

Bloodstream Infections and Delayed Antibiotic Coverage Are Associated With Negative Hospital Outcomes in Hematopoietic Stem Cell Transplant Recipients



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BACKGROUND: Bloodstream infections (BSIs) are common after hematopoietic stem cell transplantation (HSCT) and are associated with increased long-term morbidity and mortality. However, short-term outcomes related to BSI in this population remain unknown. More specifically, it is unclear whether choices related to empiric antimicrobials for potentially infected patients are associated with patient outcomes.

RESEARCH QUESTION: Are potential delays in appropriate antibiotics associated with hospital outcomes among HSCT recipients with BSI?

STUDY DESIGN AND METHODS: We conducted a retrospective cohort study at a large comprehensive inpatient academic cancer center between January 2014 and June 2017. We identified all admissions for HSCT and prior recipients of HSCT. We defined potential delay in appropriate antibiotics as > 24 h between positive blood culture results and the initial dose of an antimicrobial with activity against the pathogen.

RESULTS: We evaluated 2,751 hospital admissions from 1,086 patients. Of these admissions, 395 (14.4%) involved one or more BSIs. Of these 395 hospitalizations, 44 (11.1%) involved potential delays in appropriate antibiotics. The incidence of mortality was higher in BSI hospitalizations than in those without BSI (23% vs 4.5%; $P < .001$). In multivariable analysis, BSI was an independent predictor of mortality (OR, 8.14; 95% CI, 5.06-13.1; $P < .001$). Mortality was higher for admissions with potentially delayed appropriate antibiotics than for those with appropriate antibiotics (48% vs 20%; $P < .001$). Potential delay in antibiotics was also an independent predictor of mortality in multivariable analysis (OR, 13.8; 95% CI, 5.27-35.9; $P < .001$).

INTERPRETATION: BSIs were common and independently associated with increased morbidity and mortality. Delays in administration of appropriate antimicrobials were identified as an important factor in hospital morbidity and mortality. These findings may have important implications for our current practice of empiric antibiotic treatment in HSCT patients.

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KEY WORDS: antibiotics; bacteremia; bloodstream infection; bone marrow transplant; fungemia; hematopoietic stem cell transplant; mortality

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; BSI = bloodstream infection; CoNS = coagulase-negative staphylococci; DTR = difficult-to-treat resistance; HSCT = hematopoietic stem cell transplantation; IQR = interquartile range; LOS = length of stay; MDR = multidrug resistance; PAC = post-acute care;

SHR = subhazard ratio; SNF = skilled nursing facility; VRE = vancomycin-resistant *Enterococcus faecium*

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Although hematopoietic stem cell transplantation (HSCT) is curative for many patients with hematologic malignancies, this procedure is not without morbidity and mortality. Among the most common and severe complications are bloodstream infections (BSIs), which occur in 13% to 65% of HSCT recipients depending on patient demographics, HSCT protocols (ie, type of transplant, conditioning, prophylactic antimicrobial regimen), and length of follow-up.¹⁻⁶ The epidemiology of BSI has evolved as protocols and types of transplants have changed over time: gram-positive organisms remain the predominant cause of BSI in HSCT patients,^{1,5,7-9} although gram-negative organisms have become increasingly common.^{2,4,8,10} In addition, antibiotic resistance has increased significantly, including multidrug resistance.^{4,7,8,10-12}

BSI has been associated with increased nonrelapse mortality among HSCT patients, particularly for

patients infected with gram-negative, multidrug resistance, or fungal organisms.^{1,2,5,6,10,11,13-15}

Recently, a large multicenter cohort study identified factors correlated with nonrelapse mortality in HSCT patients, including age, advanced disease, performance status, comorbidities, donor type, and BSI occurring between days 15 and 100 after neutrophil engraftment.⁶ However, short-term outcomes related to BSI in this population remain unknown. More specifically, it is unclear whether choices related to empiric antimicrobials for potentially infected patients are associated with patient outcomes.

Thus, we aimed to evaluate the epidemiology of BSI at our cancer center, and to evaluate important outcomes among patients with BSI, and to determine whether potential delays in appropriate antibiotic therapy were associated with hospital outcomes.

Methods

Setting and Study Population

We performed an observational cohort study within Siteman Cancer Center, the National Cancer Institute (NCI)-designated Comprehensive Cancer Center at Barnes-Jewish Hospital. Siteman Cancer Center contains 138 inpatient oncology beds, which are geographically distinct from the remaining 1,200 beds at Barnes-Jewish Hospital. Using a previously described deidentified database of adult oncology admissions from January 2014 through June 2017,¹⁶ we identified all patient admissions for HSCT and all hospitalizations for prior recipients of HSCT (*e-Fig 1*). The Institutional Review Board at Washington University approved this study (No. 201707080).

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Data Collection and Definitions

We collected patient age, sex, race, laboratory, and medication data from the electronic health record, as well as comorbidity diagnoses and insurance information from administrative data. To estimate initial severity of illness, we calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 h of admission for each inpatient.¹⁷

Exposures

The primary exposure was BSI, defined as one or more positive blood culture results for any organism known or believed to be pathogenic in immunosuppressed patients.^{18,19} During the study period, our hospital did not use rapid microbiologic diagnostic tests for bloodstream infections. Notably, standard practice at our institution involves regarding even a single positive blood culture result for coagulase-negative staphylococci (CoNS) as pathogenic BSI in neutropenic or immunocompromised patients. Gram-negative bacteria were evaluated for multidrug resistance (MDR), extensive drug resistance (XDR), and difficult-to-treat resistance (DTR) per standard criteria.²⁰ If a patient experienced more than one BSI during a hospitalization, only the index BSI was evaluated. Cultures positive for multiple organisms within a 4-h period were indexed according to the first-occurring time stamp and recorded as polymicrobial BSI.

