Biol Blood Marrow Transplant 25 (2019) 1648–1653

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Incidence and Outcomes of Bacterial Bloodstream Infections during Acute Graft-versus-Host Disease Involving the Gastrointestinal Tract after Hematopoietic Cell Transplantation

Jenna Petersen[1], Christian Lindner[2], Morgan Hakki[1,3,*]

[1] Department of Medicine, Oregon Health and Science University, Portland, Oregon
[2] School of Medicine, Oregon Health and Science University, Portland, Oregon
[3] Division of Infectious Diseases, Oregon Health and Science University, Portland, Oregon

Article history:
Received 12 March 2019
Accepted 11 April 2019

Key Words:
Bloodstream infection
Bacteremia
Hematopoietic cell transplant
Graft-versus-host disease
Infection

A B S T R A C T

Despite the association of acute graft-versus-host disease (aGVHD) and bacterial bloodstream infections (BSIs) in hematopoietic cell transplant (HCT) recipients, relatively little is known about BSIs, specifically during gastrointestinal (GI) tract aGVHD (aGHVD-GI). The purpose of this study was to evaluate the incidence, risk factors, and mortality of BSIs complicating aGVHD-GI. This was a retrospective review of adult HCT recipients with grades I to IV aGVHD-GI between January 2009 and October 2017 at Oregon Health and Sciences University. BSIs occurring within 30 days of onset of aGVHD-GI were included. BSIs were categorized as "clinical" or "surveillance" based on chart review. A subgroup analysis of patients with grade IV aGVHD-GI examined potential BSI risk factors and cumulative survival at 30 and 45 days after onset of aGVHD-GI. Included were 229 patients. There were 45 unique BSIs in 39 patients (17%): 31 clinical (68.9%) and 14 surveillance (32.1%). The median time from aGVHD-GI onset to BSI was 18.5 days. BSIs were significantly more common during grade IV aGVHD-GI compared with grades I, II, or III. Fifty-two organisms were isolated during BSIs: 23 (44.2%) gram-positive and 29 (55.8%) gram-negative. Sixteen BSIs (36%) occurred during antibiotic exposure, and those were more likely to be caused by multidrug-resistant organisms. Prior BSI occurring between the time of HCT and onset of aGVHD-GI and receipt of etanercept for steroid-refractory aGVHD-GI were independently associated with BSI. Eight patients, all with grade IV aGVHD, representing 30.8% of patients with BSI in this subgroup, experienced infection-associated mortality. Cumulative survival at days 30 and 45 after onset of grade IV aGVHD-GI was similar among patients with and without BSI. BSI is a common complication of grade IV aGVHD-GI, resulting in significant infection-associated mortality. Interventions targeting those at highest risk may be warranted.

INTRODUCTION

Bloodstream infections (BSIs) are among the most common infectious complications of allogeneic hematopoietic cell transplantation (HCT) [1]. Most BSIs occur in the early (<30 days after HCT) or pre-engraftment periods after HCT [2–6] as a result of neutropenia, mucositis, and the presence of central venous catheters [1]. However, up to 40% of BSIs occur in the postengraftment or late (after day 30) periods and affect up to 20% of allogeneic HCT recipients [2,3,6–8].

Acute graft-versus-host disease (aGVHD) has been shown to increase the risk for postengraftment BSIs [3,7,9–12]. Specifically, aGVHD involving the gastrointestinal tract (aGVHD-GI), a frequent complication of allogeneic HCT [13], may increase the risk for bacteremic events with enteric organisms through disruption of GI mucosal barriers and augmented immune suppression. However, data pertaining to the incidence and outcome of BSIs in the setting of aGVHD-GI are relatively lacking becasue most studies have not distinguished aGVHD-GI from aGVHD involving the skin or liver [3,7,9–11]. Among pediatric allogeneic HCT recipients, aGVHD-GI was associated with an increased risk of BSIs with enteric organisms in the postengraftment period, and increased transplant-related mortality was observed among patients with BSI compared with those without BSI [14].

