Oncology Advances **2024** vol. 2(1) | 10–17
DOI: 10.14218/OnA.2023.00047

Original Article

Features of Bloodstream Infection Among Immunocompromised Oncology Patients Presenting to the Emergency Department with Fever: An Observational Study

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Received: December 12, 2023 | **Revised:** January 16, 2024 | **Accepted:** March 11, 2024 | **Published online:** March 25, 2024

Abstract

Background and objectives: Oncology patients undergoing cancer treatment and experiencing episodes of fever are known to be at increased risk for invasive bacterial infection, including bloodstream infection. This study aimed to identify the incidence of bacteremia along with the bloodstream isolates for immunocompromised oncology patients referred to the emergency department (ED) due to fever.

Methods: Oncology patients with fever were referred to the ED according to a protocol previously reported. Virtually all children had central venous access devices (CVAD) that underwent sterile access according to Hematology-Oncology (Hem-Onc) and ED protocol. Antibiotics were administered to all patients once CVAD were accessed and laboratory studies, including blood culture, were obtained. Data collected included patient demographic features, complete blood count profiles, proportions receiving antibiotics within 60 minutes of ED arrival and subsequent blood culture results.

Results: Of 1,088 consecutively referred Hem-Onc patients, 439 were eligible for inclusion. The overall blood culture positive rate was 5.7%. Fifty-six percent of patients with positive blood cultures had an absolute neutrophil count greater than 500 μL at the time of ED presentation. Gram-positive organisms comprised 64% of isolates while gram-negative organisms accounted for 36% of the total isolates.

Conclusions: Immunocompromised oncology patients presenting to the ED with fever are susceptible to bloodstream infection caused by an array of gram-positive and gram-negative organisms. Bloodstream infection during episodes of fever includes many patients without severe neutropenia at presentation and with bloodstream isolates not typically associated with catheter-related bloodstream infection alone, highlighting the diversity and variability within this patient population.

Keywords: Febrile; Neutropenia; F&N Guidelines, Pediatric, Oncology; Bloodstream infection.

Abbreviations: ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; BMT, bone marrow transplantation; CBC, complete blood count; CNS, central nervous system; CVAD, central venous access device; ED, emergency department; F&N, fever and neutropenia; Hem-Onc, hematology-oncology; Hgb, hemoglobin; NF1, neurofibromatosis, type 1; WBC, white blood cells.

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How to cite this article: Carolan PL, Lammers SM, Anderson CM, Messinger YH. Features of Bloodstream Infection Among Immunocompromised Oncology Patients Presenting to the Emergency Department with Fever: An Observational Study. *Oncol Adv* 2024;2(1):10–17. doi: 10.14218/OnA.2023.00047.

Introduction

Pediatric oncology patients who experience fever during cancer treatment represent a heterogeneous patient group with varying levels of risk for serious bacterial infection, including bloodstream infection.[1] The International Pediatric Fever and Neutropenia (F&N) Guideline Panel recently published an updated version of their clinical practice guideline for the evaluation and management of pediatric cancer patients experiencing fever.[2] A point of emphasis in the updated guidelines calls for risk stratification, recognizing the heterogeneity within this group of patients. High-risk patients include those with the following diagnoses: acute myeloid leukemia, Burkitt's lymphoma, recipients of hematopoietic stem cell transplantation (HSCT), and acute lymphoblastic leukemia (ALL)

