgical site infection (<i>enterococcus species</i> ; <i>vancomycin</i> & <i>gentamicin</i> → <i>ampicillin</i> 5 days)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Normal (WMI = 0)
19	Male 39 weeks 3040g UCSF	Pneumonia (<i>Escherichia coli</i> ; <i>cefotaxime</i> & <i>clindamycin</i> 10 days)	<i>MRI 1</i> : > three foci of white matter injury, frontal lobes (WMI = 2) <i>MRI 2</i> : Extensive bilateral cystic white matter injury (WMI = 3)
Other heart lesion			
20	Female 38 weeks 2428g UCSF	Bloodstream infection (<i>staphylococcus aureus</i> ; <i>nafcillin</i> & <i>gentamicin</i> 6 weeks)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Normal (WMI = 0)
21	Female 40 weeks 2990g UBC	Surgical site infection (<i>Staphylococcus aureus</i> ; <i>cephalexin</i> >5 days)	<i>MRI 1</i> : not done <i>MRI 2</i> : Normal (WMI = 0)
22	Female 39 weeks 2892g UCSF	Pneumonia (<i>staphylococcus aureus</i> ; <i>ampicillin</i> and <i>cefotaxime</i> 7 days)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : R MCA stroke (WMI = 0)
23	Female 41 weeks 3250g UCSF	Viral pneumonia (<i>Respiratory syncytial virus</i>)	<i>MRI 1</i> : Normal (WMI = 0) <i>MRI 2</i> : Normal (WMI = 0)

UCSF University of California, San Francisco; UBC University of British Columbia; MRI magnetic resonance imaging; TGA transposition of the great arteries; VSD ventricular septal defect; SVA hypoplastic left heart syndrome; MCA middle cerebral artery; PCA posterior cerebral artery

* Overlapping antibiotic regimens

Table 3

Nosocomial infection in 127 infants with CHD

Type of infection	N (%)
Bloodstream infection	13 (10%)
- <i>Staphylococcus epidermidis</i>	4
- <i>Escherichia coli</i>	2
- <i>Enterobacter cloacae</i>	2
- <i>Bacillus</i>	2
- <i>Staphylococcus aureus</i>	1
- <i>Enterococcus</i>	1
- <i>Klebsiella</i>	1
Surgical site infection	8 (6%)
Pneumonia	7 (6%)
Total with 1 or more infections	23 (18%)

Table 4

Bloodstream infection and white matter injury among 64 infants with transposition of the great arteries (TGA) and 29 infants with single ventricle anatomy (SVA), and stratified by presence of stroke

	WMI	No WMI	RR (95% CI)	P
<i>Transposition of the great arteries; N = 64</i>				
All TGA	N = 16	N = 48		
	3 (19%)	3 (6%)	2.2 (0.8 – 6.5)	0.1
TGA without stroke	N = 10	N = 32		
	3 (30%)	2 (6%)	3.2 (1.0 – 9.8)	0.04
<i>Single ventricle anatomy; N = 29</i>				
All SVA	N = 12	N = 17		
	2 (17%)	4 (24%)	0.8 (0.2 – 2.5)	0.7
SVA without stroke	N=10	N=9		
	2 (20%)	1 (11%)	1.3 (0.4 – 4.0)	0.6

WMI white matter injury