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ARTICLE

Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation

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Abstract

We analyzed CIBMTR data to evaluate the incidence of non-relapse mortality (NRM) and association with overall survival (OS) for bacterial blood stream infections (BSIs) occurring within 100 days of alloHCT in 2 different phases: pre-/peri-engraftment (BSI very early phase, BSI-VEP) and BSI post-engraftment (BSI occurring between 2 weeks after engraftment and day 100, late early phase, BSI-LEP). Of the 7128 alloHCT patients, 2656 (37%) had ≥1 BSI by day 100. BSI-VEP, BSI-LEP, and BSI-Both constituted 56% ($n = 1492$), 31% ($n = 824$), and 13% ($n = 340$) of total BSI, respectively. Starting in 2009, we observed a gradual decline in BSI incidence through 2012 (61–48%). Patients with BSI-VEP were more likely to receive a myeloablative conditioning (MAC) regimen with total body irradiation (TBI). NRM was significantly higher in patients with any BSI (RR 1.82 95% CI 1.63–2.04 for BSI-VEP, RR 2.46, 95% CI 2.05–2.96 for BSI-LEP, and RR 2.29, 95% CI 1.87–2.81 for BSI-Both) compared with those without BSI. OS was significantly lower in patients with any BSI compared with patients without BSI (RR 1.36, 95% CI 1.26–1.47 for BSI-VEP; RR 1.83, 95% CI 1.58–2.12 for BSI-LEP: RR 1.66, 95% CI 1.43–1.94 for BSI-Both). BSIs within day 100 after alloHCT are common and remain a risk factor for mortality.

Introduction

Bacterial blood stream infections (BSIs) are common after allogeneic hematopoietic cell transplantation (alloHCT), occurring in 20–45% of patients [1–7]. The main predisposing factor for pre-engraftment BSI are mucosal injury (mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI)) [8] or the presence of an indwelling central catheter (central line-associated BSI (CLABSI)) [9]. Higher incidence of BSI has been reported for umbilical cord blood (UCB) [6, 10] or bone marrow (BM) [7] allografts (compared with peripheral blood), unrelated donors (URD) [1, 6] (compared with related), HLA-mismatched donors [11] (compared with mismatched), myeloablative conditioning (MAC) [12] (compared with nonmyeloablative conditioning), and advanced leukemia [1]. In addition, graft-vs-host disease (GVHD) [5] and steroid use [13, 14] have been associated with higher BSI incidence. In single-center studies, BSI is associated with increased mortality at 1 year after alloHCT [6, 11, 14, 15].

We analyzed the registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to assess the impact of early BSI (by day 100) on transplant outcomes including overall survival (OS), non-relapse mortality (NRM), disease-free survival (DFS), and relapse at 1 year after alloHCT. Two BSI time frames were examined: pre-/peri-engraftment phase [very early phase (VEP)], and post-engraftment phase, 2 weeks after

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engraftment through day 100 [late early phase (LEP)]. Transplant outcomes for patients with BSI-VEP, BSI-LEP, and both BSIs were compared with patients without BSI.

Material and methods

Study population

The study population included all patients receiving first alloHCT for acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS) in pediatric and adult patients between January 2008 and December 2012. Grafts from related donors (including haploidentical) and URD were included. Graft sources included BM, peripheral blood stem cells (PBSC), and UCB. T cell-depleted grafts were also included. Patients who had a prior alloHCT were excluded.

Data source

The CIBMTR is a voluntary working group of >450 transplantation centers worldwide that contribute detailed data on consecutive hematopoietic cell transplants to a statistical center located at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. The CIMBTR maintains an extensive database of detailed patient-, transplant-, and disease-related information and prospectively collects data longitudinally with yearly follow-ups. Observational studies conducted by the CIBMTR are performed in compliance with HIPAA regulations as a public health authority and also in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by a continuous review by the Institutional Review Boards of NMDP and the Medical College of Wisconsin. The CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED data include disease type, age, gender, pre-transplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (BM- and/or blood-derived stem cells), conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR centers contribute TED data. CRF data are collected on a subset of registered patients, selected by weighted randomization. CRF data include more detailed disease and pre-transplant and post-transplant clinical information, including infection data. TED- and CRF-level data are collected pretransplant, 100 days, and 6 months post-HCT and annually thereafter or until death. This analysis includes only CIBMTR CRF data.

Infection data

Data for infections are captured on the CRF using an organism code, site of infection, and date of infection. BSI was defined as the isolation of a bacterial pathogen from the blood/buffy coat obtained from peripheral blood or a central venous catheter. Patients from 50 centers ($n = 268$) were excluded from the analysis due to the center reporting 100% of patients with BSI, 0% of patients with BSI, or 100% of BSI due to coagulase negative *Staphylococcus* spp. BSI was considered "recurrent" if there was at least 7 days between the dates of reported infection for the same organism. Data regarding antibacterial prophylaxis, treatment, and infection severity are not collected in the registry and therefore unavailable for analyses.