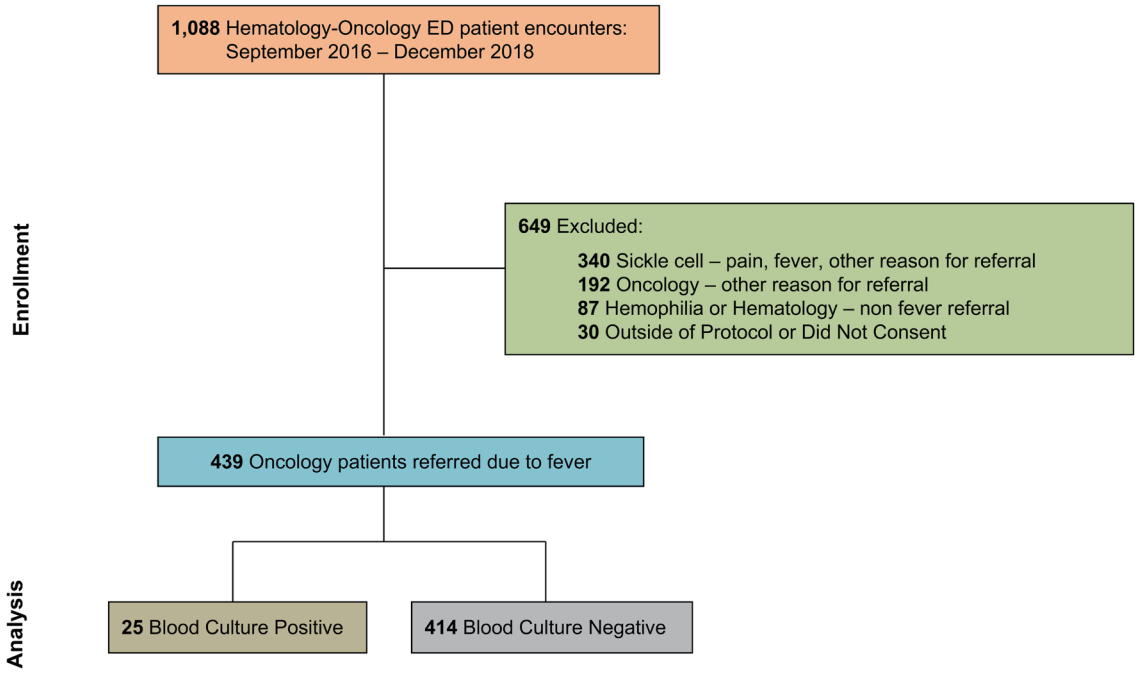

Fig. 1. Patient flow diagram. ED, emergency department.

receiving induction therapy, with progressive disease, or with relapsed bone marrow involvement. Clinical factors at presentation with fever considered high risk include hypotension, tachypnea, hypoxia (SaO_2 < 94%), chest X-ray changes, altered mental status, severe mucositis, vomiting, abdominal pain, or focal infection.[3] The Panel's updated clinical practice guideline further highlights the importance of "local epidemiology", including knowledge of local bloodstream isolates and patterns of antimicrobial resistance, as essential information to guide decision-making on the choices for empiric antibiotic treatment.

We report the incidence of bloodstream infection along with the bacterial isolates, demographic variables and hematologic values identified among a cohort of immunocompromised pediatric oncology patients referred to our emergency department (ED) due to fever.

Methods

Patients and setting

The data for this study were obtained as part of a quality improvement project that examined the time to antibiotics for immunocompromised oncology patients referred to the ED due to fever.[4] Fever was defined as a single oral temperature ≥38.3°C or ≥38.0°C and persisting for longer than one hour. This study was conducted at a single site, tertiary care children's hospital ED and involved staff from the ED and Hematology-Oncology (Hem-Onc) departments. This study was approved by the Children's Minnesota Institutional Review Board (IRB# 1905-056).

Data collection

The data collected for this study included patient demographic features, cancer type, neutropenic status, shift arrival time, the results of complete blood cell count (CBC) and blood culture isolates obtained as part of the ED evaluation, as well as the proportion of patients receiving antibiotics within 60 minutes of ED arrival. Virtually all the children had implanted central venous access devices (CVADs) that underwent sterile access according to Hem-Onc and ED protocol following their arrival to the ED. Antibiotics were administered to all patients after the CVAD was accessed and laboratory studies, including blood cultures, were obtained.

Statistical analysis

Descriptive statistics were used to define patient characteristics. Chi-square tests, Fisher's exact tests, Monte Carlo exact tests, and independent samples t-tests were used to distinguish differences between groups. All analyses were conducted with SPSS version 23. P values <0.05 were considered statistically significant. The EQUATOR ESMO-GROW (Guidance for Reporting Oncology Real-World Evidence) checklist was utilized for this study (Supplemental Data).

Results

Patient selection

Of the 1,088 consecutively referred Hem-Onc patients, 439 were eligible for inclusion, as shown in Figure 1. The majority of exclusions involved patients referred to the ED with sickle cell disease or hemophilia or who were oncology patients with a "non-fever" reason for referral. The remaining 439 unique ED encounters for fever involved 201 individual Hem-Onc patients. The cancer diagnoses for the entire group of patients referred to the ED due to fever are listed in Table 1. Categories of cancer diagnoses among this group included hematologic malignancies (67%), solid tumors (21%), and central nervous system tumors (11%).

