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MAJOR ARTICLE

Microbiology and Risk Factors for Hospital-Associated Bloodstream Infections Among Pediatric Hematopoietic Stem Cell Transplant Recipients

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Background. Children undergoing hematopoietic stem cell transplantation (HSCT) are at high risk for hospital-associated bloodstream infections (HA-BSIs). This study aimed to describe the incidence, microbiology, and risk factors for HA-BSI in pediatric HSCT recipients.

Methods. We performed a single-center retrospective cohort study of children and adolescents (<18 years of age) who underwent HSCT over a 20-year period (1997–2016). We determined the incidence and case fatality rate of HA-BSI by causative organism. We used multivariable Poisson regression to identify risk factors for HA-BSI.

Results. Of 1294 patients, the majority (86%) received an allogeneic HSCT, most commonly with umbilical cord blood (63%). During the initial HSCT hospitalization, 334 HA-BSIs occurred among 261 (20%) patients. These were classified as gram-positive bacterial (46%), gram-negative bacterial (24%), fungal (12%), mycobacterial (<1%), or polymicrobial (19%). During the study period, there was a decline in the cumulative incidence of HA-BSI ($P = .021$) and, specifically, fungal HA-BSIs ($P = .002$). In multivariable analyses, older age (incidence rate ratio [IRR], 1.03; 95% confidence interval [CI], 1.01–1.06), umbilical cord blood donor source (vs bone marrow; IRR, 1.69; 95% CI, 1.19–2.40), and nonmyeloablative conditioning (vs myeloablative; IRR, 1.85; 95% CI, 1.21–2.82) were associated with a higher risk of HA-BSIs. The case fatality rate was higher for fungal HA-BSI than other HA-BSI categories (21% vs 6%; $P = .002$).

Conclusions. Over the past 2 decades, the incidence of HA-BSIs has declined among pediatric HSCT recipients at our institution. Older age, umbilical cord blood donor source, and nonmyeloablative conditioning regimens are independent risk factors for HA-BSI among children undergoing HSCT.

Keywords. antifungal prophylaxis; conditioning regimen; mortality; umbilical cord blood.

Hematopoietic stem cell transplantation (HSCT) is an essential treatment option for some patients with malignancies, bone marrow disorders, and genetic or metabolic disorders. Although outcomes after HSCT have improved over the past several decades, bloodstream infections occur in nearly one-third of HSCT recipients and are associated with substantial morbidity and mortality [1–4]. The incidence and associated mortality of bloodstream infections are particularly high soon after HSCT, when patients are hospitalized and typically experience prolonged neutropenia and mucositis [2, 3, 5]. Over the past decades, several interventions were developed to reduce the risk of hospital-associated bloodstream infections (HA-BSIs) among HSCT recipients [2, 5]. In particular, infection prevention bundles for central venous catheters, improved skin care practices, use of antimicrobial prophylaxis, and steroid-sparing graft-vs-host disease (GvHD) prophylaxis are associated with a lower risk of HA-BSI in HSCT recipients [6–8]. Although a number of studies have investigated HA-BSI in adults undergoing HSCT, comparatively little is known about HA-BSI in pediatric HSCT recipients [1, 9, 10]. In particular, the effect of these recent changes in practice on the incidence of HA-BSI and patient-level risk factors for HA-BSI among pediatric HSCT recipients is unknown. This gap in knowledge has hindered efforts to prevent and effectively manage HA-BSI in children undergoing HSCT.

In this study, using the largest single-center cohort of pediatric HSCT recipients reported to date, we sought to identify risk factors for HA-BSI during the transplant hospitalization.

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As secondary objectives, we evaluated for a change in the incidence of HA-BSI over time and determined the case fatality rate according to the causative pathogens.

METHODS

Population and Study Design

We conducted a retrospective cohort study of children and adolescents (<18 years of age) who underwent their first HSCT through the Duke Pediatric Blood and Marrow Transplant Program between January 1, 1997, and December 31, 2016. The analyses focused on HA-BSI episodes occurring during the initial patient hospitalizations for HSCT. The Duke University Institutional Review Board approved this study.

