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Microbiology and Risk Factors for Central Line-Associated Bloodstream Infections among Pediatric Oncology Outpatients – a Single Institution Experience of 41 Cases

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Abstract

Background—Risk factors for central line-associated bloodstream infections (CLABSI) among children with cancer in the outpatient setting remain poorly defined, and the microbiology may differ from hospital-onset CLABSI.

Materials and Methods—We conducted a matched case-control study of oncology patients followed at the Dana Farber/Children's Hospital Cancer Center. Cases (N=41) were patients with CLABSI as per National Healthcare Safety Network criteria who had not been hospitalized in the preceding 48 hours. For each case we randomly selected two oncology outpatients with a central venous catheter and a clinic visit within 30 days of the case subject's CLABSI. Multivariate conditional logistic regression models were used to identify independent risk factors for CLABSI. We compared the microbiology to that of 54 hospital-onset CLABSI occurring at our institution during the study period.

Results—Independent predictors of community-onset CLABSI included neutropenia in the prior week (odds ratio [OR] 17.46, 95% confidence interval [CI] 4.71-64.67) and tunneled externalized catheter (vs. implantable port; OR 10.30, 95% CI 2.42-43.95). Non-enteric Gram-negative bacteria were more frequently isolated from CLABSI occurring among outpatients.

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Discussion—Pediatric oncology outpatients with recent neutropenia or tunneled externalized catheters are at increased risk of CLABSI. The microbiology of community-onset CLABSI differs from hospital-onset CLABSI.

Keywords

catheter infections; pediatric oncology; community-onset CLABSI; neutropenia

Introduction

Remarkable progress has been made in the development of curative treatment regimens for children with cancer.[1] Central venous catheters (CVCs) are indispensable in caring for patients receiving these intensified chemotherapeutic regimens, facilitating laboratory monitoring and the administration of medications, parenteral nutrition, and blood products. However, these devices put patients at risk for bloodstream infection.[2] Central line-associated bloodstream infections (CLABSI) result in prolongation of hospital stay, increased mortality, and substantial costs to the healthcare system.[3-5] Prevention of CLABSI will be essential to further improving the long-term outcomes of pediatric malignancies.

With ongoing efforts to decrease healthcare expenditures and avoid complications associated with hospitalization, the treatment of children with cancer increasingly takes place in ambulatory settings. Determining the incidence of community-onset CLABSI among pediatric oncology patients is difficult due to frequent transitions between inpatient and outpatient settings and because febrile outpatients with CVCs may be evaluated at other hospitals.[6] However, several studies suggest that community-onset CLABSI are at least twice as frequent as hospital-onset CLABSI among pediatric oncology patients.[7,8]

As CLABSI have increasingly been recognized as preventable, reducing the rate of CLABSI has become an important patient safety goal.[6,9,10] The Centers for Disease Control and Prevention (CDC) recently established infection prevention guidelines for outpatient oncology settings, including standards for the access and maintenance of CVCs.[11] However, many of these recommendations are based on studies conducted in intensive care units, the results of which may not generalize to ambulatory settings. For instance, line insertion practices are critical to CLABSI prevention in intensive care units but may have little impact on CLABSI among outpatients with long-term CVCs, in whom line maintenance strategies are likely to be more important.[6,12,13] The National Association of Children's Hospitals and Related Institutions (NACHRI) Hematology/Oncology Quality Transformation Network Collaborative expanded its CLABSI prevention efforts to ambulatory settings in November 2011.[8] An improved understanding of the epidemiology of CLABSI among pediatric oncology outpatients might guide these and other preventive efforts in this setting. We sought to define the microbiology and identify risk factors for CLABSI among outpatient children with cancer.

Materials and Methods

We conducted a matched case-control study among pediatric oncology patients with CVCs receiving outpatient care at the Dana-Farber/Children's Hospital Cancer Center between May 2007 and July 2009. Data pertaining to potential risk factors for community-onset CLABSI were collected retrospectively through review of patient electronic medical records. This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Selection of Case and Control Subjects

Surveillance for CLABSI was conducted prospectively throughout the study period by the Infection Prevention and Control and Oncology programs at Boston Children's Hospital. CLABSI was defined per the National Healthcare Safety Network (NHSN) 2008 surveillance definition as 1) a recognized pathogen cultured from one or more blood cultures, 2) fever (core temperature >38°C), chills, or hypotension and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions, or 3) patient ≤1 year of age has fever, hypothermia (core temperature <37°C), apnea, or bradycardia and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.[14] In each of these scenarios, a CVC must be in place at the time of, or within 48 hours before, onset of the infection, and the subject's symptoms and positive laboratory results must not be related to infection at another site.[14] CLABSI were considered to be community-onset if occurring among patients who had not been hospitalized in the 48 hours preceding CLABSI diagnosis.

