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Moving CLABSI Prevention Beyond the ICU: Risk Factors in Pediatric Oncology Patients

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Abstract

Background and Objective—Central line-associated bloodstream infections (CLABSIs) frequently complicate the use of central venous catheters (CVCs) among pediatric patients with cancer. Our objectives were to describe the microbiology and identify risk factors for hospital-onset CLABSI in this patient population.

Design—Retrospective case-control study.

Setting—Oncology and stem cell transplant units of a freestanding, 396-bed quaternary care pediatric hospital.

Participants—Case subjects (N=54) were patients with a diagnosis of malignancy and/or stem cell transplant recipients with CLABSI occurring during admission. Controls (N=108) were identified using risk set sampling of hospitalizations among patients with a CVC, matched on date of admission.

Methods—Multivariate conditional logistic regression was used to identify independent predictors of CLABSI.

Results—The majority of CLABSI isolates were Gram-positive bacteria (58%). The most frequently isolated organism was *Enterococcus faecium*, and 6 of 9 isolates were resistant to vancomycin. In multivariate analyses, independent risk factors for CLABSI included platelet

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transfusion within the prior week (odds ratio [OR], 10.90 [95% confidence interval {CI}, 3.02–39.38], P<0.001) and CVC placement within the previous month (<1 week vs. ≥1 month: OR, 11.71 [95% CI, 1.98–69.20], P=0.02; ≥1 week and <1 month vs. ≥1 month: OR, 7.37 [95% CI, 1.85–29.36], P=0.004).

Conclusions—Adjunctive measures to prevent CLABSI among pediatric oncology patients may be most beneficial in the month following CVC insertion and in patients requiring frequent platelet transfusions. Vancomycin-resistant enterococci may be an emerging cause of CLABSI in hospitalized pediatric oncology patients and are unlikely to be treated by typical empiric antimicrobial regimens.

Introduction

Central venous catheters (CVCs) are indispensable in the treatment of cancer in children, minimizing the need for venipuncture and facilitating the administration of chemotherapy, parenteral nutrition and blood products. However, these devices are associated with several complications, the most frequent of which is bloodstream infection.[1] Central line-associated bloodstream infections (CLABSIs) are among the most common healthcare-associated infections, and result in prolongation of hospital stay, considerable morbidity, and an increase in crude mortality.[2–4] Moreover, with an estimated attributable cost of approximately $40,000 per episode, the financial consequences to the health care system are substantial.[2,5]

The incidence of CLABSI among pediatric oncology patients is comparable to that of other high-risk populations. In the most recent report from the National Healthcare Safety Network, the pooled mean CLABSI rates per 1,000 catheter-days among hospitalized pediatric hematology/oncology patients were 2.3 for permanent CVCs and 4.6 for temporary CVCs, while the rate observed in pediatric intensive care units was 3.0.[6] Moreover, the cumulative risk for CLABSI among pediatric oncology patients likely exceeds that of children in intensive care units given the frequent need for prolonged venous access. While several studies have assessed risk factors for CLABSI among critically ill children, surprisingly little research has been conducted among pediatric patients with cancer. The literature does support a decreased rate of infection with implantable ports compared with tunneled externalized catheters, but the role of other factors remains poorly defined.[7–10]

As treatments for pediatric malignancies continue to be refined, prevention of CLABSI will be critical to achieving further reductions in the morbidity and mortality of children with cancer. Evidence-based line insertion and maintenance bundles decrease the incidence of CLABSI in critically ill adults and children, and are now considered standard practice.[11–15] However, adjunctive measures such as antibiotic-coated catheters, antimicrobial-impregnated sponges, and antibiotic lock solutions may further reduce the incidence of CLABSI in selected patients, although widespread use remains limited by cost and a lack of prospective data in children.[16–18] Identifying a subset of patients who are most at-risk for CLABSI could guide the application of these interventions in pediatric oncology. We sought to determine risk factors for hospital-onset CLABSI among pediatric oncology patients

following the implementation of standardized line insertion and maintenance practices at our institution.