Definitions

Bacterial BSI was analyzed from day −10 (D−10) through 100 days after transplant (D100). BSI reported after D100 was not included in the analyses. Based on onset of BSI relative to neutrophil recovery, BSIs were grouped into pre-/peri-engraftment and post-neutrophil engraftment. Pre-/peri-engraftment or very early phase ("BSI-VEP") BSI was defined as infection occurring between D−10 and 14 days after neutrophil engraftment. Post-engraftment or late early phase ("BSI-LEP") BSI was defined as infection occurring between 15 days after neutrophil engraftment and D100. Patients with both BSI-VEP and BSI-LEP were designated as "BSI-Both". Patients who did not develop any BSI by D100 are defined as "no BSI" and served as the control population. Recurrent bacterial infections required a minimum of 7 days between cultures with the same organism reported. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) ≥500/mm^3. Platelet engraftment was defined as a platelet count ≥20,000/mm^3 without platelet transfusions in the prior 7 days. Acute GVHD (aGVHD) and chronic GVHD was scored by standard criteria [16–18]. The use of growth factors between day −3 and day 15 post-transplant was collected.

Statistics

Patient-, disease-, and transplant-related factors were compared between groups using the Chi-square test for categorical variables and Wilcoxon two-sample testing for continuous variables. Time-dependent variables (neutrophil and platelet engraftment and aGVHD) occurring after transplant and prior to D100 are descriptive only since these events occurred

variably by patient in relation to the bacterial BSI event that categorized the cohorts. Probabilities of OS and DFS were calculated using the Kaplan–Meier estimator. Values for relapse and NRM were generated using cumulative incidence estimates to account for competing risks. Because the patient populations are determined by an event occurring (or not) by D100, we performed univariate analyses for both the entire population from the time of transplant (D0) as well as a left-truncated analysis for only those patients alive at D100 (data not shown). As trends and statistical significance for all events were the same, this manuscript reports the results for the entire population unless otherwise specified. A Cox model for the entire population was fit to determine factors important for OS, DFS, relapse, and NRM and the main effect variable was the time-dependent variable of no BSI (reference) vs BSI-VEP vs BSI-LEP vs BSI-Both forced into every model. The proportional hazards assumption was checked; when violated, the co-variate was included as a time-dependent covariate. Center effect was tested using the score test of Commenges and Andersen [19]. If a center effect was found, then the results are adjusted accordingly to account for this. Variables examined in the multivariable models included: age (≤20 years vs 21–40 years vs 41–50 years vs >60 years); Karnofsky performance status (≥90% vs <90%); Disease stage (AML/ALL early (CR1) vs AML/ALL intermediate (≥CR2) vs AML/ALL advanced (relapsed/refractory), vs MDS early (RA, RARS, RCMD, RCMD/RS) vs MDS advanced (RAEB1, RAEB2)); HCT-CI (0 vs 1–2 vs ≥3); donor/recipient cytomegalovirus (CMV) serostatus (both negative vs any positive); conditioning intensity (myeloablative vs non-myeloablative/reduced intensity); donor/HLA-Match (HLA-identical sibling vs 8/8 unrelated vs mismatched unrelated vs UCB vs other [mismatched related/haploidentical or unrelated with HLA missing]); ATG/Campath use (no vs yes); GVHD prophylaxis (calcineurin inhibitor [CNI] + methotrexate ± others vs CNI + mycophenylate mofetil ± others vs T cell depletion [in vivo or ex vivo] vs Other); and year of HCT (2008–2009 vs 2010–2012). Owing to clinical suspicion of an impact of aGVHD and its therapy on the development of BSI and transplant outcomes, separate Cox models were fit forcing in the co-variate of development of aGVHD at any time, aGVHD occurring prior to the development of the BSI, and without aGVHD in the model. Important co-variates, relative risks, and statistical significance were unchanged between these three models for all transplant outcomes; therefore, the models shown do not include aGVHD.

Results

Blood stream infections

Of the total 7128 alloHCT, 2656 (37%) had ≥1 BSI by D100 (Table 1). Of these 2656 patients, 1891 (71%) had one BSI [762 (66%) by one single organism and 129 (5%) by >1 organisms (polymicrobial)] and 765 (29%) had >1 BSIs. (Fig. 1 and Supplemental Table 1). BSI-VEP comprised 56% of total BSI ($n = 1492$); BSI-LEP or BSI-Both comprised 31% ($n = 824$) and 13% ($n = 340$), respectively.

The median time to first BSI-VEP was 7 days (range, D −1 to D74); and the median time to first BSI-LEP was 58 days (range, D21 to D100) (Table 2). *Staphylococcus species* (spp.) were the most common bacteria, and coagulase negative *Staphylococcus* (CoNS) accounted for over a quarter ($n = 647$; 28%) of the infections reported (Fig. 1a, Supplemental Table 1).

Of note, for the entire population the cumulative incidence by day 100 of fungal infection (any reported) was 8% and that of viral infections (any reported) was 44%. Because of the issues of timing of three time-dependent variables (BSI vs fungal vs viral) for infection and the added complication of the time-dependent of aGVHD, this was not statistically compared across the BSI groups.

Comparison of factors among BSI groups

Patients with no BSI were older, had more early stage disease at the time of alloHCT, were more likely to receive a reduced-intensity conditioning (RIC) regimen with an HLA-identical sibling PBSC donor using tacrolimus and methotrexate for GVHD prophylaxis, and were less likely to receive TBI-based conditioning or post-transplant granulocyte colony-stimulating factor (GCSF) (Table 1). Patients with BSI-VEP were more likely to receive a MAC regimen with total body irradiation (TBI) (Table 1). White blood cell count, ANC at the time of alloHCT, or history of clinically significant fungal infection prior to alloHCT were similar across the four groups.