Among the subset of patients identified as having BSI, the secondary exposure was potential delay in appropriate antibiotic treatment, defined as greater than 24 h between positive blood culture results (identification of an organism at the morphologic level) and the initial dose of an antimicrobial with activity against the identified pathogen(s) based on *in vitro* susceptibility testing results. This time period was chosen on the basis of the frequency with which “no growth to date” results are updated for blood cultures at our institution.

Empirical therapy for suspected BSI at our cancer center is directed by institutional guidelines for febrile neutropenia, which are based on recommendations from the Infectious Diseases Society of America²¹ and the National Comprehensive Cancer Network.²² Cefepime is the preferred broad-spectrum agent, and vancomycin is added when

concerns exist for resistant gram-positive organisms; alternative agents such as daptomycin or linezolid are reserved for vancomycin intolerance or prior culture results indicating a need for alternative agents. Aztreonam plus vancomycin is the preferred empiric regimen in the case of severe β -lactam allergies.

In keeping with National Comprehensive Cancer Network guidelines,²² high-risk outpatients (ie, those with acute leukemias, relapsed/refractory lymphoma, and allogeneic HSCT recipients) expected to be neutropenic for more than 10 days receive ciprofloxacin prophylaxis (or either cefdinir or amoxicillin/clavulanate if allergic to fluoroquinolones) against bacterial infections and fluconazole prophylaxis against *Candida* infections. Lower risk outpatients (ie, those with solid tumors or multiple myeloma, or patients with lymphoma receiving first-line therapy) expected to be neutropenic for fewer than 10 days do not receive bacterial or *Candida* prophylaxis while neutropenic. Hospital guidelines recommend *Candida* prophylaxis while inpatient, but not bacterial prophylaxis. Allogeneic HSCT recipients receive *Candida* prophylaxis regardless of neutrophil count until 100 days post-HSCT and all immunosuppressive therapy has been discontinued. Neutropenic autologous HSCT recipients do not receive *Candida* prophylaxis unless severe mucositis is present.

Our hospital initiated an antimicrobial stewardship program in June 2016. This program involves clinical pharmacist review of certain antimicrobials (eg, daptomycin, ceftaroline) after 72 h of continuous use, followed by discussion with the clinical team if questions about clinical appropriateness remain. The stewardship program does not apply to commonly used drugs including ceferipime, meropenem, piperacillin-tazobactam, vancomycin, and linezolid, and it does not require approval for the initial dose of any agent.

Outcomes

The primary outcome of the study was hospital mortality. Secondary outcomes included hospital length of stay (LOS), discharge disposition (ie, discharge home, to a post-acute care [PAC] setting such as a skilled nursing facilities [SNF], rehabilitation facility, or long-term acute care hospitals, or discharge to hospice).

Statistics

Data are expressed as No. (%), or as medians (interquartile range [IQRs]), as appropriate. We used frequency distributions and χ^2 or McNemar tests to analyze categorical data, and Mann-Whitney *U* and Kruskal-Wallis tests to analyze continuous variables. The data set contained no missing data, allowing us to perform complete case analysis.

For the primary outcome and for binary secondary outcomes, we estimated separate multivariable mixed-effects logistic regression models to account for patient-level clustering (as some patients experienced multiple hospitalizations during the study period). We adjusted for potential confounders selected a priori on the basis of prior literature: age, sex, race, BMI, van Walraven Elixhauser comorbidity scores, admission severity of illness (APACHE II), insurance type, hospital admission source (ED, ICU, or direct admission), primary malignancy, type of HSCT (autologous, related allogeneic, unrelated allogeneic), conditioning regimen (myeloablative

vs nonmyeloablative),²³ relapse status, mucositis, and engraftment status⁶ (pre- or periengraftment, early engraftment [within 100 days of engraftment], and late engraftment [after 100 days of transplant]).

Within these models, age, BMI, van Walraven comorbidity measure,²⁴ APACHE II score, and days since transplant were modeled continuously; the remaining variables were modeled categorically. Neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count $\geq 500/\text{mm}^3$.²⁵ Pre- and periengraftment status was defined as between day -10 (D-10) and day 14 (D+14) after neutrophil engraftment.⁶ Early engraftment was defined as between day 15 (D+15) and day 100 (D+100), and late engraftment was defined as after D+100.⁶

We evaluated hospital LOS (with time origin at the moment of first vital sign recording in the hospital) using an extended multivariable Fine and Gray model to account for the fact that hospital death acts as a competing risk for live hospital discharge. In the Fine and Gray model, the subhazard ratio (SHR) relates the relative probability of experiencing discharge alive at any point in time (ie, SHR < 1 indicates lower adjusted probability of discharge and suggests increased LOS).²⁶ We produced cumulative incidence curves representing the fraction of patients discharged alive or dead from the hospital, stratified by BSI and receipt of timely appropriate antimicrobials.

Within the subgroup of patients with BSI, we repeated each analysis to estimate the adjusted association between delayed appropriate antimicrobial therapy and each outcome. Given a paucity of outcomes for this analysis, we a priori excluded from the model demographic covariates not expected to be significant confounders related to recognition of BSI (eg, sex, race). In these models, we also adjusted for ICU exposure before development of BSI under the hypothesis that prior critical illness may confound the relationship between antibiotic timing and adverse outcomes.

To evaluate the associations of interest in hospitalizations occurring specifically for complications, we performed a sensitivity analysis for each binary outcome excluding hospital admissions in which transplantation occurred. Because we hypothesized a priori that age and comorbidity burden could influence both conditioning choice and risk for the study's outcomes, and that HSCT type may be influenced by a patient's underlying disease, we also performed a sensitivity analysis including interaction terms between age and conditioning, comorbidity score and conditioning, and primary disease and type of HSCT. In addition, we conducted a sensitivity analysis in which the exposure was the continuous time, in hours, between blood culture results and administration of appropriate antimicrobials. Finally, we performed subgroup analyses to investigate the associations between BSI and hospital mortality across the following groups: initial APACHE II score tertiles, time posttransplantation (0-30, 30-60, 60+ days), and allogeneic vs autologous transplants.