Materials and Methods

Selection of Case and Control Subjects

Surveillance for CLABSI was performed prospectively by the Infection Prevention and Control and Oncology programs at Children's Hospital Boston throughout the study period. CLABSI was defined per the Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definition as 1) a recognized pathogen cultured from 1 or more blood cultures and organism cultured is not related to infection at another site, 2) fever (>38°C), chills, or hypotension and common skin contaminant is cultured from 2 or more blood cultures drawn on separate occasions and signs and symptoms and positive laboratory results are not related to an infection at another site, or 3) patient ≤1 year of age has fever (>38°C, rectal), hypothermia (<37°C, rectal), apnea, or bradycardia and common skin contaminant is cultured from 2 or more blood cultures drawn on separate occasions and signs and symptoms and positive laboratory results are not related to an infection at another site.[19] Case subjects were patients with a diagnosis of malignancy and/or stem cell transplant recipients who were hospitalized after May 1 2007 and developed a CLABSI before July 31 2009 and had no symptoms of infection at the time of admission. Eligible controls were patients with a diagnosis of malignancy and/or stem cell transplant recipients admitted during the study period and hospitalized for more than 48 hours with a CVC who did not develop a CLABSI. Two control subjects were matched to each case based on date of admission (±1 month). Patients with multiple hospitalizations were permitted to be selected as a control more than once, while a case subject could serve as a control if the date of discharge was more than one month prior to the date of admission for the CLABSI hospitalization. If a case subject experienced multiple CLABSI during the study period, only the first episode was included in the analysis.

Risk Factor Assessment

We considered 30 potential predictors after reviewing published literature regarding risk factors for CLABSI in pediatric oncology patients and other populations. These variables included patient characteristics, oncologic disease and treatment factors, blood product transfusions, medications and procedures, CVC characteristics, and indicators of CVC maintenance or malfunction (Table 1).

Poor nutritional status was determined using Centers for Disease Control and Prevention growth charts and was defined as weight-for-age <5th percentile for patients 0–35 months, body mass index-for-age <5th percentile for patients 3–19 years, and body mass index <18.5 for patients ≥20 years.[20] Oncologic diagnosis was classified as either hematologic malignancy or solid tumor. Patients who had undergone stem cell transplantation for a non-malignant condition were not included in the bivariate analysis of oncologic diagnosis but contributed to all other analyses including the multivariate analysis. Patients with leukemia were classified as having uncontrolled disease following diagnosis or relapse but before laboratory-confirmed remission in bone marrow (or other known sites of disease). Patients

with lymphomas or solid tumors were considered to have uncontrolled disease if malignancy was identified on the most recent imaging and, for solid tumors, if the patient had not undergone gross total resection in the interim. Several indicator variables were created to assess specific chemotherapeutic medications with each agent classified by mechanism (alkylating agent, antimetabolite, or antibiotic [anthracyclines, bleomycin, actinomycin]), anticipated degree of bone marrow suppression (none-minimal, moderate-severe), and mucosal toxicity (yes, no). Mucositis was assessed through review of nursing and physician notes on the date of CLABSI for cases and the date of discharge or death for controls. Neutropenia was determined based on the lowest absolute neutrophil count (ANC) reported in the patient's chart for the preceding 1 week. Number of line accesses was derived from medication administration records and documentation of transfusions or blood draws. Procedure was defined as any invasive procedure with the exception of venous or arterial blood draw, peripheral intravenous line placement, or nasogastric tube placement. CVC type was classified as tunneled externalized catheter, non-tunneled catheter, or implantable port. For case subjects with multiple catheters, the CVC from which the initial positive blood culture was drawn was used in the analysis. In addition, one control subject had multiple catheters; in this situation, we included the tunneled externalized CVC in the analysis rather than a more recently placed non-tunneled catheter.

Data pertaining to potential risk factors were collected retrospectively. We assessed all risk factors among case subjects in relation to the date of CLABSI. For control subjects, we assessed risk factor information in relation to the date of discharge or death.