Table 2 reports the time-dependent events of engraftment and GVHD among the four BSI-defined patient cohorts. As cohorts were defined by BSI developing before neutrophil engraftment and/or by D100 and platelet engraftment and aGVHD generally occurred prior to D100, it is not possible to formally compare by univariate analysis the cumulative incidence of aGVHD and platelet engraftment across the cohorts. When assessing only patients who were alive at 100 days, the cumulative incidence of chronic GVHD was similar at 1 year for the four cohorts [BSI-VEP: 45% (42–48%) vs BSI-LEP: 43% (39–47%) vs BSI-Both: 44% (38–50%) vs no BSI: 46% (45–48%); $p = 0.2007$].

Survival

NRM was significantly higher in patients with any BSI compared with those with no BSI in multivariable analyses (Table 3, Fig. 2). NRM was lower for BSI-VEP compared with BSI-LEP (hazard ratio (HR), 0.74; 95% confidence

Table 1 Comparison of clinical characteristics among the four patient groups

Characteristic	BSI-VEP total, *n* (%)	BSI-LEP total, *n* (%)	BSI-Both total, *n* (%)	No BSI total, *n* (%)	*p* Value
Number of patients	1492	824	340	4472	
Number of centers	165	138	105	177	
Gender, male	836 (56)	446 (54)	187 (55)	2483 (56)	0.840
Age (years), median (range)	42 (<1–75)	46 (<1–79)	42 (1–74)	49 (<1–78)	<0.001
≤10	214 (14)	93 (11)	56 (16)	405 (9)	
11–20	179 (12)	98 (12)	40 (12)	338 (8)	
21–30	162 (11)	84 (10)	31 (9)	430 (10)	
31–40	163 (11)	87 (11)	30 (9)	452 (10)	
41–50	222 (15)	120 (15)	58 (17)	725 (16)	
51–60	327 (22)	175 (21)	75 (22)	1064 (24)	
>60	225 (15)	167 (20)	50 (15)	1058 (24)	
KPS					0.915
<90	470 (32)	265 (32)	103 (30)	1392 (31)	
90–100	995 (67)	541 (66)	233 (69)	2996 (67)	
Missing	27 (2)	18 (2)	4 (1)	84 (2)	
HCT-CI					0.530
0	650 (44)	353 (43)	140 (41)	1927 (43)	
1	224 (15)	114 (14)	55 (16)	649 (15)	
2	159 (11)	91 (11)	44 (13)	536 (12)	
≥3	433 (29)	321 (30)	95 (28)	1263 (28)	
Missing	26 (2)	13 (2)	6 (2)	97 (2)	
Conditioning intensity					<0.001
Myeloablative	1207 (81)	617 (75)	276 (81)	3149 (70)	
RIC/NMA	285 (19)	207 (25)	64 (19)	1323 (30)	
TBI dose					<0.001
No TBI	664 (45)	430 (52)	156 (46)	2480 (55)	
≤1200 cGy	454 (30)	265 (32)	110 (32)	1297 (29)	
>1200 cGy	374 (25)	129 (16)	74 (22)	695 (16)	
Disease status at HCT					<0.001
AML/ALL early	596 (40)	325 (39)	132 (39)	1908 (43)	
AML/ALL intermediate	378 (25)	192 (23)	88 (26)	884 (20)	
AML/ALL advanced	254 (17)	115 (14)	57 (17)	613 (14)	
MDS early	95 (6)	70 (8)	26 (8)	415 (9)	
MDS advanced	156 (10)	119 (14)	34 (10)	630 (14)	
Missing	13 (<1)	3 (<1)	3 (<1)	22 (<1)	
Time to AlloHCT, median (range), months	7 (<1–313)	7 (<1–173)	7 (1–224)	6 (<1–291)	0.059
Donor age, in decades					<0.001
UCB	593 (40)	210 (25)	113 (33)	918 (21)	
Related donor	366 (25)	211 (26)	87 (26)	1454 (33)	
18–20	43 (3)	28 (3)	8 (2)	148 (3)	
21–30	193 (13)	157 (19)	43 (13)	857 (19)	
31–40	118 (8)	98 (12)	34 (10)	479 (11)	
41–50	96 (6)	63 (8)	38 (11)	321 (7)	
51–60	28 (2)	24 (3)	4 (1)	97 (2)	
Missing	55 (4)	33 (4)	13 (4)	198 (4)	

Table 1 (continued)