Because the impact of BSIs in adult allogenic HCT patients with aGVHD-GI is poorly understood, we performed a retrospective analysis of BSIs in this patient population at our institution. The purpose of this study was to determine the incidence of BSIs during aGV````HD-GI, to identify risk factors for BSIs in this setting, and to determine the mortality associated with BSIs.

Financial disclosure: See Acknowledgments on page 1652.

* Correspondence and reprint requests: Morgan Hakki, MD, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, L-457, Portland, OR 97239.
E-mail address: hakki@ohsu.edu (M. Hakki).

https://doi.org/10.1016/j.bbmt.2019.04.016
1083-8791/

METHODS

Study Design, Patient Population, and Data Collection

This was a retrospective study of adult (≥18 years of age) allogeneic HCT recipients at Oregon Health & Science University (OHSU). Patients with biopsy-proven aGVHD-GI of the upper and/or lower GI tract occurring between January 1, 2009 and October 31, 2017 were identified from OHSU's HCT Registry Database. Clinical onset of aGVHD-GI was determined by review of the electronic medical record (EMR), and only patients with clinical onset of aGVHD-GI ≤ 100 days after the date of HCT were included.

The maximum grade of aGVHD-GI was obtained from the HCT registry and was retrospectively assigned by a registry coordinator according to established criteria [15] after a review of the EMR. Uncertainty pertaining to aGVHD grading was resolved by case review by an HCT physician.

At our institution, aGVHD-GI is typically managed with glucocorticoids and nonabsorbable steroids as first-line agents, with doses at the discretion of the primary HCT team. Etanercept has traditionally been the most frequently used agent for steroid-refractory disease.

Results of all blood cultures performed on all patients with aGVHD-GI included in this study were reviewed in the EMR. Patient characteristics, additional laboratory data, and clinical outcomes were obtained from review of OHSU's HCT Registry Database and the EMR. This study was approved by the OHSU institutional review board.

Definitions

Patients were categorized as having had a BSI if a blood culture was positive for a bacterium within 30 days of onset of aGVHD-GI. The 30-day interval was chosen to maximize capture of BSIs related to severe aGVHD-GI based on the mean interval to clinical response of severe aGVHD after treatment initiation [16]. Fungemic events were not included in this study. Multiple bacteria present in the same blood culture were considered as a single BSI episode. Cultures positive for *Staphylococcus epidermidis*, other coagulase-negative staphylococci, *Corynebacterium*, and *Propionibacterium* that did not meet at least 1 of the following 3 criteria were defined as contaminants and not included as BSIs: positive cultures on 2 consecutive days, 2 sets of positive cultures within 72 hours, or simultaneous positive cultures from both a peripheral site and a central venous catheter or peripherally inserted central catheter [3,11,12].

BSIs were categorized as "clinical" if the blood culture was obtained for symptoms or signs of infection, including but not limited to fever, hypotension, tachycardia, mental status change, or other change in clinical condition as determined by review of the EMR. BSIs were categorized as "surveillance" if no clinical indication for obtaining the blood culture could be determined or if the culture was specifically documented to be a surveillance culture in the EMR. Per OHSU institutional protocol, surveillance blood cultures are routinely obtained once weekly in patients receiving ≥.5 mg/kg/day of prednisone (or equivalent) for GVHD.