Features of patients with positive blood cultures

The specific cancer diagnoses, patient characteristics, blood counts

Table 1. Patient oncologic diagnosis

Groups	Disease	n	%
Leukemia & Lymphoma	Acute lymphoblastic leukemia	257	58.5
	Acute myelogenous leukemia	6	1.4
	Chronic myelogenous leukemia	2	0.5
	Lymphoma[a]	30	6.8
Total		295	67.2
Solid Tumors	Ewing sarcoma	28	6.4
	Rhabdomyosarcoma	26	5.9
	Wilms	16	3.6
	Neuroblastoma	13	3.0
	Clear cell sarcoma	3	0.7
	Germ cell tumor	2	0.5
	Hepatoblastoma	2	0.5
	Desmoplastic small round cell tumor	2	0.5
Total		92	21.0
CNS Tumors	Medulloblastoma	19	4.3
	Juvenile pilocytic astrocytoma	9	2.1
	Ependymoma	7	1.6
	Ganglioglioma	5	1.1
	Germinoma	4	0.9
	Chordoma	1	0.2
	Neurofibromatosis type 1 malignant peripheral nerve sheath tumor	3	0.7
Total		48	10.9
Other	Histiocytosis[b]	4	0.9

N = 439; [a]Includes: Hodgkin, Burkitt and lymphoblastic lymphoma; [b]Includes: Langerhans cell histiocytosis and hemophagocytic lymphohistiocytosis. CNS, central nervous system.

and bloodstream isolates for blood culture-positive patients are depicted by neutropenia status in Table 2. Overall, 25 positive blood cultures were obtained during 25 unique patient encounters involving 23 individual patients. One patient had a repeat encounter within 3 days of the first ED visit involving the same organism, suggesting persistent bacteremia. The second "repeater" experienced bacteremia involving different organisms from encounters for fever separated by nearly one year. Among blood culture-positive patients, 44% were severely neutropenic with an absolute neutrophil count (ANC) <500 µL, while 32% had a normal ANC (>1,500 µL). Acute lymphoblastic leukemia was the most common diagnosis (64%) among the severely neutropenic patients with bacteremia. Virtually all blood cultures yielded a single organism; one culture yielded a mixture of two gram-positive organisms. The overall blood culture-positive rate was 5.7%. Among patients with an ANC ≥ 500 µL, the blood culture-positive rate was 3.2%.

Comparisons of blood culture-positive and -negative patients

Table 3 depicts the demographic comparisons of blood culture-positive and -negative groups. These two groups were similar with respect to age, sex, cancer type, neutropenic classification and whether antibiotics were received within 60 minutes of arrival to the ED. Oncology patients with fever were significantly more likely to arrive for evaluation on the evening shift compared to presentations on the dayshift ($P = 0.035$). The majority of patients with positive blood cultures (56%) had an ANC ≥ 500 µL at the time of presentation to the ED with fever. For the group, 81% of patients received antibiotics within 60 minutes of arrival to the ED.

Comparison of CBC values for blood culture-positive and -negative patients

Table 4 provides a comparison of CBC values for blood culture-positive and -negative patients. Mean values for total white blood cell (WBC) count, ANC and hemoglobin were similar for the blood culture-positive and -negative patients. However, an independent samples t-test revealed that the mean platelet values were significantly lower in the blood culture-positive group (M = 84,437, SD = 93,664) compared to the blood culture-negative patients (M = 172,562, SD = 131,607; $P = 0.001$).

Bacterial taxonomy

The bacterial bloodstream isolates obtained from this patient cohort are grouped by taxonomic classification in Table 5. Gram-positive organisms comprised 64% of all isolates. Viridans group