Characteristic	BSI-VEP total, *n* (%)	BSI-LEP total, *n* (%)	BSI-Both total, *n* (%)	No BSI total, *n* (%)	*p* Value
Donor–recipient sex match					0.799
Male–male	522 (35)	269 (33)	108 (32)	1554 (35)	
Male–female	359 (24)	231 (28)	88 (26)	1128 (25)	
Female–male	310 (21)	174 (21)	78 (23)	909 (20)	
Female–female	292 (20)	145 (18)	63 (19)	851 (19)	
Missing	9 (<1)	5 (<1)	3 (<1)	30 (<1)	
Donor–recipient CMV status	9 (<1)	5 (<1)	3 (<1)	30 (<1)	<0.001
+/+	291 (20)	179 (22)	77 (23)	1043 (23)	
+/−	98 (7)	49 (6)	27 (8)	418 (9)	
−/+	646 (43)	328 (40)	142 (42)	1627 (36)	
−/−	441 (30)	256 (31)	85 (25)	1307 (29)	
Both missing	16 (1)	12 (1)	9 (3)	77 (2)	
Graft type					<0.001
Bone marrow	239 (16)	114 (14)	52 (15)	662 (15)	
PBSC	660 (44)	500 (61)	175 (51)	2892 (65)	
Umbilical cord blood	593 (40)	210 (25)	113 (33)	918 (21)	
Donor/recipient HLA match					<0.001
Umbilical cord blood	593 (40)	210 (25)	113 (33)	918 (21)	
HLA-identical siblings	337 (23)	196 (24)	78 (23)	1379 (31)	
Matched/mismatched related	5 (<1)	2 (<1)	3 (<1)	20 (<1)	
Haplo-identical	24 (2)	13 (2)	6 (2)	55 (1)	
8/8 unrelated	382 (26)	277 (34)	85 (25)	1558 (35)	
7/8 unrelated	114 (8)	98 (12)	42 (12)	401 (9)	
≤6/8 unrelated	10 (<1)	5 (<1)	7 (2)	27 (<1)	
Unrelated (HLA match information missing)	27 (2)	23 (3)	6 (2)	114 (3)	
ATG/Alemtuzumab as conditioning/ GVHD prophy					0.240
ATG alone	442 (30)	244 (30)	102 (30)	1367 (31)	
Alemtuzumab alone	36 (2)	9 (1)	11 (3)	89 (2)	
No ATG or Alemtuzumab	1014 (68)	571 (69)	227 (67)	3016 (67)	
GVHD prophylaxis					<0.001
CSA/TAC + MTX ± others	659 (44)	411 (50)	159 (48)	2398 (54)	
CSA/TAC + MMF ± others	541 (36)	297 (36)	128 (38)	1393 (31)	
CSA/TAC + others	166 (11)	66 (8)	31 (9)	392 (9)	
CSA/TAC alone	52 (3)	20 (2)	9 (3)	145 (3)	
SIRO ± others (not TAC/CSA)	3 (<1)	1 (<1)	0	15 (<1)	
ATG/ Alemtuzumab only	0	0	0	7 (<1)	
Ex vivo T cell depletion	29 (2)	10 (1)	2 (<1)	26 (<1)	
CD34 selection	19 (1)	2 (<1)	5 (1)	48 (1)	
Cyclophosphamide	20 (1)	15 (2)	5 (1)	81 (2)	
Other GVHD prophylaxis	3 (<1)	2 (<1)	1 (<1)	17 (<1)	
G-CSF, GM-CSF use, yes	901 (60)	498 (60)	205 (60)	2379 (53)	<0.001
Supplemental IVIG, yes	712 (48)	389 (47)	191 (56)	1766 (39)	<0.001
Year of AlloHCT					<0.001
2008	448 (30)	248 (30)	121 (36)	1194 (27)	

Table 1 (continued)

Characteristic	BSI-VEP total, *n* (%)	BSI-LEP total, *n* (%)	BSI-Both total, *n* (%)	No BSI total, *n* (%)	*p* Value
2009	410 (27)	240 (29)	97 (29)	1073 (24)	
2010	284 (19)	158 (19)	56 (16)	837 (19)	
2011	177 (12)	98 (12)	42 (12)	642 (14)	
2012	173 (12)	80 (10)	24 (7)	726 (16)	

AlloHCT allogeneic hematopoietic cell transplantation, *ALC* absolute lymphocyte count, *ANC* absolute neutrophil count, *ATG* anti-thymocyte globulin, *BSI* blood stream infections, *CMV* cytomegalovirus, *CSA* cyclosporine, *G-CSF* granulocyte-colony forming factor, *GM-CSF* granulocyte monocyte colony-stimulating factor, *GVHD* graft-vs-host disease, *HCT-CI* hematopoietic cell transplant comorbidity index, *HLA* human leukocyte antigens, *IVIG* intravenous immunoglobulin, *KPS* Karnofsky Performance score, *LEP* late early phase, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NMA* non-myeloablative, *PBSC* peripheral blood stem cells, *RIC* reduced-intensity conditioning, *SIRO* sirolimus, *TAC* tacrolimus, *TBI* total body irradiation, *WBC* white blood cells, *VEP* very early phase