For the grade IV aGVHD-GI subgroup BSI risk factor analysis, the following definitions were used: receipt of etanercept, defined as initiation of etanercept within 30 days of onset of aGVHD-GI; *Clostridium difficile* infection, defined as positive PCR assay for *C. difficile* toxin B gene or toxin enzyme immunoassay from the date of HCT until day 30 after the onset of aGVHD-GI in those without BSI or the date of BSI in those with BSI; cytomegalovirus reactivation, define as positive quantitative cytomegalovirus serum PCR from the date of transplant to day 30 after the onset of aGVHD-GI or the date of BSI; neutropenia, defined as absolute neutrophil count ≤ 500/mm^3 within 30 days of onset of aGVHD-GI in those without BSI or between onset of aGVHD-GI and BSI in those with BSI; and prior BSI, defined as a BSI meeting study criteria occurring any time from the date of HCT to the clinical date of onset of aGVHD-GI. A breakthrough BSI was defined as a BSI occurring during receipt of ≥24 hours of any antibacterial agent used at standard treatment doses for any indication. Infection-attributable mortality was defined as death within 7 days of a BSI.

Statistical Methods

Categorical variables were compared using Fisher's 2-tailed exact test or logistic regression analysis, and continuous variables were compared using the Mann-Whitney U test. Statistical analyses were performed with SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

Two hundred twenty-nine patients with grades I to IV aGVHD-GI were included in this study (Table 1). The median age was 57 years (range, 21 to 80), and most (62%) were men. The most common underlying indication for HCT was acute myeloid leukemia, and most patients received a transplant from an unrelated donor. The median time to onset of aGVHD-GI after HCT was 35 days (interquartile range, 25 to 57). The distribution of aGVHD-GI grades among patients was fairly equal, with 85 (37%) having maximum grade I, 49 (21%) grade II, 41 (18%) grade III, and 54 (24%) grade IV.

Table 1
Patient Characteristics (N = 229)

Characteristic	Value
Median age, yr (range)	57 (21-80)
Gender	
Male	142 (62)
Female	87 (38)
Race	
White	207 (90)
Other	22 (10)
Underlying disease	
Acute myeloid leukemia	90 (39)
Myelodysplastic syndrome	55 (24)
Acute lymphoblastic leukemia	28 (12)
Other	56 (24)
Donor type	
Unrelated	163 (71)
HLA-matched sibling	63 (28)
HLA-mismatched sibling	3 (1)
Stem cell source	
Peripheral blood stem cells	217 (95)
Bone marrow	8 (3)
Cord blood	4 (2)
Median aGVHD-GI onset, days after HCT (interquartile range)	35 (25-57)
aGVHD-GI maximum grade	
I	85 (37)
II	49 (21)
III	41 (18)
IV	54 (24)

Values are n (%) unless otherwise defined.

Incidence and Distribution of BSIs

Overall, there were 45 unique BSI episodes in 39 patients, representing 17% of the total study population. The median time to BSI from clinical onset of aGVHD-GI was 18.5 days (interquartile range, 9.7 to 23). Thirty-one BSIs (68.9%) were categorized as clinical and 14 (32.1%) as surveillance.

The incidence of BSIs within 30 days of onset of aGVHD-GI was compared among patients for each grade of aGVHD-GI (Table 2). Three patients with grade I aGVHD-GI (3.5%) had a BSI, 2 clinical and 1 surveillance. The incidence of BSIs among patients with grade II aGVHD-GI (8.2%) was not significantly different from those with grade I aGVHD-GI. Among the 41 patients with grade III aGVHD-GI, 6 (14.6%) had a BSI (P = .06 versus grade I), of which 5 were clinical BSIs (P = .04 versus grade I) and 1 was a surveillance BSI (P = .54 versus grade I). Of the 54 patients with grade IV aGVHD-GI, 26 (48.1%) experienced a BSI, with 2 patients having both a clinical and surveillance BSI. Patients with grade IV aGVHD-GI accounted for 67.7% of all aGVHD-GI patients with a BSI in this study. Both clinical and surveillance BSIs were more common among patients with grade IV aGVHD-GI compared with grade I (P < .0001 and P = .002, respectively) and grade III aGVHD-GI (P = .009 and P = .07, respectively).