All tests of significance used a two-sided *P* value of less than .05. Data were cleaned in Stata 15.1 (StataCorp), and analyzed in R, version 3.4.3 (R Project for Statistical Computing), using the following packages: tidyverse,²⁷ tableone,²⁸ lme4,²⁹ dotwhisker,³⁰ and cmprsk.³¹

Results

Hospitalization Characteristics

our study cohort included 2,751 hospital admissions from 1,086 unique patients. Within these admissions,

395 of 2,751 (14.4%) involved at least one BSI; overall, 324 of 1,086 unique patients (29.8%) experienced a BSI. Patient admissions with and without BSI were similar in terms of demographics, malignancy and HSCT categories, and conditioning regimens (Table 1).

TABLE 1] Characteristics of Hematopoietic Stem Cell Transplantation Patients Hospitalized With and Without Bloodstream Infections

Patient Characteristic	BSI Hospitalization	Non-BSI Hospitalization	<i>P</i> Value
	(n = 395)	(n = 2,356)	
Age, median (IQR), y	58 (49-64)	57 (47-64)	.249
Female, No. (%)	170 (43.0)	981 (41.6)	.641
Race, No. (%)			.707
White	342 (86.6)	2,051 (87.1)	
Black	38 (9.6)	202 (8.6)	
Other	15 (3.8)	103 (4.4)	
Insurance, No. (%)			.454
Private	183 (46.3)	1,008 (42.8)	
Medicare	85 (21.5)	495 (21.0)	
Medicaid	46 (11.6)	301 (12.8)	
Other/unknown	81 (20.5)	552 (23.4)	
Transplant category, (%)			.085
Autologous	123 (31.1)	855 (36.3)	
Allogeneic, related donor	207 (52.4)	1,182 (50.2)	
Allogeneic, other	65 (16.5)	319 (13.5)	
Indication for HSCT, No. (%)			.299
Acute myelogenous leukemia	129 (32.7)	689 (29.2)	
Acute lymphocytic leukemia	33 (8.4)	196 (8.3)	
Multiple myeloma	80 (20.3)	541 (23.0)	
Lymphoma	62 (15.7)	446 (18.9)	
Myelodysplastic syndrome	54 (13.7)	309 (13.1)	
Other	37 (9.4)	175 (7.4)	
HSCT conditioning, No. (%)			.973
Myeloablative	347 (87.8)	2,068 (87.8)	
Nonmyeloablative	40 (10.1)	236 (10.0)	
Unknown	8 (2.0)	52 (2.2)	
Days since HSCT on hospital admission, median (IQR)	0 (0-129)	43 (0-183)	< .001
Engraftment status, No. (%)			< .001
Pre- or periengraftment	245 (62.0)	1,144 (48.6)	
Early engraftment	53 (13.4)	447 (19.0)	
Late engraftment	97 (24.6)	765 (32.5)	
Neutropenia during encounter, No. (%)	336 (85.1)	1,311 (55.7)	< .001
Mucositis, No. (%)	113 (28.6)	426 (18.1)	< .001
Source of hospital admission, No. (%)			< .001
ED	157 (39.7)	690 (29.3)	
Direct ward admission	228 (57.7)	1,618 (68.7)	
Direct ICU admission	10 (2.5)	48 (2.0)	
Arrhythmia, No. (%)	135 (34.2)	668 (28.4)	.022
Congestive heart failure, No. (%)	371 (15.8)	68 (17.2)	.461
Valvular disease, No. (%)	20 (5.1)	117 (5.0)	1
Pulmonary circulation disorder, No. (%)	9 (2.3)	55 (2.3)	1
Peripheral vascular disorder, No. (%)	10 (2.5)	97 (4.1)	.171
Hypertension, uncomplicated, No. (%)	233 (59.0)	1,318 (55.9)	.283

(Continued)

TABLE 1] (Continued)

Patient Characteristic	BSI Hospitalization	Non-BSI Hospitalization	<i>P</i> Value
	(n = 395)	(n = 2,356)	
Hypertension, complicated, No. (%)	72 (18.2)	486 (20.6)	.303
Paralysis, No. (%)	22 (5.6)	85 (3.6)	.084
Other neurologic disorder, No. (%)	50 (12.7)	247 (10.5)	.23
Chronic pulmonary disease, No. (%)	79 (20.0)	511 (21.7)	.49
Diabetes, uncomplicated, No. (%)	94 (23.8)	486 (20.6)	.173
Diabetes, complicated, No. (%)	56 (14.2)	275 (11.7)	.183
Hypothyroidism, No. (%)	46 (11.6)	290 (12.3)	.772
Renal failure, No. (%)	92 (23.3)	574 (24.4)	.691
Liver disease, No. (%)	62 (15.7)	322 (13.7)	.318
Collagen vascular disease, No. (%)	25 (6.3)	93 (3.9)	.043
Coagulopathy, No. (%)	231 (58.5)	1,278 (54.2)	.131
Obesity, No. (%)	29 (7.3)	209 (8.9)	.366
Weight loss, No. (%)	202 (51.1)	1,098 (46.6)	.106
Fluid and electrolyte disorder, No. (%)	301 (76.2)	1,791 (76.0)	.988
Blood loss anemia, No. (%)	4 (1.0)	19 (0.8)	.906
Deficiency anemia, No. (%)	271 (68.6)	1,604 (68.1)	.881
Alcohol abuse, No. (%)	4 (1.0)	9 (0.4)	.195
Drug abuse, No. (%)	24 (6.1)	155 (6.6)	.791
Psychoses, No. (%)	45 (11.4)	299 (12.7)	.522
Depression, No. (%)	139 (35.2)	906 (38.5)	.237
BMI, median (IQR)	27.7 (24.1-32.6)	27.0 (23.4-31.2)	.004
Initial APACHE score, median (IQR)	6 (4-8)	5 (4-7)	.011

APACHE = Acute Physiology and Chronic Health Evaluation; BSI = bloodstream infection; HSCT = hematopoietic stem cell transplantation; IQR = interquartile range.