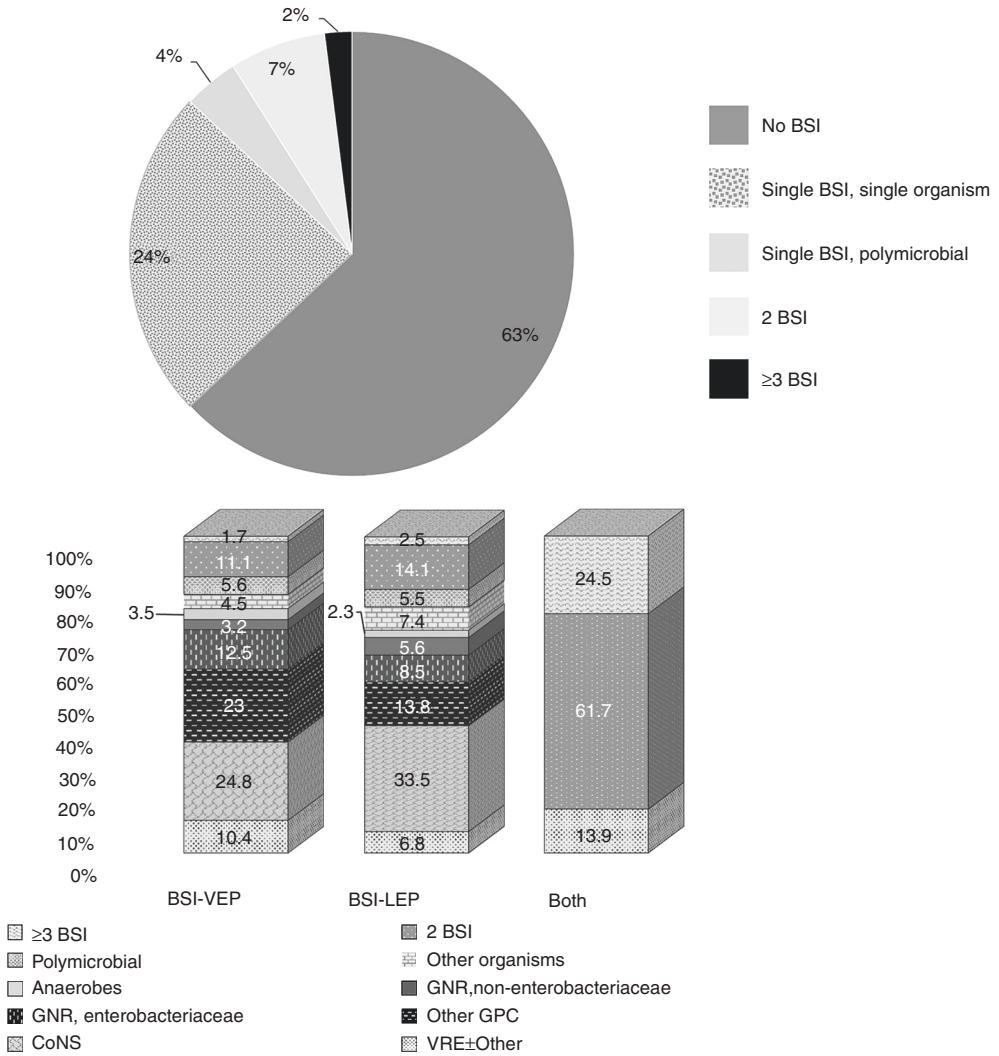

Fig. 1 **a** Patients with BSI per documented bacteria involved in BSI-VEP (left column) and BSI-LEP (middle column) and BSI-Both (right column) within 100 days (presented as percentage). Most of the BSI in VEP and LEP are composed of CoNS, Enterobacteriaceae, and other GPC. **b** Patients with BSI divided by episodes and single organism or polymicrobial infections. In all, 63% of patients had no BSI, whereas 9% of patients had ≥2 BSI

Table 2 Description of time-dependent variables of engraftment and acute GVHD among the four groups

Variable	VEP-BSI	LEP-BSI	Both-BSI	No BSI
Number of patients	1492	824	340	4472
Days to first BSI (range)	7 (<1–74)	58 (21–100)	8 (<1–36)	
Time to ANC >500, *n* (%)				
Yes	1299 (87)	824	340	4321 (97)
No	188 (13)	0	0	138 (3)
Missing	5 (<1)	0	0	13 (<1)
Time to ANC >500 days (range)	17 (<1–99)	15 (<1–42)	16 (1–50)	15 (<1–111)
Platelet engraftment >20 × 10^9/L, *n* (%)				
Yes	1103 (74)	721 (88)	277 (81)	4049 (91)
No	368 (25)	96 (12)	57 (17)	395 (9)
Missing	21 (1)	7 (<1)	6 (2)	28 (<1)
Time to platelet >20 × 10^9/L, days (range)	27 (1–180)	20 (<1–293)	26 (1–640)	19 (<1–753)
aGVHD, *n* (%)				
Yes	546 (37)	433 (53)	195 (57)	1673 (37)
No	940 (63)	387 (47)	141 (41)	2783 (62)
Missing	6 (<1)	4 (<1)	4 (1)	16 (<1)
Time to aGVHD diagnosis, days (range)	28 (7–175)	27 (7–176)	26 (7–168)	29 (7–178)
Median follow-up of survivors, months (range)	60 (3–87)	60 (3–81)	60 (12–85)	59 (3–87)

aGVHD acute graft-vs-host disease, *ANC* absolute neutrophil count, *cGVHD* chronic graft-vs-host disease, *VEP* very early phase, *LEP* late early phase

interval (CI): 0.57–0.97, $p = 0.003$) and BSI-Both (HR, 0.80; 95% CI: 0.67–1.0, $p = 0.03$).

DFS was lower for BSI-VEP, BSI-LEP, or BSI-Both compared with no BSI; and BSI-LEP or BSI-Both had the lowest DFS among these groups. Relapse was similar among the four groups.

OS was significantly lower in patients with any BSI compared with patients without BSI (Table 3, Fig. 3). However, OS was higher for BSI-VEP compared with BSI-LEP (HR, 0.74; 95% CI: 0.62–0.90, $p < 0.0001$) and BSI-Both (HR, 0.82; 95% CI: 0.64–1.06, $p = 0.008$). Besides infections, graft failure, or organ failure were more important in BSI-VEP patients, whereas GVHD was more common in BSI-LEP and BSI-Both as a cause of NRM (Supplemental Table 1). Of note, in all subgroups, relapse was the most common cause of death.