Case subjects included those patients with a diagnosis of malignancy or a history of stem cell transplantation who had a community-onset CLABSI between May 2007 and July 2009. For each case, two control subjects were randomly selected using incidence density sampling of outpatients with a clinic visit within 30 days of the date of the case subject's CLABSI diagnosis. Eligible controls included those patients with a CVC and a diagnosis of malignancy or a history of stem cell transplantation who had not been hospitalized in the prior 48 hours. Patients with multiple clinic visits during the study period were permitted to be selected as a control more than once. A case subject could also serve as a control if the clinic visit was more than 30 days prior to the subject's CLABSI diagnosis. If a case subject experienced multiple CLABSI during the study period, we only considered the first infection.

Microbiology

We previously described the microbiology for the 54 hospital-onset CLABSI identified at our institution during the study period (May 2007 to June 2009).[15] CLABSI were considered hospital-onset if occurring among subjects (with a diagnosis of malignancy or a history of stem cell transplantation) who had been hospitalized at any point in the preceding 48 hours.

Organisms isolated from blood cultures among subjects with community-onset CLABSI or hospital-onset CLABSI were classified as Gram-positive bacteria, Gram-negative bacteria, or yeast. We compared the distribution of organisms from community-onset CLABSI to that of hospital-onset CLABSI using a Chi-square test.

Risk Factor Assessment

We considered 20 potential risk factors for community-onset CLABSI among pediatric oncology patients. These variables included demographic characteristics, oncologic disease and treatment factors, blood product transfusions, medications and procedures, and CVC characteristics. Risk factors were assessed in relation to the date of CLABSI for cases and the date of clinic visit for controls.

Oncologic diagnosis was classified as either hematologic malignancy or solid tumor. Two 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. Patients with leukemia were classified as having uncontrolled malignancy from diagnosis or relapse until laboratory-confirmed remission in bone marrow (or other known sites of disease). Lymphomas or solid tumors were considered to be uncontrolled if malignancy had been 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 the risk associated with specific classes and toxicities of chemotherapeutic medications. Each chemotherapeutic agent received by the subject within the prior 6 weeks was 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 physician or nursing notes on the date of CLABSI for cases and the date of clinic visit for controls. Neutropenia was determined based on the lowest absolute neutrophil count (ANC) reported in the patient's electronic medical record during the preceding 7 days. CDC growth charts were used to assess nutritional status, with poor nutrition defined as weight-for-age $<5^{th}$ percentile for patients aged 0-35 months, body mass index-for-age $<5^{th}$ percentile for patients aged 3-19 years, and body mass index <18.5 kg/m^2 for patients ≥20 years of age.[16] Procedure was defined as any invasive procedure except venous or arterial blood draw, peripheral intravenous line insertion, or nasogastric intubation. CVC type was classified as tunneled externalized catheter, non-tunneled catheter, or implantable port. For case subjects with multiple catheters, we only considered the CVC from which the initial positive blood culture was drawn. In addition, one control subject had multiple catheters; we included the patient's tunneled externalized CVC rather than a more recently placed implantable port.

Statistical Analysis

We used a two-stage approach based on bivariate and multivariate conditional logistic regression models to identify risk factors for CLABSI. In the first stage, we assessed each risk factor individually, selecting significant predictors ($P<0.05$) for further consideration. These covariates were 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 the case's CLABSI. All analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Forty-one community-onset CLABSI occurred among eligible patients during the study period. We matched 82 controls to these cases. Characteristics of the sample are presented in the first two columns of Table 1. The median age of the population was 6.9 years (range 4 months – 22 years), and 55% were male. The majority (54%) of patients had hematologic malignancies, with acute lymphoblastic leukemia being the most frequent diagnosis. Twelve (10%) patients had ever undergone stem cell transplantation, including five patients who had autologous transplants. The most frequent indications for stem cell transplantation were acute lymphoblastic leukemia and acute myelogenous leukemia, while two patients had been transplanted for a non-malignant condition (sickle cell anemia, congenital immunodeficiency). The majority (80%) of CVCs were implantable ports, and four patients had multiple CVCs.