Data Sources

Patient demographics and clinical data were obtained from a secure database maintained by the transplant program and the Duke Enterprise Data Unified Content Explorer (DEDUCE) research portal [11]. Two investigators (I.C.A., M.S.K.) independently identified deaths associated with HA-BSI through review of the transplant program database and patient electronic medical records including physician notes, laboratory results, autopsy reports, and diagnostic imaging. A third independent reviewer (S.M.H.) resolved discrepancies.

Transplant Practices

Throughout the study period, patients were cared for in positive-pressure ventilation– and high-efficiency particulate air (HEPA)–filtered rooms on a 16-bed dedicated pediatric inpatient unit. All patients had a double-lumen or triple-lumen tunneled central venous catheter placed before admission for HSCT. Standard best practices were routine during the study period and included daily bathing, antiseptic oral rinses, and sterile care for central venous catheters. In addition, surveillance blood cultures were collected weekly (Sunday nights) from at least 1 central venous catheter lumen throughout the study period. Before 2006, prophylaxis administered for GvHD was routinely cyclosporine and corticosteroids for allogeneic HSCT recipients. In 2006, cyclosporine and mycophenolate mofetil or cyclosporine and methotrexate became the most frequent GvHD prophylaxis. Recipients of an autologous HSCT or a matched sibling bone marrow transplant received fluconazole for antifungal prophylaxis throughout the study period. Patients undergoing HSCT from other donor sources (including umbilical cord blood) were routinely given low-dose intravenous (IV) amphotericin B lipid complex (0.2 mg/kg once daily) before 2003 and voriconazole (4 mg/kg IV or oral twice daily) during or after 2003. Throughout the study period, antifungal prophylaxis was continued for at least 100 days after HSCT and as long as the patient remained on immunosuppressive prophylaxis or therapy for GvHD. Routine antibacterial prophylaxis was not used throughout the study period.

Definitions

HA-BSI episodes were retrospectively identified in accordance with National Healthcare Safety Network (NHSN) criteria as (1) growth of a recognized pathogen from blood culture or (2) growth of a commensal organism (eg, coagulase-negative staphylococci [CoNS], *Micrococcus* species) from 2 blood cultures drawn from different sites at the same time or from the same site at different times on the same or consecutive days [12]. To account for possible identification of contaminants in surveillance cultures with organism growth, we excluded commensal organisms from cultures collected between Sunday 8:00 PM and Monday 4:00 AM. Growth of the same or different organisms from blood cultures obtained within 14 days of the first positive blood culture in an HA-BSI episode was considered part of the same episode. Only HA-BSI episodes starting on or after the HSCT date and before the day of hospital discharge were included in these analyses. HA-BSI episodes were considered exclusively polymicrobial if >1 species was isolated.

Statistical Analysis

The primary outcome was the number of HA-BSIs during the HSCT hospitalization for each patient. Secondary outcomes were the incidence and case fatality rate for HA-BSI, evaluated independently in HA-BSI categories based on the causative organisms. The Spearman correlation test was used to evaluate for a temporal association between HSCT year and the cumulative incidence of HA-BSIs. Similar calculations were performed for HA-BSI episodes in the following mutually exclusive categories: gram-positive bacterial, gram-negative bacterial, fungal, and polymicrobial. The case fatality rates of HA-BSIs in these pathogen categories were compared using chi-square goodness-of-fit tests. Next, the following factors were evaluated for association with the risk of HA-BSI: age, sex, HSCT donor source, conditioning intensity, and GvHD prophylaxis. Each variable was included in a Poisson regression model adjusted only for HSCT year with an offset to account for varying hospital lengths of stay. All variables were then included in a Poisson regression model with HSCT year and an offset for varying hospital lengths of stay to identify independent risk factors for HA-BSI. Finally, these same methods were used to evaluate specific risk factors for HA-BSI caused by gram-positive bacteria, gram-negative bacteria, and fungi. For these analyses, any HA-BSI episode that contained 1 or more species from the pathogen category met the outcome definition. Additionally, antifungal prophylaxis was included in the multivariable model evaluating risk factors for fungal HA-BSI. No patient was excluded from the analyses due to missing data. Analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