However, patients developing BSI were more likely to be in the pre- or periengraftment transplant phase (62% vs 49% in early or late engraftment) and less likely to be in the late engraftment phase (25% vs 33%; *P* < .001 for both comparisons). On hospitalization, patients who developed BSI had higher initial APACHE II scores (6 [IQR, 4-8] vs 5 [4-7]; *P* = .011), were more frequently ED admissions (40% vs 29%; *P* < .001), and were more likely to have complications such as mucositis (29% vs 18%; *P* < .001). Prior isolation of an MDR organism was rare overall but was more common among patients developing BSI (1% vs < 1%; *P* = .007).

Among the 395 hospitalizations with bloodstream infections, 44 (11.1%) involved potential delays in appropriate antibiotic therapy. There were differences between patients with potential delays in appropriate antibiotic therapy and those receiving timely appropriate antimicrobials (Table 2). Specifically, patients with BSI

with potentially delayed appropriate antibiotics were more likely to have received an allogeneic HSCT (89% vs 66%; *P* = .008), been transplanted for acute leukemias (acute myelogenous leukemia, 43% vs 31%; acute lymphocytic leukemia, 18% vs 7%; *P* = .022), have been admitted through the ED or as an outside ICU transfer (59% vs 40%; *P* = .002), and were less likely to be an index HSCT hospitalization (8% vs 16%; *P* = .01).

Overall, the most common microbial species identified among patients with BSI were polymicrobial infections: *Enterococcus* species, *Staphylococcus* species, and gram-negative rods including *Escherichia coli*, *Klebsiella*, and *Pseudomonas* (e-Tables 1,2). One *Pseudomonas* isolate met DTR criteria; this isolate was treated with early appropriate antibiotics. Notably, *Enterococcus* (16 of 48 [33%]), including vancomycin-resistant *E. faecium* (VRE) (11 of 30 [36%]); *Candida* (five of 12, 42%); *Pseudomonas* (four of 27, 15%); and *Stenotrophomonas* (two of six, 33%) were among the pathogens most

TABLE 2] Characteristics of Hematopoietic Stem Cell Transplantation Patients Hospitalized With Bloodstream Infections With and Without Potential Delays in Appropriate Antibiotics

Patient Characteristic	Potentially Delayed Antibiotics	No Evidence of Appropriate Antibiotic Delays	<i>P</i> Value
	(n = 44)	(n = 351)	
Age, median (IQR), y	56 (50-62)	59 (49-64)	.361
Female, No. (%)	21 (47.7)	149 (42.5)	.614
Race, No. (%)			.040
White	33 (75.0)	309 (88.0)	
Black	7 (15.9)	31 (8.8)	
Other	4 (9.1)	11 (3.1)	
Transplant category, (%)			.085
Autologous	5 (11.4)	118 (33.6)	
Allogeneic, related donor	28 (63.6)	179 (51.0)	
Allogeneic, other	11 (25.0)	54 (15.4)	
Indication for HSCT, No. (%)			.022
Acute myelogenous leukemia	19 (43.2)	110 (31.3)	
Acute lymphocytic leukemia	8 (18.2)	25 (7.1)	
Multiple myeloma	3 (6.8)	77 (21.9)	
Lymphoma	4 (9.1)	58 (16.5)	
Myelodysplastic syndrome	6 (13.6)	48 (13.7)	
Other	4 (9.1)	33 (9.4)	
HSCT conditioning, No. (%)			.950
Myeloablative	38 (86.4)	309 (88.0)	
Nonmyeloablative	5 (11.4)	35 (10.0)	
Unknown	1 (2.3)	7 (2.0)	
Days since HSCT on hospital admission, median (IQR)	0 (0-117)	63 (0.00-218)	.009
Engraftment status, No. (%)			.097
Pre- or periengraftment	21 (47.7)	224 (63.8)	
Early engraftment	7 (15.9)	46 (13.1)	
Late engraftment	16 (36.4)	97 (24.6)	
Neutropenia during encounter, No. (%)	39 (88.6)	297 (84.6)	.481
Mucositis, No. (%)	12 (27.2)	101 (28.8)	.917
Source of hospital admission, No. (%)			.002
ED	22 (50.0)	135 (38.5)	
Direct ward admission	18 (40.9)	210 (59.8)	
Direct ICU admission	4 (9.1)	6 (1.7)	
Initial APACHE score, median (IQR)	6 (4-9)	6 (4-8)	.128
Received vasopressors within 24 h of positive blood culture, No. (%)	5 (11.4)	31 (8.8)	< .001
Received vasopressors > 24 h after positive blood culture, No. (%)	26 (59.1)	204 (58.1)	.87

See Table 1 legend for expansion of abbreviations.

commonly found in hospitalizations with potentially delayed appropriate antibiotic therapy.