Microbiology of Community-Onset CLABSI

Seven (17%) community-onset CLABSI and 5 (9%) hospital-onset CLABSI were polymicrobial. A total of 49 microorganisms were isolated from the 41 community-onset CLABSI; 25 (51%) were Gram-positive bacteria and 24 (49%) were Gram-negative bacteria (Table 2). Fifty-nine organisms were isolated from the 54 hospital-onset CLABSI; 34 (58%) were Gram-positive bacteria, 19 (32%) were Gram-negative bacteria, and 6 (10%) were Candida species. The frequency of enteric Gram-negative bacteria was similar between

community-onset and hospital-onset CLABSI (31% vs. 29%). However, non-enteric Gram-negative bacteria were more frequently isolated from community-onset CLABSI (18% vs. 3%). The distribution of Gram-positive bacteria, Gram-negative bacteria, and yeast isolated from the community-onset CLABSI differed significantly from that of hospital-onset infections (P=0.03).

Risk Factors

Table 1 presents the results of the bivariate analyses. Patient-dependent factors significantly associated with community-onset CLABSI included age, history of stem cell transplantation, neutropenia, and transfusion of red blood cells or platelets. In addition, CVC type and duration since CVC insertion were associated with CLABSI in bivariate analysis. Patient and CVC characteristics not associated with the outcome included gender, oncologic diagnosis, uncontrolled oncologic disease, mucositis, poor nutritional status, parenteral nutrition, procedure within the prior 72 hours, days since last chemotherapy, the variables evaluating risk associated with specific classes and toxicities of chemotherapeutic agents, and the presence of multiple catheters. The results of multivariate analyses are presented in Table 3. Children with tunneled externalized catheters had ten times the odds of CLABSI compared to patients with implantable ports (OR 10.30, 95% CI 2.42-43.95), while neutropenia within the prior week increased the odds of CLABSI seventeen-fold (OR 17.46, 95% CI 4.71-64.67).

Discussion

In this study of children with cancer being treated in the ambulatory setting, tunneled externalized catheters and neutropenia in the prior week were independent predictors of CLABSI. Moreover, we found that the microbiology of CLABSI among these patients differed from the microbiology of hospital-onset CLABSI.

Prior studies among pediatric oncology patients, including several conducted prospectively, have reported a reduced risk of infection associated with the use of totally implantable devices.[7,17-19] It is likely that implantable ports are less prone to microbial contamination and catheter colonization, factors which are presumed to precede the majority of CLABSI.[19-21] Although the vast majority of children with CVCs have totally implantable devices at our institution, use of these devices may not be possible or routine in some patients. Given that tunneled externalized catheters were associated with ten times the odds of CLABSI as implantable ports in our study, emphasizing line maintenance strategies might be of particular importance in children with these devices.

We found that neutropenia, defined as an ANC<500 cells/μL in the prior week, was associated with CLABSI among pediatric oncology outpatients. This finding is perhaps not surprising considering the role of neutrophils in protection from invading microbes. However, prior studies among pediatric oncology patients have not consistently demonstrated an association between neutropenia and CLABSI.[22-25] However, most of these studies examined neutropenia only at the time of CLABSI diagnosis as a risk factor for infection, an approach that may be problematic for a number of reasons. First, ANC can fluctuate on a daily basis, and there may be a delay between catheter colonization and the development of overt signs of infection. Moreover, assessing exposure and outcome concurrently creates the possibility of reverse causation (e.g. severe CLABSI might result in neutropenia). To address this potential bias, we chose to consider neutropenia as the lowest ANC in the preceding week. Finally, most prior studies also included hospitalized patients, and it is likely that a different set of risk factors predict CLABSI among children in this setting. To this point, we did not find neutropenia to be a risk factor for the 54 hospital-onset CLABSI that occurred at our institution during the study period.[15]

We found that the microbiology of community-onset CLABSI differed from that of hospital-onset CLABSI among pediatric oncology patients. Specifically, non-enteric Gram-negative bacteria were more frequently isolated and Candida less frequently isolated from infections among outpatients. Our results are consistent with prior research among pediatric oncology patients receiving care in ambulatory settings.[26,27] These studies suggest that hospital-onset CLABSI are most frequently caused by Gram-positive bacteria, while prolonged immunosuppression and treatment with broad-spectrum antimicrobials may also place some hospitalized patients at risk of fungal CLABSI.[26,27] In contrast, there appears to be an increased risk of CLABSI caused by non-enteric Gram-negative organisms among outpatients.[26,27] Although the reasons for this observation are poorly understood, self-administered intravenous infusion, bathing habits, and less frequent needleless device changes were associated with Gram-negative CLABSI in a study of outpatient hematopoietic stem cell transplant recipients.[28] Clinicians should be aware of these differences when considering empiric antimicrobial regimens for pediatric oncology outpatients with CVCs and fever or other signs of infection.