Of 1294 HSCT recipients, 59% were male and the median (interquartile range [IQR]) age at transplant was 5.5 (2.1–11.0) years

(Table 1). Hematological malignancies (43%) and genetic or metabolic disorders (21%) were the most common HSCT indications; the median (IQR) age at HSCT was 8.7 (4.7–13.7) years for patients with hematologic malignancies, 3.7 (2.5–7.3) years for those with solid tumors, and 2.1 (0.8–7.2) years for those with immunodeficiency. Children with hematologic malignancies had significantly higher ages at transplant ($P < .001$) than children with solid tumors or immunodeficiency. More than half (63%) of patients received umbilical cord blood transplants, and the vast majority (93%) received a myeloablative conditioning regimen. The median (IQR) length of stay after HSCT was 36 (27–52) days, and 167 (13%) patients died during the HSCT hospitalization.

Incidence and Microbiology of HA-BSI

Figure 1 depicts the incidence of HA-BSI among the study population by HSCT year. The incidence of HA-BSI declined over the 20-year study period ($P = .021$), such that the estimated number of HA-BSI episodes per patient-year at risk was 3.21 (95% confidence interval [CI], 1.69–4.73) in 1997 and 2.06 (95% CI, 0.55–3.58) in 2016. This was accounted for, in part, by a marked lowering of the risk of fungal HA-BSI over time ($P = .002$). The predicted cumulative incidence of fungal HA-BSI episodes per patient-year at risk was 0.57 in 1997 and 0.04 in 2016. There was no evidence to support a decline in incidence of gram-positive bacterial HA-BSI over the study period ($P = .102$). The incidence of gram-negative bacterial BSI episodes was stable during the study period ($P = .58$).

Three hundred thirty-four HA-BSI episodes occurred among the study population. One thousand thirty-three (80%) patients had no HA-BSI episode, 207 (16%) had 1 HA-BSI episode, 41 (3%) had 2 HA-BSI episodes, and 13 (1%) had 3 or more HA-BSI episodes (Table 1). HA-BSI episodes occurred a median (IQR) of 15 (5–40) days after the HSCT date. The microbiology of the HA-BSI episodes is shown in Table 2. Gram-positive bacteria accounted for 152 (46%) HA-BSI episodes, with *Enterococcus faecium* (n = 35), CoNS (n = 32), *Enterococcus faecalis* (n = 27), and viridans group streptococci (n = 26) representing the majority of these episodes. Gram-negative bacteria accounted for 79 (24%) HA-BSI episodes, with *Escherichia coli* (n = 22), *Pseudomonas aeruginosa* (n = 15), *Enterobacter cloacae* (n = 8), and *Klebsiella pneumoniae* (n = 7) being the most commonly identified. Only 39 (12%) HA-BSI episodes were fungal, and the vast majority (97%) of these episodes were caused by *Candida* species. There were 63 (19%) polymicrobial HA-BSI episodes most commonly with *Enterococci* species (n = 33, 52%) and CoNS (n = 14, 22%) isolated (Supplementary Table 2). We noted 1 mycobacterial HA-BSI episode caused by *Mycobacterium fortuitum*.

Table 1. Characteristics of the Study Population (n = 1294)

Characteristic	No.	%
Age, median (IQR), y	5.5	(2.1–11.0)
In-hospital mortality	167	13
Sex		
Female	527	41
Male	767	59
Transplant year		
1997 to 2001	381	29
2002 to 2006	402	31
2007 to 2011	280	22
2012 to 2016	231	18
No. of HA-BSIs		
0	1033	80
1	207	16
2	41	3
3	8	1
4	4	0
5	1	0
HSCT indication		
Genetic or metabolic disorder	274	21
Hematological malignancy	555	43
Nonmalignant hematological disorder	154	12
Immunodeficiency	143	11
Solid tumor	168	13
Conditioning intensity		
Myeloablative	1230	95
Nonmyeloablative or reduced intensity	64	5
HSCT type		
Autologous	185	14
Bone marrow	295	23
Umbilical cord blood	814	63
Steroid-containing GvHD prophylaxis	792	61
Antifungal prophylaxis		
Fluconazole	253	20
Amphotericin B lipid complex	395	31
Voriconazole	556	44
Other	90	7

Abbreviations: GvHD, graft-vs-host disease; HA-BSI, hospital-associated bloodstream infection; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range.