In multivariate analyses, additional factors associated with higher NRM and lower OS were older age, lower KPS, higher HCT-CI score (≥3), advanced acute leukemia, CMV seropositivity in either the donor or the recipient, use of alternative donor (HLA-mismatched URD, UCB, or other donor), and earlier transplantation (Table 3). In addition, MDS was associated with a higher NRM.

Discussion

We analyzed the CIBMTR registry data to assess the impact of early BSI (by D100) on long term (by D365) transplant outcomes. Our cohort consists of >7000 patients from 181 Centers who received alloHCT from 2008 to 2012. This is to our knowledge the largest analysis examining the impact of BSI after HCT in the contemporary era. Our main findings are that (1) Patients with BSI by D100 after alloHCT had increased NRM and lower OS compared with patients without BSI. (2) BSI-LEP was associated with increased NRM compared with no BSI or BSI-VEP.

Consistent with single-center studies [3, 20], the majority of BSI occurred in the pre-/peri-engraftment phase (i.e., BSI-VEP). However, the risk for mortality was higher for patients with BSI-LEP and for patients with both BSI-VEP and BSI-LEP. Interestingly, both in univariate and multivariable analyses, the increased NRM was similar for those with BSI-LEP and the cohort with both BSI-VEP and BSI-LEP. We postulate that differences in mortality could be partially explained by different risk factors and causative organisms between VEP and LEP BSIs. Patients with BSI-VEP were more likely to have received MAC that are associated with more severe and protracted mucosal injury and longer time to neutrophil engraftment. As a result, BSI-VEP were predominantly caused by pathogens found in gastrointestinal flora BSI (e.g., *Enterobacteriaceae* spp, anaerobes). In contrast, patients with BSI-LEP were more likely to have received RIC regimens associated with later onset GVHD. BSI-LEP were predominantly caused by skin organisms (e.g., CoNS) suggesting possibly related to central venous catheter (CVC) use. While in general skin organisms are associated with low pathogenicity (with exception of *Staphylococcus aureus*), such organisms may be a

Table 3 Multivariate analyses for non-relapse mortality, disease-free survival, and overall survival

Variables	*N*	Non-relapse mortality			Disease-free survival			Overall survival		
		RR (99% CI)	*p* Value	Overall *p* value	RR (99% CI)	*p* Value	Overall *p* value	RR (99% CI)	*p* Value	Overall *p* value
BSI										
No BSI	4472	1.00		<0.0001	1.00		<0.0001	1.00		<0.0001
VEP	1493	1.82 (1.63–2.04)	<0.0001		1.24 (1.15–1.34)	<0.0001		1.36 (1.26–1.47)	<0.0001	
LEP	824	2.46 (2.05–2.96)	<0.0001		1.53 (1.35–1.74)	<0.0001		1.83 (1.58–2.12)	<0.0001	
Both	339	2.29 (1.87–2.81)	<0.0001		1.49 (1.30–1.71)	<0.0001		1.66 (1.43–1.94)	<0.0001	
Age at HCT, years										
≤20	1423	1.00		<0.0001	1.00			1.00		<0.0001
21–40	1439	1.75 (1.44–2.11)	<0.0001		1.28 (1.13–1.45)	0.0001	<0.0001	1.40 (1.23–1.60)	<0.0001	
41–50	1125	1.98 (1.57–2.51)	<0.0001		1.35 (1.20–1.52)	<0.0001		1.56 (1.36–178)	<0.0001	
51–60	1641	2.17 (1.74–2.71)	<0.0001		1.44 (1.25–1.66)	<0.0001		1.76 (1.54–2.02)	<0.0001	
>60	1500	2.52 (2.00–3.10)	<0.0001		1.59 (1.36–1.86)	<0.0001		2.02 (1.76–2.33)	<0.0001	
KPS at HCT										
≥90	4765	1.00		0.0010	1.00		0.0018	1.00		0.0001
<90	2230	1.18 (1.05–1.32)	0.0039		1.18 (1.08–1.30)	0.0005		1.20 (1.10–1.31)	<0.0001	
Missing	133	1.38 (1.09–1.74)	0.0067		1.14 (0.94–1.38)	0.1978		1.20 (0.99–1.44)	0.0574	
Disease–disease stage variable										
AML/ALL early	2961	1.00		<0.0001	1.00		<0.0001	1.00		<0.0001
AML/ALL intermediate	1542	1.06 (0.92–1.23)	0.4336		1.17 (1.08–1.26)	0.0001		1.17 (1.08–1.26)	0.0002	
AML/ALL advanced	1039	1.27 (1.06–1.53)	0.0100		2.06 (1.89–2.25)	<0.0001		2.07 (1.88–2.27)	<0.0001	
MDS early	606	1.32 (1.10–1.58)	0.0027		0.87 (0.78–0.96)	0.0087		1.00 (0.87–1.14)	0.9747	
MDS advanced	939	1.44 (1.24–1.68)	<0.0001		1.20 (1.10–1.32)	0.0001		1.31 (1.19–1.44)	<0.0001	
Missing	41	1.48	0.1703		1.28 (0.82–1.99)	0.2831		1.25 (0.83–1.88)	0.2955	
HCT-CI										
0	3070	1.00		0.0012	1.00		0.0003	1.00		<0.0001
1–2	1872	1.09 (0.95–1.24)	0.2121		1.06 (0.97–1.15)	0.1914		1.07 (0.98–1.17)	0.1097	
≥3	2044	1.27 (1.12–1.43)	0.0001		1.14 (1.06–1.23)	0.0004		1.21 (1.12–1.31)	<0.0001	
Missing	142	1.05 (0.69–1.59)	0.8137		0.78 (0.62–0.98)	0.0302		0.78 (0.61–0.99)	0.0453	
Donor/recipient HLA match										
HLA-identical siblings	1990	1.00		<0.0001	1.00		<0.0001	1.00		<0.0001
8/8 unrelated	2302	1.26 (1.09–1.45)	0.0017		0.97 (0.90–1.06)	0.5015		1.03 (0.95–1.13)	0.4696	
≤7/8 unrelated	704	2.12 (1.78–2.53)	<0.0001		1.22 (1.09–1.36)	0.0007		1.31 (1.16–1.48)	<0.0001	
Cord blood	1834	2.15 (1.83–2.53)	<0.0001		1.23 (1.09–1.38)	0.0007		1.46 (1.29–1.64)	<0.0001	
Other	298	1.60 (1.28–2.02)	<0.0001		1.15 (0.97–1.37)	0.1040		1.26 (1.04–1.52)	0.0161	
Conditioning regimen intensity										
Myeloablative				1.0000		<0.0001				
RIC/NMA					1.24 (1.12–1.37)					
Donor/recipient CMV status										
−/−	2089	1.00		0.0035				1.00		0.0032
Any positive	4925	1.26 (1.10–1.43)	0.0008					1.13 (1.05–1.22)	0.0008	
Missing	114	1.11 (0.75–1.65)	0.6035					1.07 (0.86–1.34)	0.5438	
Year of HCT										
2008–2009								1.00		0.0046
2010–2012								0.91 (0.85–0.97)	0.0046	