Table 2. Blood culture positive patient features

Diagnosis	Sex	Age (years)	WBC[a]	ANC[a]	Hgb[b]	Platelet Count[a]	Blood Culture Isolate
Medulloblastoma	M	14.3	100	10[A]	6.1	4,000	*Streptococcus oralis* (mitis group)
Medulloblastoma	M	7.6	100	10 [A]	8.2	44,000	*Clostridium* species, not perfringens
Acute lymphoblastic leukemia	M	9.1	100	10 [A]	10.6	9,000	*Escherichia coli*
Acute lymphoblastic leukemia[1]	F	8.3	100	15 [A]	8.5	21,000	*Staphylococcus aureus*, methicillin resistant
Acute lymphoblastic leukemia	M	2.4	200	20 [A]	7.2	3,000	*Streptococcus oralis* (mitis group)
Desmoplastic small round cell tumor	M	18.4	200	20 [A]	12.7	18,000	*Leptotrichia wadei*
Ewing Sarcoma	M	9.4	100	20 [A]	7.3	17,000	*Pseudomonas aeruginosa*
Acute lymphoblastic leukemia	M	4.6	200	20 [A]	12.1	50,000	*Pseudomonas aeruginosa*
Acute lymphoblastic leukemia[1]	F	9.3	300	20 [A]	5.7	19,000	*Streptococcus oralis* & *Enterococcus gallinarum*
Acute lymphoblastic leukemia	F	9.9	400	120 [A]	10	11,000	*Escherichia coli*
Acute lymphoblastic leukemia	F	8.6	600	444 [A]	12.1	35,000	*Escherichia coli*
Acute lymphoblastic leukemia	M	19.6	1,100	671[B]	10.9	109,000	*Corynebacterium pseudodiphtheriticum*
Acute lymphoblastic leukemia	F	9.2	1,000	690[B]	9.8	4,000	*Staphylococcus epidermidis*
Medulloblastoma[2]	F	9.7	2,200	902 [B]	9.8	57,000	*Staphylococcus epidermidis*
Acute lymphoblastic leukemia	F	5.1	2,000	940 [B]	11.8	420,000	*Escherichia coli*
Acute lymphoblastic leukemia	F	3.1	4,100	1,025 [C]	8.7	123,000	*Staphylococcus aureus*, methicillin sensitive
Medulloblastoma[2]	F	9.7	3,400	1,156 [C]	10.3	46,000	*Staphylococcus epidermidis*
Embryonal rhabdomysacroma	F	4.4	2,900	2,407[D]	9.2	80,000	*Streptococcus parasanguinis*
Acute lymphoblastic leukemia	M	14.8	4,500	4,365[D]	7.9	166,000	*Micrococcus luteus*
Anaplastic ependymoma	M	1.9	6,700	5,494[D]	9.6	77,000	*Klebsiella pneumoniae*
NF1 with malignant peripheral nerve sheath tumor	F	2.6	8,000	5,680[D]	12.3	219,000	*Enterococcus faecalis*
Chordoma	M	6.8	11,300	9,920[D]	12.4	284,000	*Stenotrophomonas maltophilia*
Relapsed T-cell lymphoma s/p BMT	F	12.1	20,400	12,820[D]	12.7	250,000	*Streptococcus pneumoniae*
Acute lymphoblastic leukemia	M	20.6	15,700	14,287[D]	14.3	157,000	*Corynebacterium pseudodiphtheriticum*
Acute lymphoblastic leukemia	F	4.1	16,200	15,228[D]	10.5	305,000	*Streptococcus pneumoniae*

[1]Interval between visits: 356 days; [2]Interval between visits: 3 days; [a]cells μL; [b]grams/Dl. [A]Severe Neutropenia: < 500 μL, 11/25 = 44%; [B]Moderate Neutropenia: 500–1,000 μL, 4/25 = 16%; [C]Mild Neutropenia: 1,000–1,500 μL, 2/25 = 8%; [D]ANC > 1,500 μL, 8/25 = 32%. ANC, absolute neutrophil count; BMT, bone marrow transplantation; F, female; Hgb, hemoglobin; M, male; NF1, neurofibromatosis, type 1; WBC, white blood cells.

Table 3. Demographic comparisons of patients with positive and negative blood cultures

Baseline Characteristic	Positive Blood Culture (*n* = 25)		Negative Blood Culture (*n* = 414)		*P*
	n	%	*n*	%	
Sex					0.475
Male	12	48.0	229	55.3	
Female	13	52.0	185	44.7	
Age in years					0.258~
0–4	7	28.0	178	43.0	
5–9	12	48.0	123	29.7	
10–14	3	12.0	48	11.6	
15+	3	12.0	65	15.7	
Cancer Type					0.400
Hematologic	15	60.0	282	68.1	
Solid Tumor	10	40.0	132	31.9	
Neutropenic Classification[a]					0.449
ANC levels ≤ 500/μL	11	44.0	151	36.5	
ANC levels > 500/μL	14	56.0	263	63.5	
Shift Arrival Time (Day/Evenings/Night)					0.035*
7am–3pm	4	16.0	72	17.4	
3pm–11pm	10	40.0	255	61.6	
11pm–7am	11	44.0	87	21.0	
Antibiotics given in 60 mins or less					0.443∧
Yes	22	88.0	334	80.7	
No	3	12.0	80	19.3	

N = 439; [a]ANC, absolute neutrophil count; ∧ Fisher's exact test; ~ Monte Carlo exact test; * *P* < 0.05, Monte Carlo exact test.