Risk Factors for HA-BSI

Associations between HA-BSI, patient factors, and HSCT characteristics are shown in Table 3. Patient age was associated with risk of HA-BSI such that every 1-year increase in age corresponded to a 3% increase in the risk of HA-BSI (incidence rate ratio [IRR], 1.03; 95% CI, 1.01–1.06). Nonmyeloablative or reduced-intensity conditioning (vs myeloablative; IRR, 1.85; 95% CI, 1.21–2.82) and umbilical cord blood donor source (vs bone marrow; IRR, 1.69; 95% CI, 1.19–2.40) were similarly associated with a higher risk of HA-BSI. Patient sex and steroid-containing GvHD prophylaxis were not associated with risk of HA-BSI. Supplementary Table 1 presents associations between potential risk factors and gram-positive bacterial HA-BSI, gram-negative bacterial HA-BSI, and fungal HA-BSI. In general, the associations observed between these factors and the pathogen-specific categories of HA-BSI were similar to those observed with HA-BSI overall. Notably, antifungal prophylaxis was not an independent risk factor for fungal HA-BSI in the multivariable model. Fungal HA-BSI occurred in 3 of 253

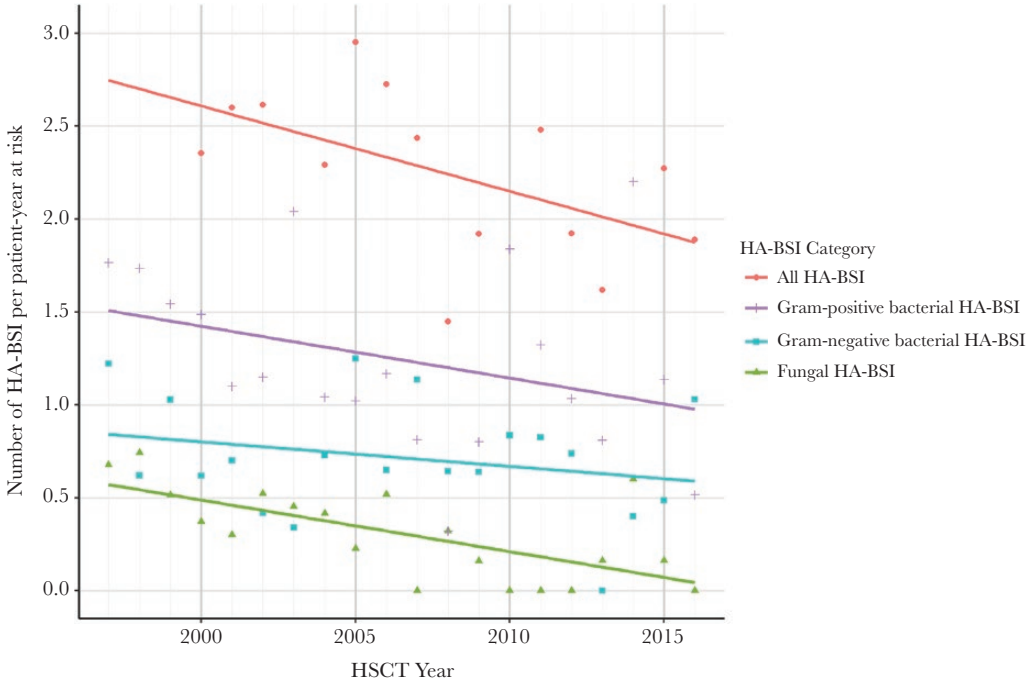

Figure 1. Incidence of pediatric HA-BSI among HSCT recipients (1997–2016). The number of HA-BSIs per year at risk during the study period is shown by HA-BSI category. The incidence of HA-BSIs ($P = .021$) and fungal HA-BSIs ($P = .002$) decreased over time. The incidence of gram-positive bacterial HA-BSIs also declined ($P = .102$), whereas the incidence of gram-negative bacterial HA-BSIs did not change during the study period ($P = .583$). Abbreviations: HA-BSI, hospital-associated bloodstream infection; HSCT, hematopoietic stem cell transplantation.