Sixteen of 45 BSI episodes (36%) occurred during antibiotic exposure and were classified as "breakthrough" BSIs; of these, 11 (68.7%) were clinical BSIs. The relative proportion of clinical BSIs were not different between breakthrough versus non-breakthrough BSIs (data not shown). Ten breakthrough BSIs

Table 2
Unique Patients with BSIs according to Grade of aGVHD-GI

	Grade aGVHD-GI							
	I (n = 85)	II (n = 49)	P*	III (n = 41)	P*	IV (n = 54)	P*	P†
Total BSIs	3 (3.5)	4 (8.2)	.26	6 (14.6)	.06	28‡ (51.8)	<.0001	.0002
Clinical culture	2 (2.4)	2 (4.1)	NS	5 (12.2)	.04	20‡ (37)	<.0001	.009
Surveillance culture	1 (1.2)	2 (4.1)	NS	1 (2.4)	.54	8‡ (14.8)	.002	.07

Values are n (%).
* *P* value vs. grade I.
† *P* value grade III vs. IV.
‡ Two patients had positive clinical and surveillance cultures.

(62.5%) occurred during fluoroquinolone prophylaxis that was used on an ad hoc basis at the discretion of the attending HCT physician to prevent BSIs in patients with severe aGVHD-GI; the remaining breakthrough BSIs occurred in patients receiving piperacillin-tazobactam (n = 2), cefepime (n = 1), aztreonam (n = 1), meropenem (n = 1), and doxycycline (n = 1).

Microbiology of BSIs

Fifty-two organisms were isolated from clinical and surveillance cultures (Table 3). Of those, 23 (44.2%) were gram-positive and 29 (55.8%) were gram-negative. *Staphylococcus aureus* and *Streptococcus* species were the predominant gram-positive organisms. Five of 6 *S. aureus* isolates were methicillin-sensitive. Three *Enterococcus* species isolates were vancomycin-resistant *E. faecium* and 2 were ampicillin-susceptible *E. faecalis*. *Pseudomonas aeruginosa* (n = 7) and *Klebsiella pneumoniae* (n = 7) were the predominant gram-negative pathogens, with *Bacteroides fragilis* (n = 5) and *Escherichia coli* (n = 4) also frequently isolated. *S. aureus*, coagulase-negative *Staphylococcus*, and *P. aeruginosa* were the only organisms found exclusively during clinical BSIs (excluding those organisms isolated only once), whereas other organisms encountered with frequency were typically found evenly distributed between clinical and surveillance BSIs.

Table 3
Microbiology of BSIs

	Clinical BSI	Surveillance BSI	Total
No. of total isolates	36	16	52
Gram-positive, n (% of total isolates)	17 (47.2)	6 (37.5)	23 (44.2)
Staphylococcus aureus	6	0	6
Streptococcus species	3	3	6
Enterococcus species	3	2	5
Coagulase-negative *Staphylococcus*	4	0	4
Clostridium species	0	1	1
Bifidobacterium	1	0	1
Gram-negative, n (% of total isolates)	19 (52.8)	10 (52.5)	29 (55.8)
Pseudomonas aeruginosa	7	0	7
Klebsiella pneumoniae	4	3	7
Bacteroides fragilis	3	2	5
Escherichia coli	3	1	4
Fusobacterium nucleatum	1	1	2
Enterobacter cloacae	0	1	1
Serratia liquefaciens	0	1	1
Acinetobacter species	0	1	1
Neisseria species	1	0	1

There was a trend toward a greater proportion of gram-positive organisms during breakthrough BSIs (43%) versus nonbreakthrough BSIs compared with gram-negative organisms (31%) that did not reach statistical significance (*P* = .6) (Supplemental Table 1). This finding was due largely to breakthrough BSIs with *Streptococcus* species (n = 5), all of which occurred during fluoroquinolone exposure. We next evaluated whether organisms isolated during breakthrough BSIs were more likely to be multidrug-resistant compared with organisms isolated during nonbreakthrough BSIs. We limited this analysis to organisms for which definitions of multidrug resistance have been established, specifically *S. aureus, Enterococcus* species, Enterobacteriaceae, *Acinetobacter* species, and *P. aeruginosa* [17]. Eight of 9 organisms (88.9%) isolated during breakthrough BSIs met criteria for multidrug resistance compared with 2 of 23 organisms (13%) during nonbreakthrough BSIs (*P* = .0001) (Table 4).

