Risk Factors for Catheter-associated Bloodstream Infections in a Pediatric Cardiac Intensive Care Unit

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Background: Catheter-associated bloodstream infections (CA-BSIs) are an important complication of care in children hospitalized with complex congenital heart disease; however, little is known about risk factors for CA-BSI in these patients.

Methods: We conducted a retrospective nested case-control study in the 26-bed Cardiac Intensive Care Unit (CICU) at the Children's Hospital of Philadelphia. We identified all primary CA-BSIs in the CICU between January 1, 2004 and June 30, 2005. Controls were selected from rosters of CICU patients that were admitted during the same time period. Incidence density sampling was used to match cases and controls on time at risk. Data on demographic features and clinical characteristics were abstracted from the medical record. In addition, detailed data on exposures to medical devices, interventions, and therapeutic agents were gathered during a 4-day period immediately before the onset of infection (cases) or study entry (controls).

Results: We identified 59 children who developed a CA-BSI. The median time from catheter insertion to onset of infection was 9 days. Over half of infections were caused by gram positive organisms. On multivariable analysis, only tunneled catheters emerged as an independent risk factor for infection.

Conclusion: In this study population, tunneled catheters were associated with a higher risk of CA-BSI, possibly because of the catheter material. Additionally, we did not find that the burden of catheters and medical devices was associated with an increased risk of infection. Because most CA-BSIs in our study population occurred ≥7 days after catheter insertion, strict attention to aseptic technique when using or dressing a catheter might reduce CA-BSI rates in the pediatric CICU.

Key Words: catheter-associated bloodstream infections, pediatrics, cardiac intensive care

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Catheter-associated bloodstream infections (CA-BSI) are an important complication experienced by critically and chronically ill children and are associated with significant morbidity and mortality.[1–3] Previous studies have demonstrated that factors such as underlying disease, presence of intravascular devices, and use of selected medications are associated with increased risk for CA-BSI among children or adults admitted to medical intensive care units.[1,2,4–6]

Several observations suggest that the risk factors for CA-BSI might differ between children with and without complex congenital cardiac disease. Abnormal vascular anatomy and the need to preserve vessel patency for future repairs can limit the sites available for placement of a central venous catheter (CVC) in children with structural heart disease. Many characteristics of critically ill children with cardiac disease may alter their response to infection and breach natural barriers to infection. These children may experience end-organ dysfunction and systemic inflammation secondary to cardiopulmonary bypass,[7] hyperglycemia,[8] and intraoperative hypothermia.[9,10] Critically ill children with cardiac disease often require multiple transfusions,[11] as well as multiple intravascular devices[2] and other percutaneous medical devices (such as chest tubes and mediastinal drains). In addition, pediatric patients who experience mediastinitis or require extracorporeal membrane oxygenation (ECMO) after cardiac surgery are at increased risk of bloodstream infections.[12] Finally, factors such as hypoxia and poor tissue perfusion attributable to their underlying cardiac physiology may alter their risk of infection.[1] Studies of pediatric patients who undergo cardiac surgery show that factors such as increased length of stay (LOS) in the intensive care unit, increased duration of central venous catheterization, delayed sternal closure, and neonatal age are associated with an increased risk of healthcare associated infections.[13,14]

As previous studies have primarily focused on patient characteristics as risk factors for CA-BSI, the purpose of our study was to identify potential modifiable risk factors for CA-BSI in the pediatric cardiac intensive care unit (CICU) patient population.

MATERIALS AND METHODS

We conducted a retrospective, nested case-control study among patients admitted to the 26-bed CICU at the Children's Hospital of Philadelphia during an 18-month study period (January 1, 2004–June 30, 2005). The conduct of this study was approved by the Committee for the Protection of Human Subjects at the Children's Hospital of Philadelphia.

Case Ascertainment

CICU patients with primary CA-BSI were identified by certified Infection Control practitioners through an ongoing active surveillance program that relies on the application of standard definitions of CA-BSI developed by the Centers for Disease Control's National Nosocomial Infection Surveillance system, 1996.[15] Patients were included if they developed CA-BSI for >48

hours after admission to CICU. Standard data gathered included patient name, date of reported infection, and organism isolated.