(1%) children who received fluconazole prophylaxis, 16 of 556 (3%) children who received voriconazole prophylaxis, and 18 of 395 (5%) children who received low-dose amphotericin B prophylaxis.

HA-BSI Outcomes

Of the 167 in-hospital deaths among the study population, we classified HA-BSI episode as the primary cause of death for 27 (16%) patients. The majority of the patients who died of HA-BSI had comorbid GvHD (n = 11, 41%) or graft failure (n = 10, 37%). Eight of 39 (21%) fungal, 7 of 79 (9%) gram-negative bacterial, 8 of 152 (5%) gram-positive bacterial, 4 of 63 (6%) polymicrobial, and 0 of 1 (0%) mycobacterial HA-BSI episodes were fatal. The case fatality rate for fungal HA-BSI was higher than the case fatality rate observed in other BSI categories (21% vs 6%; $P = .002$). Children who had an HA-BSI episode during the initial HSCT hospitalization had higher mortality during the first year after HSCT (122 of 267, 46%) than children who did not have an HA-BSI episode (241 of 1027, 23%; $P < .0001$).

DISCUSSION

We retrospectively studied 1294 pediatric HSCT recipients at our institution and observed a reduction in risk of HA-BSI over the past 2 decades. In particular, the incidence of fungal HA-BSI declined markedly during the study period, but the risk of gram-positive and gram-negative bacterial HA-BSI showed negligible changes. Factors associated with an increased risk of HA-BSI included older age, use of umbilical cord blood as the donor source, and nonmyeloablative or reduced-intensity conditioning regimens. Patients with fungal HA-BSI episodes had a higher case fatality rate than patients with other HA-BSI episodes.

Numerous factors may have contributed to the observed decline in HA-BSI in our cohort. Central venous catheters are ubiquitous among HSCT recipients and pose a significant risk for BSI. Therefore, practices such as use of scheduled chlorhexidine baths for hospitalized patients as part of central catheter maintenance bundles may have decreased the rates of catheter contamination and HA-BSI [7, 8, 13]. With the rise in the nosocomial burden of multidrug-resistant organisms, the use of isolation precautions for colonized or infected patients has been shown to reduce transmission of some resistant organisms among hospitalized patients and may have contributed to a decline in HA-BSI [14]. Strict adherence to hand hygiene among medical providers and optimal environmental cleaning also contributed to decreased incidence of health care–associated infections and may have contributed to the decline noted in our study [15, 16]. Broad-spectrum antimicrobial prophylaxis may also affect the risk of HA-BSI after HSCT. However, this was not routinely used in our cohort, and the beneficial effect of antimicrobial prophylaxis may be limited in children [17, 18].

Table 2. Microbiological Causes of HA-BSI in Pediatric HSCT Recipients

HA-BSI Category	Species	No. (%)
GP bacterial		152 (46)
	Enterococcus faecium	35
	Coagulase-negative staphylococci	32
	Viridans group streptococci	26
	Enterococcus faecalis	27
	Staphylococcus aureus	17
	Other	15
GN bacterial		79 (24)
	Escherichia coli	22
	Pseudomonas aeruginosa	15
	Enterobacter cloacae	8
	Klebsiella pneumoniae	7
	Stenotrophomonas maltophilia	5
	Neisseria species	5
	Other	17
Fungal		39 (12)
	Candida albicans	10
	Candida glabrata	8
	Candida krusei	7
	Candida tropicalis	7
	Candida parapsilosis	3
	Other	4
Mycobacterial		1 (<1)
	Mycobacterium fortuitum	1
Polymicrobial	GP bacteria + GP bacteria	63 (19) 13
	GP bacteria + GN bacteria	15
	GP bacteria + fungus	12
	GN bacteria + GN bacteria	5
	GN bacteria + fungus	5
	Fungus + fungus	2
	≥3 organisms	11

Abbreviations: GN, gram-negative; GP, gram-positive; HA-BSI, hospital-associated bloodstream infection; HSCT, hematopoietic stem cell transplantation.