Risk Factors for BSIs in Patients with Grade IV aGVHD-GI

Analysis of possible risk factors associated with BSIs was limited to episodes occurring in those with grade IV aGVHD-GI to minimize heterogeneity among patients with and without BSIs, because patients with grade IV aGVHD-GI experienced a disproportionately high incidence of BSIs compared with other grades of aGVHD-GI. Factors were assessed during 30 unique BSI episodes in these patients and compared with 28 patients who did not experience a BSI. In a univariate analysis, only prior BSI, defined as BSI occurring between the time of HCT and onset of aGVHD-GI, and receipt of etanercept as treatment for steroid-refractory aGVHD-GI were associated with BSIs (Table 5). Both remained independently associated with BSIs when these factors were included in a multivariable model, recognizing the wide confidence intervals seen with prior BSI due to the relatively low number of events. Notably, no patient in this subgroup analysis received antithymocyte globulin as part of aGVHD management.

Outcomes in Patients with BSIs

Overall, 8 patients, representing 3.5% of the total study population (N = 229) and 20.5% of 39 unique patients with a BSI, were considered to have infection-associated mortality, defined as death ≤ 7 days after date of the positive blood culture. All 8 cases of infection-associated mortality occurred among the 26 grade IV aGVHD-GI patients, representing 30.8% of these patients. Infection-associated mortality was similar after clinical (30%) and surveillance (25%) BSIs.

All-cause mortality at days 30 and 45 after onset of grade IV aGVHD-GI was compared among patients with and without BSI. Patients with a BSI occurring between days 31 and 45 after onset of grade IV aGVHD-GI were excluded from this analysis to avoid a confounding effect on day 45 mortality. Among 26 patients with a BSI, 17 (65.4%) and 11 (42.3%) were alive by 30

Table 4
Multidrug-Resistant Bacteria during Breakthrough and Nonbreakthrough BSIs

	Breakthrough		Nonbreakthrough	
Organism	Total n	Multidrug resistance n (%)	Total n	Multidrug resistance n (%)
Enterococcus species	2	2* (100)	3	1* (33)
Staphylococcus aureus	1	1† (100)	5	0
Enterobacteriaceae				
Klebsiella pneumoniae	1	1 (100)	6	0
Escherichia coli	3	3 (100)	1	1 (100)
Enterobacter cloacae	0	—	1	0
Serratia liquefaciens	0	—	1	0
Pseudomonas aeruginosa	2	1 (50)	5	0
Acinetobacter species	0	—	1	0
Total	9	8 (88.9)	23	2 (8.7)

* *Enterococcus faecium*.
† Methicillin-resistant S. aureus.

Table 5
Risk Factors for BSIs Among Patients with Grade IV aGVHD-GI

			Univariate		Multivariable	
Factor	BSI (n = 30)	No BSI (n = 28)	*P*	OR (95% CI)	*P*	OR (95% CI)
Median age, yr	58	60	>.5	ND		
Male sex	24 (80)	18 (64.3)	.4	1.6 (.5-5.6)		
Mean maximum steroid dose, mg/kg/day	1.9	1.8	.5	ND		
Prior BSI	8 (26.7)	1 (3.5)	.04	9.8 (1.6-189)	.05	8.7 (1.4-173)
Clostridium difficile infection	3 (10)	5 (17.9)	.3	.4 (.1-1.7)		
Cytomegalovirus reactivation	9 (30)	10 (35.7)	.6	.8 (.2-2.3)		
Receipt of etanercept	19 (63.3)	9 (32.1)	.02	3.6 (1.3-11.2)	.04	3.3 (1.1-10.8)
Neutropenia	7 (23.3)	9 (32.1)	.4	.6 (.2-2.0)		