Streptococci and Staphylococcal species accounted for 69% of the gram-positive isolates. Gram-negative organisms accounted for 36% of the total isolates, 78% of which were from the families Enterobacteriaceae and Pseudomonadaceae.

Discussion

This study reports the demographic features, blood count values and the bloodstream isolates for pediatric cancer patients presenting to the ED due to fever. The overall incidence of bloodstream infection among our group of pediatric cancer patients with fever was 5.7%. Rates of bacteremia noted in other studies of pediatric F&N range from 9.7% to 29.4%.[5–10] The lower rate of bacteremia in our study may reflect the inclusion of fewer patients that are recognized to be at higher risk of bloodstream infection. For example, recipients of HSCTs did not receive care at our institution during the study period reported here. Our patient population may also have included fewer patients with Burkitt's lymphoma, acute myelogenous leukemia, those with recurrent fever, or individuals with depths of neutropenia that are recognized to be associated with a higher risk for serious bacterial infection, including bloodstream infection, during acute episodes of fever.[11] The variability in the rates of bloodstream infection among these studies serves to highlight the clinical heterogeneity and variability in risk fac-

Table 4. Comparison of complete blood cell count profiles between blood culture-positive patients and blood culture-negative patients

Hemogram	Positive Blood Culture (*n* = 25)			Negative Blood Culture (*n* = 414)			*P*
	Mean	Median	Range	Mean	Median	Range	
WBC~	4,076	1,100	100–20,400	4,064	2,300	100–48,600	0.991
ANC~	3,052	690	10–15,228	2,708	1,237	10–23,056	0.670
Hemoglobin∧	10.0	10.0	5.7–14.3	9.7	9.7	4.7–14.1	0.395
Platelet Count~	84,337	46,000	3,000–420,000	172,562	150,000	1,000–959,000	0.001*

N = 439; ~ cells/μL; ∧ grams/dL; * Independent samples t test *P* < 0.05. ANC, absolute neutrophil count; WBC, white blood cell.

Table 5. Bloodstream infection isolates

	n	%
Gram Positive Organisms		
Enterococcus faecalis	1	4
Streptococcus oralis (mitis group)	2	8
Streptococcus oralis (mitis group) with *Enterococcus gallinarum*	1	4
Micrococcus luteus	1	4
Corynebacterium pseudodiphtheriticum	2	8
Streptococcus parasanguinis	1	4
Streptococcus pneumoniae	2	8
Staphylococcus aureus, methicillin sensitive	1	4
Staphylococcus aureus, methicillin resistant	1	4
Staphylococcus epidermidis	2	8
Staphylococcus carnosus (coagulase negative staphylococcus)	1	4
Clostridium species, not perfringens	1	4
Total	16	64
Gram Negative Organisms		
Stenotrophomonas maltophilia (Xanthomonas)	1	4
Leptotrichia wadei	1	4
Escherichia coli	4	16
Pseudomonas aeruginosa	2	8
Klebsiella pneumoniae	1	4
Total	9	36

N = 25.

tors among the fever and immunocompromised oncology patient groups.

The bloodstream infection isolates among our patients included gram-positive organisms in 64% of isolates, the majority of which were viridans group Streptococci or Staphylococcal species. Both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus* were identified. Gram-negative organisms represented 36% of bloodstream isolates, with nearly 80% from the families Enterobacteriaceae and Pseudomonadaceae. This ratio of gram-positive to gram-negative organisms is similar to that of other centers reporting 54–64% gram-positive cocci among their F&N bloodstream infection isolates.[6,7,10] These findings support clinical practice guideline recommendations to utilize anti-pseudomonal beta-lactam antibiotics for initial empiric coverage while awaiting the results of blood culture testing.[2,3]

We observed that mean values for WBC, ANC and hemoglobin were similar for blood culture -positive and -negative patients, while the mean platelet values were significantly lower among blood culture-positive patients at the time of ED evaluation. This contrasts with a prior study of pediatric cancer patients with F&N, which showed no difference among cell lines on admission when comparing blood culture-positive to blood culture-negative patients.[12] Among the blood culture-positive patients in our study, there was concordance between the presence of severe neutropenia and thrombocytopenia, especially for patients with ALL. Given our relatively small patient sample, we were unable to establish a model using absolute or grouped ANC and platelet values that would allow for the prediction of the risk for bloodstream infection. This linkage of severe neutropenia and thrombocytopenia at presentation with fever may have clinical significance, suggesting the need for a heightened level of monitoring of patients, especially ALL patients, who exhibit this concordance. This is a patient group that is likely to receive early empiric antibiotics and admission for observation. Future studies utilizing larger patient samples may further investigate this potential relationship.