Outcomes

Of 1,086 unique HSCT patients, 181 (17% of patients, 7.2% of hospitalizations) died in hospital during the

study period. Patients who ever experienced a BSI had significantly higher mortality than those who never experienced a BSI (24% vs 10%; *P* < .001). The incidence of mortality was also higher among patients hospitalized with a BSI than in those without BSI (23% vs 4.5%; *P* < .001) (Table 3). Similarly, unadjusted

TABLE 3] Outcomes Among Patients Hospitalized With and Without Bloodstream Infection

Outcome	BSI Hospitalization	Non-BSI Hospitalization	P Value
	(n = 395)	(n = 2,356)	
Hospital death, No. (%)	91 (23.0)	107 (4.5)	< .001
Discharge location, No. (%)			< .001
Home	260 (65.8)	2,084 (88.5)	
Skilled nursing facility or rehabilitation	34 (8.6)	122 (5.2)	
Hospice	7 (1.8)	30 (1.3)	
Unknown	3 (0.8)	13 (0.6)	
Hospital LOS, median (IQR), d	22.9 (16.8-35.9)	12.4 (4.4-21.0)	< .001

LOS = length of stay. See Table 1 legend for expansion of other abbreviations.

hospital length of stay was also significantly higher in admissions with BSI, with a median of 22.9 days compared with 12.4 days for those with no BSI ($P < .001$).

After adjustment for important confounders, BSI was independently associated with increased odds for mortality (OR, 8.14; 95% CI, 5.06-13.1; $P < .001$) (Fig 1A). Among patients surviving hospitalization, BSI was also an independent predictor of discharge to an SNF/PAC or hospice rather than discharge to home (OR, 3.01; 95% CI, 1.72-5.27; $P < .001$). Finally, patients with BSI had a lower adjusted probability of live hospital discharge at any point in time compared with those with no BSI (SHR, 0.43; 95% CI, 0.37-0.48; $P < .001$), indicating that—even after accounting for the competing risk of death—patients with BSI had longer adjusted LOS than patients without BSI (Fig 1B).

Among hospitalizations with BSI, the median time to appropriate antibiotic administration was significantly lower among survivors than among nonsurvivors (0 h [IQR, 0-13.4 h] vs 8.1 h [IQR, 0-23.5 h]; $P < .001$). Raw mortality was higher for admissions with potentially delayed appropriate antibiotics than for those with appropriate antibiotics (48% vs 20%; $P < .001$) (Table 4). Similarly, BSI hospitalizations with potential delay in appropriate antibiotics were longer than those without delay (median LOS, 33 vs 22 days; $P = .015$).

In mixed-effects multivariable analysis, potential delay in antibiotics was an independent predictor of adjusted mortality (OR, 13.8; 95% CI, 5.27-35.9; $P < .001$) (Fig 1C) and longer adjusted length of stay (SHR, 0.53; 95% CI, 0.34-0.81; $P < .001$) (Fig 1D). On discharge from hospital, potential delay in antibiotics was also an independent predictor of discharge to SNF/PAC or hospice rather than home (OR, 5.22; 95% CI, 2.22-12.27; $P < .001$).

Sensitivity Analysis

The sensitivity analysis excluding hospitalizations in which HSCT was performed (leaving only post-HSCT hospitalizations) involved 1,641 hospitalizations, 171 with BSI. Of these, 27 involved potential delay of appropriate antibiotics. In this analysis, both unadjusted mortality (40% vs 6.2%; $P < .001$) and adjusted mortality (OR, 10.4; 95% CI, 6.0-18.0) were higher among patients with BSI. Similarly, unadjusted mortality (63% vs 36%; $P < .001$) and adjusted mortality (OR, 16.7; 95% CI, 5.1-54.3; $P < .01$) were higher among patients with BSI with potential delays in appropriate antibiotics.

We also conducted sensitivity analysis including interaction terms between age and conditioning, van Walraven comorbidity score and conditioning, as well as primary disease and HSCT type. These analyses did not substantially alter our findings of the relationship between BSI and hospital mortality (OR, 7.91; 95% CI, 5.2-11.9; P for interaction, 0.09-0.99) or the relationship between potentially delayed antibiotics and mortality (OR, 12.1; 95% CI, 5.0-29.1; P for interaction, 0.15-0.99).

Finally, a multivariable logistic regression model including time from blood culture results to appropriate antibiotic administration showed an increase in adjusted mortality for each hour of delay (OR, 1.03; 95% CI, 1.02-1.05; $P < .001$).

Subgroup Analysis

Analysis of BSI by subgroup of HSCT category yielded similar results to the overall analysis, with BSI associated with increased adjusted odds for mortality in both groups (autologous: OR, 9.08; 95% CI, 4.60-17.9; allogeneic: OR, 8.09; 95% CI, 4.03-16.2). Similarly, subgroup analysis across various time intervals after HSCT found increased adjusted odds