Values are n (%) unless otherwise defined. OR indicates odds ratio; CI, confidence interval; ND, not determined.

and 45 days, respectively, after onset of aGVHD-GI. Among 21 patients without a BSI, 12 (57.1%) and 10 (47.6%) were alive at 30 and 45 days, respectively. Therefore, the occurrence of a BSI within 30 days of grade IV aGVHD-GI onset did not significantly impact overall survival at days 30 or 45 after aGVHD-GI onset. There was no difference in overall 30- and 45-day survival between grade IV aGVHD-GI patients with a clinical BSI and patients with a surveillance BSI (data not shown).

DISCUSSION

Despite several studies documenting aGVHD as a risk factor for BSIs [3,7,9,11,12], comparatively little is known about the incidence and outcome of BSIs specifically in the setting of aGVHD-GI in adult HCT recipients. This study provides novel, clinically relevant information pertaining to a common complication of HCT. We found a high incidence of BSIs caused by gram-positive and gram-negative pathogens equally. Interestingly, the burden of BSIs was borne largely by those with grade IV aGVHD-GI. We also identified prior BSI and use of etanercept for steroid-refractory aGVHD-GI as factors independently associated with BSIs. Infection-associated mortality was high, but overall survival was not affected by BSIs.

BSIs occurred in 17% of patients in this study, a lower incidence than reported in other studies that have included grades II to IV and III to IV aGVHD involving all sites (skin, GI, liver) [9,12,18]. The lower incidence in this study may be partially accounted for by the inclusion of patients with grades I and II aGVHD-GI because we found that the BSIs in our study population occurred predominantly (67.7%) in patients with maximum grade IV aGVHD-GI, in whom the incidence was 48.1%, which is indeed comparable with the incidence of BSIs described in those studies [9,12,18]. The novel finding that the risk of BSIs during aGVHD-GI is not equal even among those with severe aGVHD-GI, defined as grades III and IV [16], suggests that grouping these grades of aGVHD together when examining the incidence and outcomes of BSIs may not be appropriate. However, whether these findings apply to patients at other centers with aGVHD-GI and to aGVHD involving other sites such as the skin remain to be determined.

The organisms identified during BSIs in this study differ from those identified in other studies of BSIs during aGVHD [3,7,9,12] in that coagulase-negative *Staphylococcus* species were relatively uncommon in this study and gram-negative organisms represented most organisms isolated in both clinical and surveillance cultures. This finding likely reflects the focus of this work on patients with aGVHD-GI in addition to the strict criteria applied to include BSIs due to coagulase-negative staphylococci. BSIs with *S. aureus* and coagulase-negative *Staphylococcus* species may be accounted for by the presence of indwelling central venous catheters or concomitant skin GVHD at the time of BSI, because these are not typically considered endogenous flora of the GI tract.

Among patients with grade IV aGVHD-GI, we identified prior BSIs between the date of HCT and onset of aGVHD-GI and the use of etanercept for steroid-refractory aGVHD-GI as independent risk factors for BSI. Among patients who received etanercept, 19 (67.8%) developed a BSI, which is comparable with an incidence of 54% reported in small pediatric series [19]. Whether the association of etanercept use with BSIs is representative of the immunomodulatory effects of etanercept [20]

versus the increased risk that may accompany steroid-refractory aGVHD-GI remains to be determined.