Statistical Analysis

To identify predictors of CLABSI, we used a two-stage approach based on bivariate and multivariate conditional logistic regression models. In the first stage, we assessed each risk factor individually and any non-significant predictor ($P \geq 0.05$) was excluded from further consideration. The remaining covariates were then used to construct a multivariate model using a stepwise-forward selection procedure in which the entry and exit criteria were set to $P < 0.05$. In all models we conditioned on the matched set of case and control subjects defined by date of admission for the case. In addition, case subjects were hospitalized an average of 22.9 days prior to the development of CLASBI, while control subjects were hospitalized for an average of 7.8 days. To account for the difference in duration of exposure to risk factors between cases and controls, all analyses were adjusted for length of hospitalization prior to either date of CLABSI for cases or date of death or discharge for controls. All statistical analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC). This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Results

Patient Characteristics

CLABSI rates during the study period at our institution were 3.4 per 1,000 catheter-days among patients admitted to the pediatric oncology ward and 2.8 per 1,000 catheter-days among patients admitted to the stem cell transplant unit. A total of 54 hospital-onset

CLABSI occurred among eligible patients during the study period. We identified an additional 108 hospitalizations to serve as controls for these cases. Demographic features of the sample are presented in the first two columns of Table 1. The median age of the population was 8.6 years (range 2 months −20 years), and 60% were male. The majority (62%) of patients had hematologic malignancies, with acute lymphoblastic leukemia being the most frequent diagnosis. 23 cases and 12 controls had ever undergone stem cell transplantation, with 23% of these patients having received autologous transplants. The most frequent indications for stem cell transplantation were acute lymphoblastic leukemia and acute myelogenous leukemia, while six patients had been transplanted for a non-malignant condition such as aplastic anemia or myelodysplastic syndrome. Almost two-thirds of CVCs were implantable ports, and 5% of patients had multiple catheters.

Microbiology of Hospital-Onset CLABSI

The specific pathogens cultured from the 54 CLABSI are listed in Table 2. A total of 59 organisms were recovered as 2 organisms grew in culture for 5 (9%) of the cases. Of the 59 isolates, 34 (58%) were Gram-positive bacteria, 19 (32%) were Gram-negative bacteria, and 6 (10%) were yeast. *Enterococcus faecium* was the most frequently recovered organism, and 6 of 9 isolates were resistant to vancomycin. *Staphylococcus aureus* was cultured from 8 patients and all of the isolates were susceptible to methicillin. *Enterobacter cloacae* was the most frequently encountered Gram-negative organism, while the majority of fungal isolates were *Candida parapsilosis*.

Risk Factors

The final two columns of Table 1 detail the results of bivariate analyses. Patient-dependent variables that were significantly associated with hospital-onset CLABSI included hematologic malignancy, stem cell transplant recipient, days since most recent chemotherapy, neutropenia, transfusion of red blood cells or platelets, and parenteral nutrition. In addition, CVC type, number of lumens, duration since CVC placement, and >100 line accesses in the prior 72 hours were also associated with CLABSI. Bivariate analysis could not be performed for fluoroscopic line study within the prior week because of sparse data. Mucositis was also omitted because data for this variable in patient medical records were disproportionately missing among control subjects. The results of multivariate analysis are presented in Table 3. Independent predictors of CLABSI included platelet transfusion within the prior week and recent CVC placement.

Discussion

We found that platelet transfusion in the prior week and recent CVC placement were independent predictors of CLABSI in hospitalized pediatric oncology patients. Furthermore, while not a significant predictor in multivariate analyses, a high number of central line accesses was associated with CLABSI in bivariate analysis, a finding that supports current strategies to minimize line accesses in patients with CVCs.

One of the most important challenges of CLABSI surveillance is ensuring consistency in the application of the definitions. Several studies have found that variability in interpretation

exists across institutions, which has important implications for public reporting of CLABSI rates and reimbursement by third-party payers.[21,22] Oncology patients with CVCs may present a particular challenge as bacterial translocation across compromised intestinal barriers may be responsible for bacteremia, although the surveillance definition does not classify such bloodstream infections as secondary without a specific infection at another site. In order for CLABSI rates in oncology patients to be fairly compared across institutions, it is critical that the surveillance definition be applied consistently.