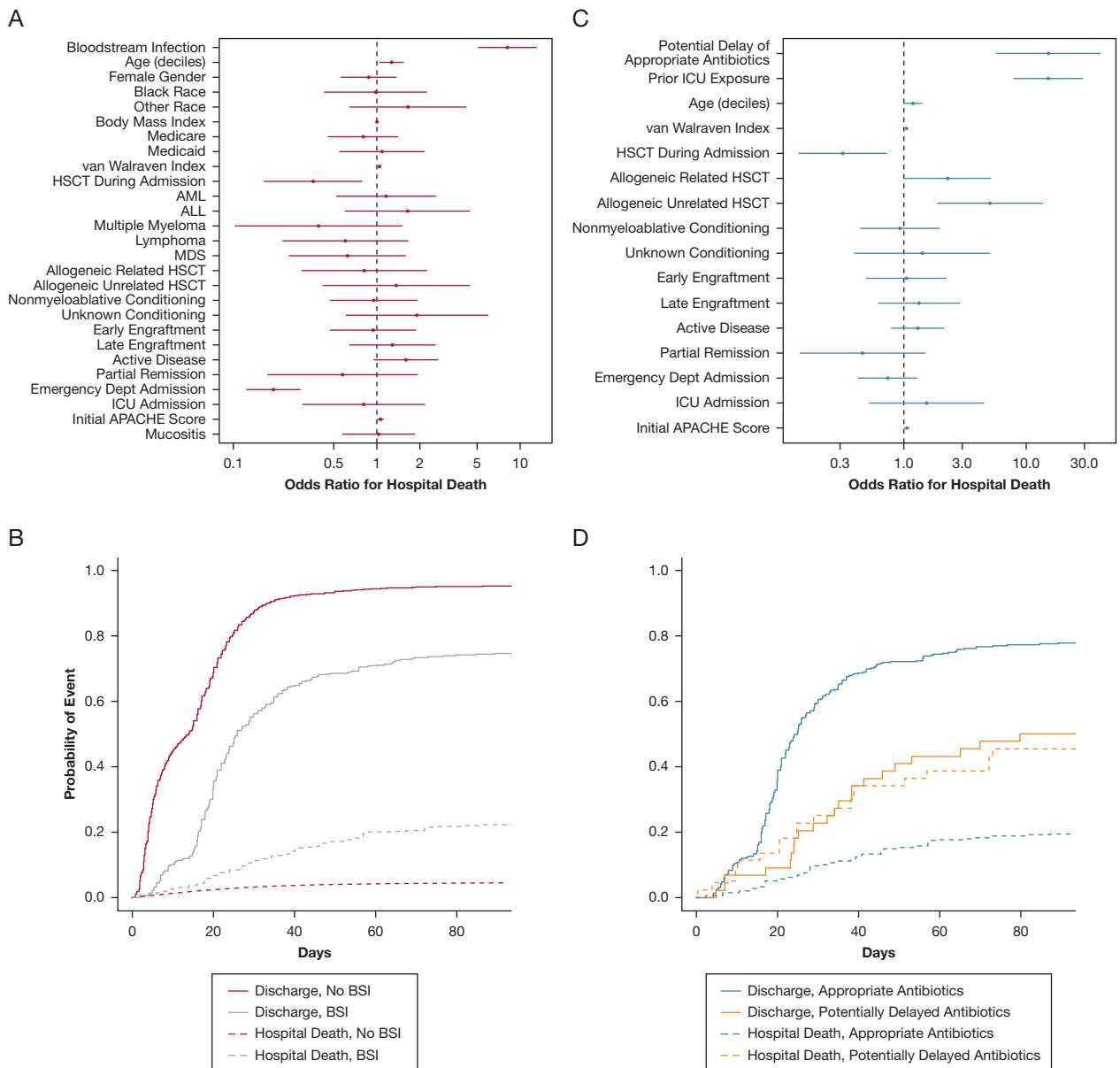


Figure 1 – Results of adjusted analyses. A and B, Bloodstream infection independently predicts hospital mortality (A) and hospital length of stay (LOS) (B) among HSCT recipients. C and D, Among HSCT recipients with bloodstream infection, potential delays in appropriate antibiotics were independently associated with hospital mortality (C) and hospital LOS (D). ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; APACHE = Acute Physiology and Chronic Health Evaluation; BSI = bloodstream infection; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome.

for mortality with BSI (post-HSCT day 0-30: OR, 11.3; 95% CI, 1.89-67.6; day 31-100: OR, 10.4; 95% CI, 2.81-38.5; day > 100: OR, 10.2; 95% CI, 5.53-19.0). Finally, analysis of BSI by tertile of APACHE II scores was also similar to the overall analysis, as BSI was associated with increased adjusted odds for mortality in all groups (lowest APACHE: OR, 7.54; 95% CI, 3.95-14.7; moderate

APACHE: OR, 9.37; 95% CI, 4.44-20.0; highest APACHE: OR, 4.21; 95% CI, 2.48-7.12).

Discussion

Here, we report an analysis of almost 400 bloodstream infections in more than 2,500 hospitalizations among recipients of hematopoietic stem cell transplants,

TABLE 4] Outcomes Among Patients Hospitalized With Bloodstream Infection With and Without Potential Delays in Antibiotics

Outcome	Potentially Delayed Antibiotics (n = 44)	No Evidence of Appropriate Antibiotic Delays (n = 351)	<i>P</i> Value
Hospital death, No. (%)	21 (47.7)	70 (19.9)	< .001
Discharge location, No. (%)			< .001
Home	14 (31.8)	246 (70.1)	
Skilled nursing facility or rehabilitation	5 (11.4)	29 (8.3)	
Hospice	3 (8.8)	4 (1.1)	
Unknown	1 (2.3)	2 (0.6)	
Hospital LOS, median (IQR), d	33.0 (20.4-49.5)	21.9 (16.6-34.9)	.015

See Table 1 and 3 legends for expansion of abbreviations.

representing a range of underlying malignancies. To our knowledge, this study is the largest single-center cohort of hospitalized HSCT patients evaluated for BSI.

Our most notable finding is that bacteremic and fungemic patients with late administration of drugs active against the infective agent had worse outcomes—increased hospital death and discharges to hospice, longer hospital LOS, and increased requirement for post-acute care—than infected patients receiving appropriate antibiotics earlier. These results persisted after adjustment for a number of important confounders, including demographics, comorbidities, and transplantation characteristics. Moreover, the magnitude of this effect was large, regardless of whether these delays were measured as continuous time or at a 24-h breakpoint. This finding is consistent with outcomes from patients with sepsis and septic shock,³² and it highlights the need to recognize and respond quickly to clinical signs of infection in this high-risk group of patients.

This finding may have several important implications for the care of hospitalized HSCT recipients. One possibility is that, because late clinical recognition of an infection leads to delayed delivery of empiric therapy, hospitalized HSCT recipients would benefit from increased infection surveillance. Although routine invasive surveillance (ie, blood cultures) is not useful among HSCT recipients,³³⁻³⁵ risk-prediction early warning systems for BSI may be effective at identifying high-risk patients requiring additional diagnostics or treatments.^{16,36} The pre- and periengraftment periods, which were associated with BSI in our study and others,⁶ could be a particularly appropriate substrate for the development and testing of such early warning systems.