The identification of patients at highest risk for BSIs during aGVHD-GI may provide guidance for strategies to prevent BSIs or mitigate their impact. Indeed, the high infection-associated mortality rate of 30.8% among patients with grade IV aGVHD-GI in this study, which is comparable with 26% 7-day mortality observed in patients with postengraftment BSIs [5], supports the need for such strategies. Because routinely performing surveillance blood cultures on all patients with aGVHD requiring high-dose steroids has proven of variable yield and utility [21–25], limiting surveillance cultures to grade IV aGVHD-GI patients with risk factors identified in this study, if validated in other studies, may be appropriate. However, given the similar infection-associated mortality and overall survival rates among patients with surveillance and clinical BSIs, the potential impact of this strategy on outcomes is unclear. The use of prophylactic antibiotics such as fluoroquinolones in the highest risk patients is another possible intervention but, to the best of our knowledge, is not supported by existing data. Concerns about this strategy include the potential to increase the risk for infections with multidrug-resistant organisms and *C. difficile* [26] and the increasing evidence supporting the role of a diverse gut microbiome in the pathogenesis and outcome of aGVHD-GI and allogeneic HCT in general [27]. The retrospective nature of our study precludes conclusions about the impact of antibiotic prophylaxis on BSIs in these patients, and, ultimately, a randomized, prospective study is required to definitively address the utility of this intervention.

Notably, cumulative survival at days 30 and 45 after the onset of aGVHD-GI was no different in those with BSI compared with those without a BSI, consistent with findings that those with severe aGVHD die mostly due to noninfectious causes [28,29]. We did not assess the impact of BSIs on mortality at time points beyond 30 and 45 days after onset of aGVHD-GI because such an analysis may not be as reflective of the direct contribution of BSIs toward mortality, and several studies have failed to demonstrate an impact of postengraftment BSIs on survival at 6- to 12-month time points after HCT [3,12].

This study has several important limitations. It was a single-center study, thereby limiting generalization of the findings to patients at other transplant centers. We did not exclude patients with concomitant aGVHD affecting the skin or liver and therefore acknowledge that aGVHD affecting these sites may have contributed to our findings. The retrospective nature of the study limits the ability to draw conclusions pertaining to the impact of antibiotic exposure on BSIs, infection-associated mortality, and the impact of BSIs on cumulative survival. We did not determine whether grade IV aGVHD-GI is an independent risk factor for postengraftment BSI because this was not the purpose of the study and is outside the scope of this work.

In conclusion, our study provides novel and clinically relevant findings pertaining to the incidence and outcome of BSIs during aGVHD-GI in adult HCT recipients, which to date has been relatively poorly understood. Further studies are needed to confirm these results and determine whether interventions targeting those at highest risk for BSIs as identified in this study will be of benefit.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Alex Stentz, MPH, OHSU HCT Registry Manager, and Jessie Myers for providing institutional HCT registry data.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.04.016.