Table 3. Risk Factors for HA-BSI in Pediatric HSCT Recipients

Characteristic	Bivariable Model (Adjusted for HSCT Year) IRR (95% CI)	Multivariable Model IRR (95% CI)
Age, y	1.03 (1.01–1.05)*	1.03 (1.01–1.06)*
Female sex	0.97 (0.78–1.21)	1.01 (0.81–1.26)
HSCT type		
Autologous	1.17 (0.71–1.94)	1.35 (0.81–2.26)
Bone marrow	1.00 (ref)	1.00 (ref)
Umbilical cord blood	1.51 (1.10–2.08)*	1.69 (1.19–2.40)*
Conditioning intensity		
Myeloablative	1.00 (ref)	1.00 (ref)
Nonmyeloablative or reduced-intensity	1.82 (1.19–2.78)*	1.85 (1.21–2.82)*
Steroid-containing GvHD prophylaxis	1.18 (0.92–1.51)	1.00 (0.74–1.34)

Abbreviations: CI, confidence interval; GvHD, graft-vs-host disease; HA-BSI, hospital-associated bloodstream infection; HSCT, hematopoietic stem cell transplantation; IRR, incidence rate ratio; ref, reference.

*$P < .05$.

The most frequently identified HA-BSI pathogens in our study were gram-positive bacteria, specifically, *Enterococcus* species and CoNS. Several prior studies conducted in adults identified gram-negative bacteria as the most common cause of HA-BSI after HSCT [5, 19, 20]. Expected prolonged bacteremia and translocation of enteric organisms in transplant patients could account for a higher incidence of gram-negative bacterial HA-BSI [21]. However, our findings are consistent with those of several other studies that demonstrated a predominance of gram-positive bacterial BSI among immunosuppressed pediatric patients [21–24]. It was previously suggested that the high prevalence of common skin contaminants (ie, CoNS, viridans group streptococci) reported in these studies may reflect high rates of blood culture contamination. However, this is unlikely to be the case in our cohort, given our use of more stringent NHSN criteria. Predominance of gram-positive bacteria is postulated to be related to frequent microscopic bone or skin trauma, low catheter removal rates, and perceived difficulty with maintaining central venous catheter sterility in young children [21, 25]. Finally, we observed a high incidence of HA-BSI caused by *Enterococci*, which could relate to the frequent empirical use of cephalosporins (eg, cefepime) for febrile neutropenia in our patient population. Enterococci have intrinsic resistance to cephalosporins, and prior studies have demonstrated that exposure to cephalosporins is a risk factor for enterococcal infections in hospitalized patients [26].

Although the incidence of HA-BSI declined at our institution, HA-BSI continues to be associated with substantial morbidity and mortality despite overall decline in mortality among HSCT patients [3]. In particular, the case fatality rate of fungal HA-BSI exceeded 20% and was higher than the case fatality rate observed for other HA-BSIs in this cohort. This also varies from prior studies in older patients or smaller pediatric cohorts in which gram-negative bacterial BSI had the highest reported mortality [19]. Severe disseminated fungal infections are often associated with higher rates of mortality, and implementation of antifungal prophylaxis has been linked to a decline in the occurrence of invasive fungal infections and associated mortality [3, 27]. Although many patients within our cohort received antifungal prophylaxis with voriconazole, amphotericin B lipid complex, or fluconazole, receipt of antifungal prophylaxis did not independently affect the risk of fungal HA-BSI. Investigators have also reported the changing epidemiology of fungal infections with the use of antifungal prophylaxis for HSCT recipients, although no associated mortality effect was noted in those studies [9, 27–29]. Other contributors to the higher mortality seen with fungal HA-BSI could be inadequate diagnostic modalities for early identification of invasive fungal infection and evolving pediatric antifungal dosing recommendations [30].