In the present study, 84% of blood culture-positive patients arrived for care in the evening or during the night shift. A study examining day-night presentations of sepsis did not identify a difference in hospital arrival time favoring either the day or night.[13] No other studies were identified examining time-of-day relationships for bacteremia among febrile, immunocompromised oncology patients. The skew toward evening and nighttime presentation observed in our patient cohort likely reflects the practical issue of hours and availability of the Hem-Onc clinic and providers to manage the evaluation of fever "off hours." The observation of "off hours" presentations in our patient group underscores the importance of having formal evaluation and treatment protocols in place when the ED becomes the referral location for evaluation and management due to these circumstances.

The majority (56%) of our cancer patients with proven bloodstream infection had ANC levels ≥ 500 μL at the time of their presentation with fever, which has been reported in previous studies.[14,15] The bloodstream isolates from patients in our study with ANC levels ≥ 500 μL included *Streptococcus pneumoniae* and

Stenotrophomonas maltophilia, organisms that are not typically associated with CRBSI (catheter-related bloodstream infection) alone,[6] suggesting that variables unique to the individual are important to the risk of bloodstream infection for pediatric cancer patients with fever. Efforts have been made to stratify the risk for serious bacterial infection among oncology patients with fever based on neutropenic status or through the use of alternative biomarkers of infection.[16–18] However, differentiating bacteremic from non-bacteremic infection on clinical grounds has proved challenging. Reliance on ANC testing or the use of biomarkers to exclude bacteremia at the initial ED presentation lacks sensitivity or have practical limitations. The use of biomarkers of infection appears to have the greatest value in the identification of individuals at high risk of an adverse outcome following the initiation of antibiotic treatment and during the subsequent period of observation or admission.[7] Our findings support the universal administration of antibiotics within 60 minutes of arrival once blood cultures and laboratory studies have been obtained for all febrile immunocompromised pediatric oncology patients, as suggested in the most recent clinical practice guidelines.[2,3]

Limitations

This study has several limitations. First, the results of our study reflect the experience of a single tertiary care children's hospital ED and may not be generalizable to other ED or non-ED sites evaluating immunocompromised pediatric cancer patients during episodes of fever. Second, the study subjects were enrolled consecutively and included individual patients with repeat episodes of fever, introducing the potential for outcome bias. However, only one of the patients in the positive blood culture group experienced febrile episodes linked in time with the same bloodstream isolate consistent with the clinical course of recurrent fever and persistent bacteremia. Finally, our sample of blood culture-positive patients was small, limiting our ability to establish a risk model for the prediction of bacteremia which is the benefit of multicenter studies and pooled patient data.

Conclusions

Immunocompromised oncology patients who present to the ED with fever are subject to bloodstream infections caused by an array of gram-positive and gram-negative organisms. "F&N" is often used to refer to this population. Our study has shown that a risk for bloodstream infection exists for subsets of immunocompromised oncology patients with fever who are mildly neutropenic or non-neutropenic at presentation and involve bloodstream isolates that are not typically associated with catheter-related bloodstream infection. Based on these observations, we believe that the term "fever and immunocompromised" (F&I) is a more appropriate general designation for this diverse group of cancer patients experiencing fever.[19]

Acknowledgments

The authors wish to acknowledge MJC and JG for their support in the preparation of this manuscript.

Funding

This study was conducted without any internal or external financial support.

Conflict of interest

The authors have no conflicts of interest to disclose related to this publication.

Author contributions

Study concept and design (PC, SL, CA, YM), acquisition of data (PC, CA), analysis and interpretation of data (PC, SL, CA, YM), drafting of the manuscript (PC, SL, CA, YM), and study supervision (PC, CA, YM). All the authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

This study (IRB# 1905-056) was approved by the Children's Minnesota Institutional Review Board. Written informed consent was obtained from all subjects, and the protocols followed in this study conformed to the ethical guidelines of the Declaration of Helsinki (as revised in 2013).

Data sharing statement

The datasets generated and/or analyzed for this study are available from the corresponding author (Patrick.carolan@childrensmn.org) upon reasonable request.

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