Importantly, 42 of the 44 patients that we categorized as receiving delayed appropriate antibiotics did receive other empiric antibiotics on day of cultures, suggesting that infection was clinically suspected. This emphasizes the need for development and implementation of rapid diagnostic tests³⁷ to quickly identify the presence of specific pathogens or pathogen resistance mechanisms, the need to consider additional or alternative empiric therapies for HSCT recipients with BSI, or both. Current recommendations²¹ for managing fever and neutropenia involve administration of antimicrobial medications active against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which most commonly cause gram-negative bacteraemia in these patients.³⁸ However, epidemiologic changes within infected HSCT recipients, including the increasing prevalence of MDR infections (eg, *Pseudomonas*) and VRE, may require changes to currently recommended antimicrobial regimens.³⁹ To this end, detailed knowledge of current hospital antibiograms is imperative for delivery of appropriate empiric therapies to potentially infected patients, especially in light of antibiotic overuse risks and the need for responsible antimicrobial stewardship efforts.⁴⁰ Future work could test whether empiric use of antimicrobials specifically directed at certain pathogens (eg, VRE, *Candida* species), or use of rapid diagnostic tests to identify these infections earlier, can improve patient outcomes. Of course, the importance of antibiotic stewardship must be weighed against any potential benefits of modifying the current standard of practice. Finally, it is important to note that although standardized inpatient protocols for empiric antimicrobial therapy existed at our center, opportunities exist to expand these protocols to environments such as the ED.

Our work validates prior and smaller epidemiologic studies of BSI among HSCT recipients, in particular the finding that *Staphylococcus aureus*, gram-negative bacilli (including *Pseudomonas*), and *Enterococcus* species^{3,39,41} were common causes of BSI. More recently, a study of neutropenic oncology patients—which included 24% of HSCT recipients—found a similar association between inappropriate antimicrobial therapy for gram-negative BSI and mortality,⁴² and a study of HSCT recipients with gram-negative bacteremia identified higher rates of inappropriate antibiotic therapy and mortality in association with resistant organisms.⁴³ Our rate of DTR among gram-negative BSIs (approximately 1%) was in line with rates reported among non-HSCT recipients.²⁰ In addition, although we identified solitary CoNS bacteremia less commonly in our study than has been described in other reports (despite including both single- and dual-positive culture results),³ we note that almost 15% of the polymicrobial BSIs identified involved CoNS, and that our analysis was restricted to index BSI events. No patients with CoNS experienced delays in appropriate antibiotics.

Our study has several important strengths. First, by conducting this work at a large academic hospital with a robust HSCT program, we were able to include data from a large number of recent hospitalizations over a relatively short time, which should increase generalizability by reflecting current practices related to transplantation, infectious prophylaxis, and infection management. Second, the availability of granular hospitalization-level data allowed us to adjust for severity of illness, comorbidities, and transplantation factors, and to evaluate individual cultures and orders for antimicrobial therapy. Third, we used rigorous modeling approaches to adjust for patient-level confounding, competing-risk analysis to account for length of stay variation in patients who died vs those who did not,⁴⁴ and multiple prespecified sensitivity and subgroup analyses, which should improve the internal validity of our work.

Limitations of our study include its single-center design, which may lend itself to unclear generalizability regarding case mix and certain practice patterns. For example, other institutions may have more restrictive antimicrobial stewardship programs than ours, which could influence empiric antimicrobial choices. Although stem cell transplantation is typically performed at tertiary care hospitals, HSCT recipients might receive

emergency or acute care at any type of hospital, thus increasing the importance of both the index of suspicion for BSI and the prompt administration of broad-spectrum antibiotics selected on the basis of local antibiograms. Relatedly, we identified BSI in only about 15% of hospitalizations, which is less than in some prior studies.¹⁻³ This difference may be explained by temporal trends, changing case mix, and by our inclusion of only index BSIs, but could further limit the generalizability of our findings. Because we used retrospective electronic health record and administrative data for this study, we were unable to obtain reliable information regarding comorbidity severity, complications, the presence or removal of central venous catheters, prior adherence to prophylactic antibiotics, and prophylaxis against graft-vs-host disease; these factors may be important confounders or mediators of the relationship between bloodstream infections, antimicrobial administration, and patient outcomes. In particular, effective source control influences the outcomes of bloodstream infection,^{45,46} and it is possible that—if delayed initiation of appropriate antibiotics is associated with greater clinical uncertainty about the diagnosis or management of BSI—these same admissions could have been at risk for delays in effective source control as well. Because BSIs were identified after the index time at the beginning of hospitalization, these results may be vulnerable to immortal time bias. Consideration of time-varying covariates might have decreased the risk of immortal time bias, but at the expense of losing estimations of the cumulative incidence function or the effects of covariates on this function.⁴⁷ Moreover, rather than inflating our results, immortal time bias would actually shift our findings toward the null if present. Finally, we did not evaluate long-term survival beyond hospital discharge, nor did we evaluate functional or other patient-centered outcomes.

Conclusion

In this analysis of more than 2,500 hospitalizations among recipients of hematopoietic stem cell transplants, we found that bloodstream infections were common and independently associated with large increases in morbidity and mortality, as were delays in administration of appropriate antimicrobial agents. These findings may have important implications for the care of hospitalized HSCT recipients in terms of empiric antimicrobial choices, the need for rapid diagnostic testing, and the potential for targeted surveillance.