We found that older age, receipt of an umbilical cord blood transplant, and nonmyeloablative or reduced-intensity conditioning regimens were associated with an increased risk of

HA-BSI in children undergoing HSCT. Older age at HSCT has previously been identified as a factor that increases the risk of HA-BSI [2]. The interactions between the immune system, baseline predisposing conditions, and exposure to the external environment could explain this finding. Acute leukemia, also associated with high infectious complications as compared with solid tumors or congenital immunodeficiency, is typically diagnosed more often in older children [31]. Additionally, decreased contamination of central venous catheters in nondiapered older children may have contributed to this finding. The increased risk of HA-BSI among recipients of umbilical cord blood transplants may be related to the prolonged neutropenia and delayed immune reconstitution observed with this graft source [19, 31–33]. Umbilical cord blood recipients have earlier onset of bloodstream infections in their post-transplant period (<50 days), which may reflect higher likelihood of HA-BSI during HSCT hospitalization [33, 34]. Prior studies in adult HSCT recipients have reported that reduced-intensity conditioning regimens are associated with a shorter duration of neutropenia and a lower risk of BSI [35, 36]. In contrast, we found that pediatric patients receiving nonmyeloablative or reduced-intensity conditioning were at higher risk of HA-BSI. This finding should be interpreted with caution, because only a small proportion of our cohort (64 patients, 5% of the study population) received a nonmyeloablative or reduced-intensity conditioning regimen. Other possible reasons for this finding may be unmeasured differences in the clinical management of patients receiving nonmyeloablative or reduced-intensity conditioning such as perceptions of the patient's ability to tolerate a myeloablative regimen due to preexisting illness, advanced disease, prior infectious history, or preemptive antimicrobial coverage in high-risk patients [4]. Notably, although steroid-sparing GvHD prophylaxis has previously been associated with a lower incidence of BSI and improved outcomes in HSCT recipients, exposure to steroid-containing GvHD prophylaxis did not alter the risk of bacterial or fungal HA-BSI in our cohort.

This study has several limitations. First, the study cohort consists of HSCT recipients from a single academic center that uniquely performs a high number of umbilical cord blood transplants. Although this may not be representative of most pediatric transplant centers, findings within this highly vulnerable group may highlight modifiable factors that influence the risk of HA-BSI in other allogeneic HSCT recipients. In addition, given the myriad of practice changes that occurred over the study period, we were unable to identify specific interventions that contributed to the reduction in HA-BSI observed over time. Third, we attempted to exclude surveillance blood cultures with probable contaminants, but this practice may still have affected the incidence of HA-BSI that we observed in this study. Notably, as this was standard practice at our institution throughout the 20-year study period, it is unlikely to have influenced the observed decline in HA-BSI. Finally, although statistical models adjusted for a number of key clinical covariates, we cannot exclude the possibility of confounding by unmeasured factors.

In summary, the incidence of HA-BSI among pediatric HSCT recipients at a single major transplant center declined over the past 2 decades. Our findings describe changes in the microbiology of HA-BSI over this period and identify unique risk factors for HA-BSI in children and adolescents undergoing HSCT. These results could inform the management of pediatric HSCT recipients and future efforts to reduce the burden of HA-BSI in this patient population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. I.C.A., R.R.Y., and M.S.K. designed the study and performed data collection, data interpretation, and initial manuscript review. R.R.Y. performed data analysis. L.P.S., L.E.M., K.J., and S.M.H. collected and interpreted data. D.J.L., P.L.M., P.C.S., Y.C., and M.J.S. interpreted data. I.C.A. prepared the initial draft of the manuscript. All authors critically reviewed and contributed to subsequent versions before approving the final manuscript for submission.

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