Control Selection

Time at risk is an important confounder in clinical epidemiologic research, particularly when assessing risk factors for disease in critically ill patients. We used a strategy of matching cases to controls based on time at risk, called incidence density sampling, to ensure similarity in exposure status among study subjects, leading to increased statistical efficiency.[16,17,18]

One case was matched to one control based on the duration of stay in the CICU before infection.[17] By matching each case to a control with an equivalent duration of stay in the CICU as the duration of stay for the case before infection, cases and controls shared equivalent time at risk for CA-BSI to minimize confounding based on time at risk. Controls were selected from rosters of patients admitted to the CICU who had 1 or more CVCs in place during the study period. In addition, cases could serve as controls for other cases that occurred before their infection date, as long as the periods of observation did not overlap. In our study, 8 cases served as controls before their infection.

Data Collection

In addition to demographic characteristics, underlying cardiac physiology, and mortality during hospitalization, we were interested in the exposures to medical devices, interventions, and therapeutic agents that occurred within close proximity to the infection. Therefore, we created a 4-day time period between the day of infection and the 3 days before infection for the purposes of data collection and characterized this as the exposure window. Data were entered on a standardized report form and included demographics variables, cardiac lesion, mortality, catheter and device status, surgical and invasive procedures, and medication history. Congenital heart defects were classified using a previously published schema based on the presence of a single or bi-ventricular circulation with or without arch obstruction.[19] Exposure to devices was quantified in terms of days, counting each device and its duration separately. Please refer to Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/A465, for the device and therapeutic agent classifications that were used to collect exposure data.

Statistical Analysis

Summary statistics were constructed using frequencies and proportions for categorical data elements and medians with interquartile ranges (IQR) for continuous variables using STATA 10.0 statistical software (College Station, TX). Univariate analyses were conducted to evaluate possible associations between CA-BSI and exposures during the 4-day exposure window. Variables found to have a P value of <0.20 in the matched univariate analysis were considered for inclusion in a multivariate conditional logistic regression model to identify independent risk factors for CA-BSI in the CICU patient population. Conditional logistic regression was used for all univariate and multivariate statistics to account for the matching of cases to controls based on LOS before infection.[20] Statistical significance was determined a priori as a P value <0.05 (two-tailed). An a priori power calculation demonstrated that assuming 80% power, minimal correlation of exposure between cases and controls (0.2), 70 patients with primary CA-BSI (cases) matched to 70 controls and the proportion of controls exposed to a risk factor of >0.2, an odds ratio (OR) of ~ 3.0 could be detected.

RESULTS

Patient Characteristics

We identified 59 patients with primary CA-BSIs in the CICU between January 1, 2004 and June 30, 2005 (8.1 infections per 1000 central catheter days). An additional 59 matched controls were also identified for analysis; 8 cases served as controls before their exposure. Although 70 patients with CA-BSI were initially identified, on careful review, we found that 11 patients had catheters of noncentral location, experienced secondary rather than primary CA-BSI, or had incomplete exposure data captured in the medical chart. The most common cardiac anatomic lesion for both cases and controls was single ventricle with arch obstruction (39% vs. 34%, respectively) (Table 1). The median age of cases and controls was 0.96 months and 1.2 months, respectively (Table 2).

Patient Outcomes

The median hospital LOS was similar for cases and controls (56 vs. 48 days, respectively). We did not detect a difference in mortality during index hospitalization between the 2 groups (14/59 [24%] cases vs. 9/59 [15%] controls, $P = 0.257$).

Epidemiology and Microbiology of CA-BSI

The median time to infection from admission to the CICU was 15 days (IQR: 8–20 days). The median time from CVC insertion to CA-BSI was 9 days (IQR: 7–15 days). Most organisms isolated from patients with confirmed primary CA-BSI were gram positive (73%). The organisms isolated from patients with confirmed CA-BSI were as follows: coagulase-negative *Staphylococci* (49%), gram negative bacilli (19%), *Staphylococcus aureus* (12%), and other organisms (20%).

Risk Factors for CA-BSI

Three categories of potential risk factors associated with the development of CA-BSI were examined: (1) exposures to CVS; (2) exposures to other medical devices; and (3) receipt of therapeutic agents. Overall, cases and controls had a similar total exposure, measured in days, to indwelling medical devices (catheters and other devices) during the 4 day exposure window ($P = 0.368$) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A466).