Several possible explanations exist for the observed association between platelet transfusion and CLABSI. First, bacterial contamination of platelet donations may have resulted in bloodstream infection in recipients, although this is unlikely with modern methods of bacterial detection.[23] Alternatively, platelet transfusion may have altered immune function among recipients, transiently increasing the risk of bloodstream infection. This effect, termed transfusion-related immunomodulation, has been recognized for decades, with studies demonstrating decreases in CD4/CD8 ratio, cytokine production, and macrophage function following allogeneic red blood cell transfusion, and more recent evidence suggesting that similar immune abnormalities occur after allogeneic platelet transfusion.[24–28] Although the clinical implications of these immune alterations remain controversial, allogeneic blood products have been shown to increase the risk of post-operative bacterial infection in several human studies.[29,30] Third, platelet transfusion was significantly associated with neutropenia ($P<0.001$), a variable that has previously been associated with bacteremia in acute leukemia patients and with CLABSI severity in pediatric oncology patients.[31,32] Finally, platelet transfusion may have been associated with an unmeasured risk factor.

The relationship between catheter duration and CLABSI has been evaluated in several pediatric studies, although, to our knowledge, never before in detail in oncology patients. The majority of these previous studies were conducted in neonatal and pediatric intensive care units and suggested an increased rate of CLABSI with prolonged catheter duration.[33,34] In contrast, we found that pediatric oncology patients are at increased risk for CLABSI during the first month following CVC placement. This finding may differ from those in other settings for several reasons. Most notably, prior research in children has involved almost exclusively non-tunneled catheters, while totally implantable or tunneled externalized devices are more frequently employed in pediatric oncology and constituted the overwhelming majority of catheters in our analysis. Furthermore, as CVCs are often inserted within several days of oncologic diagnosis at our institution, the month following placement corresponded with induction therapy for many patients in the study. However, delaying catheter insertion has not been shown to reduce the incidence of CLABSI during treatment for acute lymphoblastic leukemia, and we did not find neutropenia or chemotherapy to be independent predictors of CLABSI, suggesting that other factors are involved.[35] Our findings indicate that interventions to prevent CLABSI in these patients may be most beneficial in the month following CVC insertion. As an example, adjunctive measures such as antibiotic lock solutions or antimicrobial-impregnated sponges might be employed during the month after a CVC is inserted, although future studies will need to determine the incremental value of these interventions.

As has been observed previously among pediatric oncology patients, Gram-positive bacteria caused the majority of hospital-onset CLABSI.[8,35–37] However, in contrast to prior studies, coagulase-negative staphylococci were not the most frequent cause of CLABSI in our population. This difference likely relates to a revision of the surveillance definition for CLABSI that resulted in more stringent criteria for infection caused by common skin contaminants. The current definition states that, in addition to the presence of signs and symptoms of infection, a common skin contaminant must be isolated from two or more blood cultures drawn on separate occasions, while the prior definition had also included cases in which a common skin contaminant was isolated from one blood culture and appropriate antimicrobial therapy was initiated.[19,38] Although variations in practice do exist, clinicians at our institution typically administer broad-spectrum antibiotics to febrile oncology patients with CVCs after an initial set of blood cultures is obtained. As a result, subsequent blood cultures are frequently negative, even when a common skin contaminant is isolated from the first set of cultures. Such patients do not meet criteria for CLABSI using the current surveillance definition, even if the treating physician deems the positive culture to be the source of the signs and symptoms of infection and chooses to continue antibiotic therapy. However, even taking this factor into consideration, our results suggest that vancomycin-resistant enterococci (VRE) may be a more frequent cause of CLABSI than previously recognized. Bloodstream infections caused by VRE are associated with increased mortality and hospital costs compared to those caused by vancomycin-susceptible enterococci, and VRE are unlikely to be covered by typical empiric antimicrobial regimens for febrile oncology patients with CVCs.[39,40] Therefore, it is imperative that clinicians are familiar with the local epidemiology of CLABSI at their institutions and recognize VRE as a potential cause of bloodstream infection in pediatric oncology patients.