REFERENCES

1. Dandoy CE, Ardura MI, Papanicolaou GA, Auletta JJ. Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: new considerations for a persistent nemesis. *Bone Marrow Transplant*. 2017;52:1091–1106.
2. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. *Biol Blood Marrow Transplant*. 2009;15:47–53.
3. Almyroudis NG, Fuller A, Jakubowski A, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2005;7:11–17.
4. Collin BA, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. *Clin Infect Dis*. 2001;33:947–953.
5. Mikulska M, Del Bono V, Bruzzi P, et al. Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients. *Infection*. 2012;40:271–278.
6. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transplant*. 2007;40:63–70.
7. Gudiol C, Garcia-Vidal C, Arnan M, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. *Bone Marrow Transplant*. 2014;49:824–830.
8. Mikulska M, Del Bono V, Viscoli C. Bacterial infections in hematopoietic stem cell transplantation recipients. *Curr Opin Hematol*. 2014;21:451–458.
9. Bock AM, Cao Q, Ferrieri P, Young JA, Weisdorf DJ. Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. *Biol Blood Marrow Transplant*. 2013;19:102–108.
10. Mitchell AE, Derrington P, Turner P, Hunt LP, Oakhill A, Marks DI. Gram-negative bacteraemia (GNB) after 428 unrelated donor bone marrow transplants (UD-BMT): risk factors, prophylaxis, therapy and outcome. *Bone Marrow Transplant*. 2004;33:303–310.
11. Poutsiaka DD, Munson D, Price LL, Chan GW, Snydman DR. Blood stream infection (BSI) and acute GVHD after hematopoietic SCT (HSCT) are associated. *Bone Marrow Transplant*. 2011;46:300–307.
12. Yuen KY, Woo PC, Hui CH, et al. Unique risk factors for bacteraemia in allogeneic bone marrow transplant recipients before and after engraftment. *Bone Marrow Transplant*. 1998;21:1137–1143.
13. McDonald GB. How I treat acute graft-versus-host disease of the gastrointestinal tract and the liver. *Blood*. 2016;127:1544–1550.
14. Levinson A, Pinkney K, Jin Z, et al. Acute gastrointestinal graft-vs-host disease is associated with increased enteric bacterial bloodstream infection density in pediatric allogeneic hematopoietic cell transplant recipients. *Clin Infect Dis*. 2015;61:350–357.
15. Przepiorka D, Chan KW, Champlin RE, et al. Prevention of graft-versus-host disease with anti-CD5 ricin A chain immunotoxin after CD3-depleted HLA-nonidentical marrow transplantation in pediatric leukemia patients. *Bone Marrow Transplant*. 1995;16:737–741.
16. Castilla-Llorente C, Martin PJ, McDonald GB, et al. Prognostic factors and outcomes of severe gastrointestinal GVHD after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2014;49:966–971.
17. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18:268–281.
18. Cappellano P, Viscoli C, Bruzzi P, Van Lint MT, Pereira CA, Bacigalupo A. Epidemiology and risk factors for bloodstream infections after allogeneic hematopoietic stem cell transplantion. *New Microbiol*. 2007;30:89–99.
19. Faraci M, Lanino E, Morreale G, et al. Bacteremias and invasive fungal diseases in children receiving etanercept for steroid-resistant acute GVHD. *Bone Marrow Transplant*. 2011;46:159–160.
20. Baddley JW, Cantini F, Goletti D, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-alpha agents). *Clin Microbiol Infect*. 2018;24(Suppl 2):S10–S20.
21. Chizuka A, Kami M, Kanda Y, et al. Value of surveillance blood culture for early diagnosis of occult bacteremia in patients on corticosteroid therapy following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35:577–582.

22. Colombier MA, Lafaurie M, de Fontbrune FS, et al. Usefulness of daily surveillance blood cultures in allogeneic hematopoietic stem cell transplant recipients on steroids: a 1-year prospective study. *Transpl Infect Dis*. 2016;18:504–511.
23. Joosten A, Maertens J, Verhaegen J, Lodewyck T, Vermeulen E, Lagrou K. High incidence of bloodstream infection detected by surveillance blood cultures in hematology patients on corticosteroid therapy. *Support Care Cancer*. 2012;20:3013–3017.
24. Kameda K, Kimura SI, Akahoshi Y, et al. High incidence of afebrile bloodstream infection detected by surveillance blood culture in patients on corticosteroid therapy after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:371–377.
25. Stohs E, Chow VA, Liu C, et al. Limited utility of outpatient surveillance blood cultures in hematopoietic cell transplant recipients on high-dose steroids for treatment of acute graft-versus-host-disease. *Biol Blood Marrow Transplant*. 2019. (in press).
26. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Curr Opin Infect Dis*. 2011;24:545–553.
27. DeFilipp Z, Hohmann E, Jenq RR, Chen YB. Fecal microbiota transplantation: restoring the injured microbiome after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:e17–e22.
28. El-Jawahri A, Li S, Antin JH, et al. Improved treatment-related mortality and overall survival of patients with grade IV acute GVHD in the modern years. *Biol Blood Marrow Transplant*. 2016;22:910–918.
29. Khoury HJ, Wang T, Hemmer MT, et al. Improved survival after acute graft-versus-host disease diagnosis in the modern era. *Haematologica*. 2017;102:958–966.