Our study has several limitations. First, risk factor data were collected retrospectively, creating the potential for misclassification of exposures. To minimize this possibility, we chose variables a priori that could be reliably obtained through review of electronic medical records. Mucositis, which depended on accurate documentation of an oral examination by physicians and nurses, was the only variable for which misclassification remained a potential concern. Second, we were only able to capture community-onset CLABSI among patients who had a positive blood culture in our laboratory. This limitation would only be expected to influence our results if risk factors among patients cared for at other hospitals or with positive blood cultures at outside institutions differed systematically from our sample. While this is unlikely to be the case for CVC type, it is possible that neutropenic patients might be more likely to be transferred to a tertiary care center for treatment of CLABSI. Moreover, we used the NHSN definition of CLABSI as it is now the accepted definition for surveillance, benchmarking, public reporting, and quality improvement collaboratives. However, this definition was originally developed for use in inpatient settings, and its specificity for the diagnosis of CLABSI among severely ill or immunocompromised patients has recently been questioned.[29,30] Finally, as this study only examined risk factors for CLABSI among pediatric oncology outpatients, the results do not apply to hospitalized children with cancer.

In summary, we found that pediatric oncology patients with tunneled externalized catheters or neutropenia in the prior week were at increased risk of community-onset CLABSI. These findings are not to suggest that CLABSI prevention efforts are unlikely to be of benefit in other children with cancer in ambulatory settings. On the contrary, minimizing line accesses and employing best line maintenance strategies are likely to be of critical importance in all outpatients with CVCs. However, our results do identify those children with cancer who may be at highest risk of community-onset CLABSI, among whom additional efforts to prevent CLABSI might be of most benefit.

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Table 1

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

	Cases (N = 41) n (%)	Controls (N = 82) n (%)	Odds Ratio (95% CI)	*P*
Patient Characteristics				
Age (years), median (IQR)	5.1 (2.6-10.9)	7.9 (4.8-14.3)	0.92 (0.85-0.99)	0.02
Female Gender	18 (43.9)	37 (45.1)	0.81 (0.41-1.62)	0.56
Oncologic Diagnosis[a]				
Hematologic malignancy	23 (56.1)	43 (52.4)	1.11 (0.56-2.22)	0.77
Acute lymphoblastic leukemia (ALL)	19/23	32/43		
Lymphoblastic lymphoma	2/23	3/43		
Solid tumor	17 (41.5)	49 (46.7)	1 (reference)	-
Uncontrolled malignancy[a]	24 (60.0)	35 (43.2)	1.91 (0.88-4.15)	0.10
Stem cell transplant recipient	23 (42.6)	12 (11.1)	4.00 (1.31-13.28)	0.02
Acute lymphoblastic leukemia (ALL)	11/23	6/12		
Acute myelogenous leukemia (AML)	3/23	1/12		
Chemotherapeutic agents received within prior 6 weeks				
Alkylating agent (yes/no)	13 (31.7)	26 (31.7)	1.00 (0.46-2.16)	1.00
Antibiotic (yes/no)	14 (34.2)	27 (32.9)	1.06 (0.48-2.31)	0.89
Antimetabolite (yes/no)	22 (53.7)	34 (41.5)	1.62 (0.77-3.44)	0.21
Agent with moderate-severe myelosuppression (yes/no)	30 (73.2)	63 (76.8)	0.78 (0.47-1.30)	0.34
Agent with mucosal toxicity (yes/no)	24 (58.5)	50 (61.0)	0.90 (0.42-1.95)	0.80
Mucositis[b]	5 (12.5)	3 (3.8)	3.33 (0.80-13.95)	0.10
Minimum ANC (cells/μL) within prior 1 week[c]				
<500	27 (65.9)	13 (16.5)	10.71 (3.70-31.02)	<0.001
≥500	14 (34.1)	66 (83.5)	1 (reference)	-
Blood product transfusion within prior 1 week				
Red blood cell	19 (46.3)	10 (12.2)	6.21 (2.29-16.88)	<0.001
Platelet	17 (41.5)	4 (4.9)	15.55 (3.57-67.63)	<0.001
Poor nutritional status[d]	4 (11.1)	5 (82)	2.40 (0.73-7.86)	0.15
Parenteral nutrition or lipids within prior 1 week	1 (2.4)	1 (1.2)	2.00 (0.13-31.98)	0.62
Procedure within prior 72 hours	6 (14.6)	7 (8.5)	1.92 (0.57-6.52)	0.29
Central Venous Catheter Characteristics				
Catheter type				
Tunneled externalized catheter	14 (31.8)	9 (10.8)	4.36 (1.54-12.36)	<0.001
Non-tunneled catheter	0 (0.0)	2 (2.4)	NA[e]	-
Implantable port	30 (68.2)	72 (86.7)	1 (reference)	-
Multiple catheters	3 (7.3)	1 (1.2)	6.00 (0.62-57.68)	0.12
Duration since insertion[f]				