Our study has several limitations. First, data were collected retrospectively and misclassification of exposures is possible, although we chose variables that could be reliably obtained through medical record review to minimize this possibility. Moreover, data for controls were extracted at the time of discharge or death, and it is possible that risk factors present during the hospitalization had resolved by that time. To address this potential source of bias, variables anticipated to vary on a daily basis were considered over the preceding week rather than on any single day, and we adjusted for length of hospitalization in all analyses to account for the longer hospitalizations observed among cases in our sample. We also matched control subjects to cases by date of admission to minimize any confounding introduced by changes in treatment protocols or hospital infection prevention practices over time. Finally, as our study examined risk factors for hospital-onset CLABSI, the findings should not be extrapolated to pediatric oncology outpatients.

In summary, we found that platelet transfusion and recent CVC placement were independently associated with hospital-onset CLABSI among pediatric oncology patients. While further research is needed, our results suggest that several approaches may be effective in preventing CLABSI among these patients. For instance, more stringent criteria for platelet transfusion might reduce the incidence of CLABSI among those anticipated to require frequent platelet transfusions. Alternatively, targeted use of adjunctive interventions such as antibiotic lock solutions or antimicrobial-impregnated sponges might prevent CLABSI in the month after CVC insertion. Finally, VRE may be an emerging cause of

CLABSI in hospitalized pediatric oncology patients and are unlikely to be treated by typical empiric antimicrobial regimens.

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Table 1

Bivariate Risk Factors for Central Line-Associated Bloodstream Infection (CLABSI)

	Cases (N = 54) n (%)	**Controls (N = 108) n (%)**	**Odds Ratio[a] (95% CI)**	***P***
Patient Characteristics				
Age in years, median (IQR)	8.6 (3.6–14.4)	8.6 (3.9–15.1)	1.03 (0.97–1.11)	0.34
Male gender	34 (63.0)	63 (58.3)	1.72 (0.76–3.93)	0.20
Oncologic Diagnosis[b]				
Hematologic malignancy	45 (86.5)	56 (53.3)	2.88 (1.15–7.21)	0.02
Acute lymphoblastic leukemia (ALL)	28/45	39/56		
Acute myelogenous leukemia (AML)	11/45	5/56		
Solid tumor	7 (13.5)	49 (46.7)	1 (reference)	-
Uncontrolled oncologic disease	38 (70.4)	38 (35.2)	2.24 (0.96–5.23)	0.06
Stem cell transplant recipient	23 (42.6)	12 (11.1)	2.99 (1.17–7.68)	0.02
Acute lymphoblastic leukemia (ALL)	11/23	6/12		
Acute myelogenous leukemia (AML)	3/23	1/12		
Days since last chemotherapy, median (IQR)	4 (0–8)	1 (1–14)	0.86 (0.78–0.95)	0.002
Chemotherapy received within prior 6 weeks				
Alkylating agent (yes/no)	22 (40.7)	57 (52.8)	0.69 (0.33–1.44)	0.32
Antibiotic (yes/no)	17 (31.5)	51 (47.2)	0.75 (0.36–1.54)	0.43
Antimetabolite (yes/no)	34 (63.0)	50 (46.3)	1.87 (0.85–4.16)	0.12
Agent with moderate-severe myelosuppression (yes/no)	48 (88.9)	94 (87.0)	1.41 (0.66–3.00)	0.38
Agent with mucosal toxicity (yes/no)	36 (66.7)	72 (66.7)	1.06 (0.47–2.42)	0.88
Mucositis[c]	19 (35.2)	13 (14.4)	NA	-
Minimum ANC (cells/μL) within prior 1 week				
<100	34 (63.0)	26 (24.1)	5.00 (1.92–12.99)	0.001
≥100 and <500	7 (13.0)	12 (11.1)	1.81 (0.48–6.84)	0.38
≥500	13 (24.1)	70 (64.8)	1 (reference)	-
Blood product transfusion within prior 1 week				
Red blood cell	43 (79.6)	49 (45.4)	6.77 (2.18–21.04)	0.001
Platelet	40 (74.1)	22 (20.4)	7.09 (2.64–19.05)	<0.001