Central Venous Catheters

The median number of CVCs in place during the exposure window was 2 for both cases and controls (IQR: 1, 3). Most cases

TABLE 1. Cardiac Anatomy Category

Category	Examples	Controls (n = 59)	Cases (n = 59)	P*
No structural heart disease	Cardiomyopathy; cardiac transplant	6 (10%)	8 (14%)	REF
Two ventricles without arch obstruction	Transposition of the great arteries tetralogy of Fallot	15 (25%)	11 (19%)	0.267
Two ventricles with arch obstruction	Interrupted aortic arch ventricular septal defect with aortic coarctation	5 (8%)	8 (14%)	0.960
Single ventricle without arch obstruction	Tricuspid atresia with normally related great arteries	10 (17%)	12 (20%)	0.681
Single ventricle with arch obstruction	Hypoplastic left heart syndrome	23 (39%)	20 (34%)	0.327

*P-values have been adjusted to account for a matched analysis.

TABLE 2. Demographic and Clinical Characteristics

Characteristic	Controls (n = 59)	Cases (n = 59)	P*
Age in years (median, IQR)	0.08 (0.03, 1.6)	0.1 (0.04, 0.6)	0.079
Female sex	27 (46%)	28 (47%)	0.853
Total hospital length of stay	48 (24, 71)	56 (33, 106)	0.665
Another infection during the exposure window	5 (8%)	4 (7%)	0.739
Operative procedure: operating room	55 (93%)	53 (90%)	0.484
Operative procedure: CICU	25 (42%)	18 (31%)	0.213
Prior receipt of heart transplant	4 (7%)	4 (7%)	1.000

*P-values have been adjusted to account for a matched analysis.

and controls had 1 or more transthoracic intracardiac catheters present during the exposure window. Similar proportions of cases and controls had PICC catheters. However, a higher proportion of the cases had tunneled central catheters ($P = 0.019$). Catheter material was examined, revealing that 5 cases and 0 controls had tunneled catheters made of silicone.

Other Medical Devices and Exposures

During the exposure window, controls tended to have a chest tube in place or undergo a surgical procedure in the operating room more often than cases (statistically insignificant). Although not statistically significant, cases when compared with controls tended to have a higher frequency of radial arterial catheter use (39% vs. 24%, $P = 0.068$) and a higher frequency of nonvascular device use (ie, gastrostomy tubes, endotracheal tubes, and Foley catheters) (92% vs. 81%, $P = 0.080$).

Therapeutic Agents

Cases were more likely than controls to receive anticoagulants during the exposure window ($P = 0.014$) and less likely to receive antibiotics before the day of infection ($P = 0.006$). The most common indications for antibiotics were perioperative prophylaxis or completion of therapy for other infections.

Multivariate Analysis to Identify Independent Risk Factors for CA-BSI

We constructed a multivariable model to identify independent risk factors for CA-BSI and included all variable with a univariate $P < 0.20$. The independent risk factor for CA-BSI acquisition was presence of a tunneled central catheter (OR: 4.36, confidence interval: 1.27, 14.92, adjusted for antibiotic exposure before study entry). Individuals who received antibiotics before the last day of the exposure window were less likely to develop CA-BSI (OR: 0.27, confidence interval: 0.11, 0.70, adjusted for tunneled catheter).

DISCUSSION

In this case-control study, we attempted to identify modifiable risk factors for CA-BSI among critically ill children with complex congenital heart disease. We found that the presence of a tunneled central catheter was an independent risk factor for CA-BSI acquisition and individuals who received antibiotics before the last day of the exposure window were less likely to develop CA-BSI. Although previous studies have evaluated patient related factors such as underlying disease and demographic data in relation to CA-BSI, we also gathered information to explicitly describe the CICU patient experience surrounding devices and therapies.

The only independent risk factor for CA-BSI we identified was the presence of a tunneled central catheter. Of note, there was no association between presence of a tunneled catheter and cardiac anatomy category or surgery during the exposure window for either cases or controls. Because tunneled catheters made of silicone were available in our institution during the study period, we hypothesize that catheter material, rather than catheter type, may have driven this association. Studies in animal models have shown that catheters made of silicone are associated with increased risk of bacteremia.[21,22] Marosok et al[21] posit that neutrophil-mediated killing on silicone surfaces may not be as efficient at clearing potential pathogens. On additional review of catheter materials, we determined that 5 of 15 cases (33%) had tunneled catheters made of silicone. No controls had silicone-tunneled catheters in place during the exposure window. All other tunneled catheters were polyurethane. This observation may explain some of the risk associated with tunneled catheters on the development of CA-BSI.