RR relative risk, *CI* confidence interval

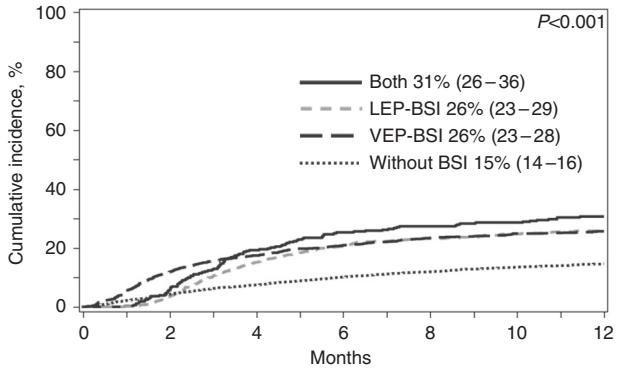

Fig. 2 NRM curve for VEP-BSI vs LEP-BSI vs Both VEP- and LEP-BSI vs No BSI), starting day 100 after transplant. Patients with no BSI had a lower NRM

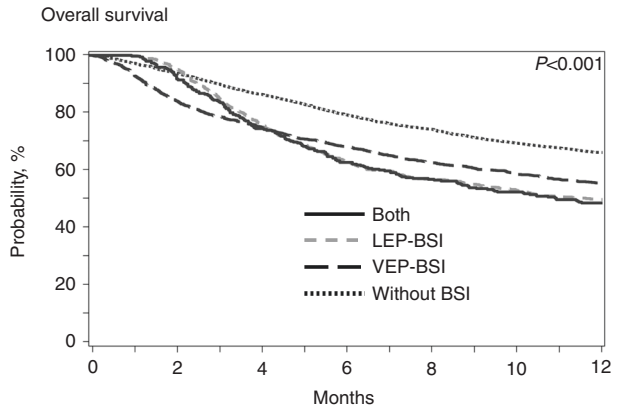

Fig. 3 OS curve for VEP-BSI vs LEP-BSI vs Both VEP- and LEP-BSI vs No BSI), starting day 100 after transplant. Patients with LEP-BSI and Both-BSI especially had worse OS

surrogate marker of increased morbidity and more frequent utilization of health-care centers. Alternatively, although difficult to prove, it is possible that monitoring and reacting to patients may vary once neutrophil engraftment occurs. As patients are generally no longer hospitalized following neutrophil engraftment, there may be less vigilance resulting in some delay in treatment leading to increased mortality. Additional possible factors that may contribute to this increased NRM for the BSI-LEP cohort including issues of drug resistance, increased degrees of immunosuppression, and/or patient deconditioning at time of BSI are unanswerable within the CIBMTR dataset.