	Cases (N = 54) n (%)	Controls (N = 108) n (%)	Odds Ratio[a] (95% CI)	*P*
Fresh frozen plasma	6 (11.1)	2 (1.9)	4.39 (0.60–32.34)	0.15
Cryoprecipitate	1 (1.9)	1 (0.9)	0.56 (0.03–9.63)	0.69
IVIG	4 (7.4)	5 (4.6)	0.34 (0.05–2.51)	0.29
Poor nutritional status	7 (14.3)	13 (12.4)	0.56 (0.17–1.83)	0.34
Parenteral nutrition or lipids within prior 1 week	21 (38.9)	11 (10.2)	2.91 (1.07–7.94)	0.04
Receipt of alteplase within prior 1 week	6 (11.1)	11 (10.2)	1.14 (0.35–3.76)	0.83
Fluoroscopic contrast study within the prior 1 week	1 (1.9)	0 (0.0)	NA	-
Procedure within prior 72 hours	9 (16.7)	13 (12.0)	1.67 (0.60–4.66)	0.32
Central Venous Catheter Characteristics				
Catheter type				
Tunneled externalized catheter	28 (51.9)	15 (13.9)	3.36 (1.41–7.97)	0.006
Non-tunneled catheter[d]	9 (16.7)	10 (9.3)	2.05 (0.69–6.08)	0.20
Implantable port	17 (31.5)	83 (76.9)	1 (reference)	-
Chest insertion site	45 (83.3)	95 (88.0)	0.81 (0.29–2.26)	0.69
General surgery insertion	45 (83.3)	97 (90.0)	0.37 (0.10–1.32)	0.13
≥2 lumens	33 (61.1)	20 (18.5)	2.92 (1.37–6.24)	0.006
Multiple catheters	7 (13.0)	1 (0.9)	6.59 (0.76–57.33)	0.09
Duration since placement				
<1 week	10 (18.5)	11 (10.2)	5.15 (1.82–14.56)	0.07
≥1 week and < 1 month	20 (37.0)	10 (9.3)	5.93 (1.52–23.16)	0.006
≥1 month	24 (44.4)	87 (80.6)	1 (reference)	-
>100 line accesses within prior 72 hours	16 (29.6)	3 (2.8)	8.18 (1.77–37.9)	0.007

CI, confidence interval; IQR, interquartile range; ANC, absolute neutrophil count; NA, not analyzed; IVIG, intravenous immunoglobulin

[a] All analyses adjusted for length of hospitalization prior to CLABSI for cases and date of discharge or death for controls.

[b] 6 patients who had undergone stem cell transplantation for non-malignant condition were not included in this analysis.

[c] Mucositis data were missing from the electronic medical records of 0 cases and 18 controls.

[d] 16 (84%) of the non-tunneled catheters were peripherally inserted central catheters (PICC).

Table 2

Microorganisms Isolated from Central Line-Associated Bloodstream Infections (N = 59)[a]

Microorganism	n (%)
Gram positive	34 (58%)
Enterococcus faecium	9
Staphylococcus aureus	8
Streptococcus viridians	6
Coagulase-negative staphylococcus	4
Lactobacillus	2
Abiotrophia	1
Actinomyces	1
Mycobacterium chelonae	1
Peptostreptococcus	1
Rothia mucilaginosa	1
Gram negative	19 (32%)
Enterobacter cloacae	5
Escherichia coli	4
Klebsiella pneumoniae	4
Klebsiella oxytoca	2
Enterobacter asburiae	1
Fusobacterium necrophorum	1
Serratia marcescens	1
Stenotrophomonas maltophilia	1
Yeast	6 (10%)
Candida parapsilosis	4
Candida albicans	1
Candida krusei	1

[a] 59 isolates were cultured from the 54 CLABSI as 2 organisms were recovered in 5 of the infections.

Table 3

Independent Risk Factors for Central Line-Associated Bloodstream Infection

	Odds Ratio[a] (95% CI)	*P*
Platelet transfusion within prior 1 week	10.90 (3.02–39.38)	<0.001
Duration since catheter placement		
<1 week	11.71 (1.98–69.20)	0.02
≥1 week and <1 month	7.37 (1.85–29.36)	0.004
≥1 month	1 (reference)	-

CI, confidence interval

[a] All analyses adjusted for length of hospitalization prior to CLABSI for cases and date of discharge or death for controls.