We found that patients who received antibiotics before the clinical onset of infection were less likely to develop a CA-BSI. We presume that antecedent antibiotic exposure may have reduced the bacterial burden in biofilm adherent to some catheters and thus reduced the risk of subsequent infection. However, important issues, such as the rapid emergence of antibiotic resistant organisms, may prohibit routinely prescribing antibiotics solely to prevent CA-BSI.

Processes of care, including the frequency and technique used to access catheters, may be the most important determinants for CA-BSI. We found that the median time to CA-BSI after catheter insertion was 9 days, with <25% of the cases occurring at <7 days from catheter placement. This finding suggests that breaches in aseptic technique for catheter maintenance, not issues with catheter insertion, were more likely to have contributed to the development of the CA-BSIs in our study population. By re-educating healthcare providers that are involved in the day-to-day care of critically ill patients on best practices surrounding central catheter maintenance, it may be possible to decrease rates of CA-BSI. In a study conducted in the pediatric intensive care unit (PICU) at The Johns Hopkins Hospital, after the introduction of a multitiered intervention surrounding best practices of CVC insertion, the investigators saw a reduction from 5.2 ± 4.5 CA-BSI cases per 1000 central catheter days to 2.7 ± 2.2 CA-BSI cases per 1000 central catheter days ($P < 0.05$).[23] A similar multidisciplinary intervention was implemented in the CICU of Children's Hospital Boston, which also reduced the CA-BSI rate from 7.8 CA-BSI per 1000 central catheter days to 2.3 CA-BSI per 1000 central catheter days.[24]

It should be noted that of the 59 infections that were identified during the time period, over half of the causative organisms are considered normal skin flora. Coagulase negative *Staphylococci* were isolated in 49% of the cases, and another 12% of the infections were caused by *Staphylococcus aureus*. These data are consistent with the hypothesis that breaks in appropriate technique for catheter care and maintenance that led to catheter colonization and subsequent CA-BSI.

By matching based on time at risk, we were able to more precisely identify truly significant differences in exposure between patients who developed CA-BSI and those who did not, although there were few differences to report. In addition, we constructed a exposure window for data collection purposes to determine whether specific events occurring close to infection onset had a significant impact on CA-BSI.

There are limitations to our study. Although the presence of a tunneled catheter was the only independent risk factor for CA-BSI that was identified, it is important to note that some patients had multiple CVSs in place during the exposure window. In these patients, it was not possible to attribute the infection to one particular catheter. As all data were collected retrospectively from medical record review, there could have been exposure misclassification. To address this information bias, we used a standardized collection form, and all data were abstracted and entered by the same trained medical record abstractor. We limited data collection to those exposures reliably obtained by chart review and to potentially modifiable factors. Although we did collect some data on patient characteristics, this was primarily performed for description of the patient population and understanding the context of the results. For example, we did not collect intraoperative support times because this was not thought to be a modifiable risk factor. There may be some known (or unknown) exposures that we did not study. In regard to this limitation, hyperglycemia is an exposure of interest but was unlikely to be prevalent during the exposure window because most of the episodes of hyperglycemia occur and resolve within the first 48 hours after cardiac surgery.[8,25] The issue of glucose management and risks in the critically ill pediatric patients is a topic of ongoing research at this time. Finally, the case-control study design we used is subject to more opportunities for bias and misclassification when compared with randomized controlled trials or cohort studies; however, because of the relatively rare nature of the outcome in our patient population, the case-control design is the most efficient mechanism for identifying risk factors for CA-BSI in the CICU.[20]

In summary, we identified that tunneled CVC were associated with a higher risk of CA-BSI and that antibiotic administration was protective against CA-BSI. Additionally, we did not find that the burden of catheters and medical devices was associated with an increased risk of infection. Because most CA-BSIs in our study population occurred $\geq$7 days after catheter insertion, we believe that deliberate aseptic catheter maintenance, and vigilant infection control practices, will lead to a decrease in CA-BSI rates in the pediatric CICU as has been observed in other critically ill patient populations.

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