Gudiol et al. found that early-onset BSI was mainly related to the presence of neutropenia, mucositis, and CVC, whereas late-onset BSI mainly affected severely immunosuppressed alloHCT recipients with GVHD and corticosteroids [21]. In our cohort, only 44% of BSI-VEP compared to 61% of BSI-LEP occurred following PBSC transplantation. PBSC transplantation is associated with more rapid neutrophil engraftment and increased GVHD compared to marrow allografts [22, 23]. In a recent prospective study comparing rates of infections between marrow and peripheral blood HCT from URD, 47.9% (95% CI, 41.5–53.9) of BM allograft recipients had infections compared with 32.8% (95% CI, 27.1–38.7) of PBSC allograft recipients ($p = 0.002$). Faster neutrophil engraftment after PBSC transplantation may at least partially explain these findings [7].

aGVHD is a recognized risk factor for late BSI after alloHCT [14, 24, 25]. Low rates of post-engraftment BSI and associated mortality have been reported after ex vivo T cell depletion, presumably due to lower incidence of GVHD [26]. GVHD prevention and treatment contribute to the immune compromise in alloHCT patients. However, both the event of infection and the event of GVHD have variable onset relative to transplant and are intertwined in transplant outcomes. As this analysis sought to examine the impact of bacterial BSI occurring by day 100 on transplant outcomes, the event of aGVHD was examined both as an event prior to infection or at any time relative to infection in multivariable models (data not shown). Notably, there was no difference in significant variables allowing the reporting of a multivariable model focused on infection impact. Therefore, our results suggest that the increased NRM for patients with BSI-LEP or BSI-Both are driven by the infection and not concomitant aGVHD alone.

Organisms of BSI differed between the two phases. *Streptococcus* spp., *Enterobacteriaceae*, and *Enterococcus faecium* comprised one third of total BSI-VEP. In contrast, *Streptococcus* spp. and *Enterobacteriaceae* were less frequent in BSI-LEP. CoNS comprised 25% and 33% of BSI-VEP and BSI-LEP, respectively. The frequency of vancomycin-resistant enterococci was similar across the two phases. Similar epidemiology has been reported from single-center studies [26, 6]. Interestingly, we observed a trend toward decrease in all BSI over the years of this study, 2008 through 2012. A number of advances in supportive care or transplant practices (e.g., more RIC alloHCT) may have had an impact on the incidence of BSI and potentially BSI-associated mortality. This is in the same line with improved outcomes and decreased NRM after alloHCT over time [27].

Growth factor and supplemental intravenous immunoglobulin (IVIG) use are common for various reasons after alloHCT [28, 29]. In this study, we found that both GCSF and IVIG were used significantly higher in patients with any BSI compared to patients without BSI. Although counter-intuitive, there was likely selection bias with use of these adjunctive preventative measures among sicker patients, i.e., patients who are high risk to develop infections (such as UCB transplantation or ATG use) or already had infection [29–31]. Furthermore, the administration of post-transplant growth factor use and IVIG are only captured as given or not, without timing in regards to the infection.

Our study has several limitations. Data on antibiotic prophylaxis or treatment or susceptibility (multidrug resistance)

data were not captured in the registry. Lack of this data limits understanding of our ability to impact the outcomes of patients with BSI following HCT; however, because of the large number of centers and patients, it does not lessen the finding that patients with BSI-LEP have inferior outcomes. Ongoing revisions to CIBMTR data collection forms should improve our understanding of antibacterial prophylaxis strategies but detailed data regarding the treatment of common infections is beyond the scope of a transplant registry. Recent studies suggest an association of antibiotic use with GVHD and NRM [32]. While a correlation of antibiotic exposures before or after BSI with mortality is beyond the scope of our study, it would be interesting to capture in future studies. BSI are not classified using the most updated Centers for Disease Control and Prevention definitions (i.e., LCBI: MBI-LCBI or CLABSI) due to how the data are gathered. While we acknowledge these limitations inherent to a registry study, our study has several strengths including a robust sample size from 181 centers from diverse geographic locations and reflecting current transplant practices. The inclusion of multiple centers provides a diverse population of all ages, stem cell sources, and transplant types; however, it also results in a small percentage of missing data. Given that it is <5% for nearly all pertinent variables, this data is unlikely to change the overall outcomes in this large dataset. It is also likely to minimize over or under-reporting biases inherent in single-center studies. Uniform definitions were used for data collection stipulated by CIBMTR and long-term follow-up is ensured.

The comparison of BSI-VEP and BSI-LEP is confounded by the inability to predict prior to transplant into which group a patient will ultimately fall. By definition, a patient can only be in the BSI-LEP group if no BSI-VEP occurred. Similarly, the patient can only be in the "no BSI" group if never developing a BSI in the first 100 days. Furthermore, if a patient dies due to BSI-VEP, they do not live long enough to become eligible for the "Both" category. However, if one compares only the patients still alive at day 100, valuable data is lost due to early deaths from infection, GVHD, or other causes. Therefore, our analysis and statistical methodology attempts to account for all these issues as meaningfully as possible. Furthermore, our analysis does not seek to imply that a BSI by day 100 is the sole reason for inferior survival; instead, we merely demonstrate an association. However, we found no difference in the cumulative incidence of cGVHD for the 4 cohorts when analyzing patients still alive at day 100. Consequently, it may be other consequences of the BSI (i.e. organ dysfunction) or a pre-disposition to later infections (beyond the scope of this analysis) that result in the inferior outcomes for patients with a BSI prior to day 100.

In summary, we show that BSI occurring in each phase by D100 post-alloHCT is associated with increased NRM. BSI-LEP was associated with a higher rate of mortality, indicating that neutrophil engraftment was likely critical to the survival of some patients with BSI-VEP, especially the ones who did not develop additional BSI-LEP (i.e., patients with BSI-Both). Therefore, patients after engraftment should continue to be diligently evaluated for BSIs. Further studies should focus on determining the reasons for BSI-LEP, its interaction with changes in gut microbiota, and modification of prevention and treatment in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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