	Cases (N = 41) n (%)	Controls (N = 82) n (%)	Odds Ratio (95% CI)	*P*
<1 month	13 (32.5)	5 (6.6)	9.95 (2.21-44.81)	0.003
≥1 month	27 (67.5)	71 (93.4)	1 (reference)	-

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

[a] 2 patients who had undergone stem cell transplantation for a non-malignant condition were not included in this analysis

[b] Data were missing from the charts of 1 case and 4 controls

[c] 3 controls did not have a neutrophil count within prior 1 week

[d] 5 cases did not have a weight and height within the preceding 1 month

[e] 2 patients with non-tunneled catheters were excluded from this analysis

[f] Duration since insertion unknown for 1 case and 6 control subjects

Table 2

Comparison of the Microbiology of Isolates from Community-Onset and Hospital-Onset Central Line-Associated Bloodstream Infections Among Pediatric Oncology Patients

	n (%)	
Microorganisms	**Community-Onset (N=49)[a]**	**Hospital-Onset (N=59)[b]**
Gram positive	25 (51%)	34 (58%)
Coagulase-negative staphylococcus	7	4
Streptococcus viridians	4	6
Enterococcus spp.	4	9
Staphylococcus aureus	3	8
Abiotrophia spp.	2	1
Other gram-positive organisms[c]	4	3
Gram negative	24 (49%)	19 (32%)
Enteric Gram negative	15/24	17/19
Escherichia coli	5	4
Klebsiella pneumoniae	4	4
Klebsiella oxytoca	4	2
Enterobacter spp.	1	6
Serratia marcescens	1	1
Non-enteric Gram negative	9/24	2/19
Pseudomonas spp.	3	0
Haemophilus influenzae	2	0
Stenotrophomonas maltophilia	1	1
Acinetobacter spp.	1	0
Moraxella spp.	1	0
Selenomonas spp.	1	0
Fusobacterium necrophorum	0	1
Yeast	0 (0%)	6 (10%)
Candida parapsilosis	0	4
Candida albicans	0	1
Candida krusei	0	1

[a] 49 isolates were cultured from the 41 community-onset CLABSI as 2 organisms were recovered in 6 of the infections and 3 organisms were recovered in 1 of the infections.

[b] 59 isolates were cultured from the 54 hospital-onset CLABSI as 2 organisms were recovered in 5 of the infections.

[c] Other gram-positive isolates were *Lactobacillus spp.* (2), *Rothia spp.* (2), *Actinomyces spp., Streptococcus agalactiae, Streptococcus pneumoniae, Mycobacterium chelonae, Mycobacterium fortuitum, Gordonia spp.*, and *Peptostreptococcus*.

Table 3

Independent Risk Factors for Community-Onset Central Line-Associated Bloodstream Infection

	Odds Ratio (95% CI)	*P*
CVC type[a]		
Tunneled externalized catheter	10.30 (2.42-43.95)	0.002
Implantable port	1 (reference)	-
Neutropenia (<500 cells/μL) within prior 1 week	17.46 (4.71-64.67)	<0.001

CI, confidence interval; CVC, central venous catheter

[a] 2 patients with non-tunneled catheters were not included in this analysis