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References

- 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(1):11-17.
- 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(7):947-953.
- Frère P, Hermanne J-P, Debouge M-H, de Mol P, Fillet G, Beguin Y. Bacteremia after hematopoietic stem cell transplantation: incidence and predictive value of surveillance cultures. *Bone Marrow Transplant*. 2004;33(7):745-749.
- 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(1):47-53.
- Poutsia DD, Price LL, Uczian 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(1):63-70.
- Ustun C, Young J-AH, Papanicolaou GA, et al. Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2019;54(8):1254-1265.
- 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(6):824-830.
- Gjærde LI, Moser C, Sengeløv H. Epidemiology of bloodstream infections after myeloablative and non-myeloablative allogeneic hematopoietic stem cell transplantation: a single-center cohort study. *Transpl Infect Dis*. 2017;19(5):e12730.
- Kikuchi M, Akahoshi Y, Nakano H, et al. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2015;17(1):56-65.
- Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplants. *Transpl Infect Dis*. 2014;16(1):106-114.
- Ferreira AM, Moreira F, Guimaraes T, et al. Epidemiology, risk factors and outcomes of multi-drug-resistant bloodstream infections in haematopoietic stem cell transplant recipients: importance of previous gut colonization. *J Hosp Infect*. 2018;100(1):83-91.
- Wang C-H, Chang F-Y, Chao T-Y, et al. Characteristics comparisons of bacteremia in allogeneic and autologous hematopoietic stem cell-transplant recipients with levofloxacin prophylaxis and influence on resistant bacteria emergence. *J Microbiol Immunol Infect*. 2018;51(1):123-131.
- Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in hematopoietic cell transplant recipients: results from the organ transplant infection project, a multicenter, prospective, cohort study. *Open Forum Infect Dis*. 2017;4(2):oxf050.
- 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(8):1091-1106.
- Montesinos P, Rodríguez-Veiga R, Boluda B, et al. Incidence and risk factors of post-engraftment invasive fungal disease in adult allogeneic hematopoietic stem cell transplant recipients receiving oral azoles prophylaxis. *Bone Marrow Transplant*. 2015;50(11):1465-1472.
- Lyons PG, Klaus J, McEvoy CA, Westervelt P, Gage BF, Kollef MH. Factors associated with clinical deterioration among patients hospitalized on the wards at a tertiary cancer hospital. *J Oncol Pract*. 2019;15(8):e652-e665.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
- Misch EA, Andes DR. Bacterial infections in the stem cell transplant recipient and hematologic malignancy patient. *Infect Dis Clin North Am*. 2019;33(2):399-445.
- Bock AM, Cao Q, Ferrieri P, Young J-AH, Weisdorf DJ. Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. *Biol Blood Marrow Transplant*. 2013;19(1):102-108.
- Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors and outcome of resistance to all first-line agents. *Clin Infect Dis*. 2018;67(12):1803-1814.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56-e93.
- National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections (version 1.2020). http://www.nccn.org/professionals/physician_gls/default.aspx. Accessed August 2, 2020.
- Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood*. 2014;124(3):344-353.
- van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009;47(6):626-633.
- Hong KT, Kang HJ, Kim NH, et al. Peri-engraftment syndrome in allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2013;48(4):523-528.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
- Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4(43):1686.
- Yoshida K, Bartel A, Chipman JJ, et al. An R package to create “Table 1,” description of baseline characteristics with or without propensity score weighting. 2019. <https://github.com/kaz-yos/tableone>. Accessed July 14, 2020.
- Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1):1-48.
- Solt F, Hu Y, Keyes O, Bolker B, Müller S, Leeper T. Dotwhisker: dot-and-whisker plots of regression results. 2018. <https://CRAN.R-project.org/>

- package=dotwhisker. Accessed July 14, 2020.
31. Gray B. Cmprsk: subdistribution analysis of competing risks. 2019. <https://CRAN.R-project.org/package=cmprsk>. Accessed July 14, 2020.
 32. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med.* 2017;196(7):856-863.
 33. Ghazal SS, Stevens MP, Bearman GM, Edmond MB. Utility of surveillance blood cultures in patients undergoing hematopoietic stem cell transplantation. *Antimicrob Resist Infect Control.* 2014;3:20.
 34. Colombier M-A, 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(4):504-511.
 35. Nesher L, Chemaly RF, Shah DP, et al. Utility of routine surveillance blood cultures in asymptomatic allogeneic hematopoietic stem cell transplant recipients with indwelling central venous catheters at a comprehensive cancer center. *Am J Infect Control.* 2014;42(10):1084-1088.
 36. Giannini HM, Ginestra JC, Chivers C, et al. A machine learning algorithm to predict severe sepsis and septic shock: development, implementation, and impact on clinical practice. *Crit Care Med.* 2019;47(11):1485-1492.
 37. Guillamet MCV, Burnham JP, Kollef MH. Novel approaches to hasten detection of pathogens and antimicrobial resistance in the intensive care unit. *Semin Respir Crit Care Med.* 2019;40(4):454-464.
 38. Trecarichi EM, Pagano L, Candoni A, et al. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. *Clin Microbiol Infect.* 2015;21(4):337-343.
 39. Satlin MJ, Walsh TJ. Multidrug-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus*: three major threats to hematopoietic stem cell transplant recipients. *Transpl Infect Dis.* 2017;19(6). <https://doi.org/10.1111/tid.12762>.
 40. Monroe S, Polk R. Antimicrobial use and bacterial resistance. *Curr Opin Microbiol.* 2000;3(5):496-501.
 41. Johnson LE, D'Agata EMC, Paterson DL, et al. *Pseudomonas aeruginosa* bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. *Transpl Infect Dis.* 2009;11(3):227-234.
 42. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, et al. Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance. *Clin Infect Dis.* 2020;70(6):1068-1074.
 43. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis.* 2017;65:1819-1828.
 44. Harhay MO, Ratcliffe SJ, Small DS, Suttner LH, Crowther MJ, Halpern SD. Measuring and analyzing length of stay in critical care trials. *Med Care.* 2019;57(9):e53-e59.
 45. Timsit JF, Ruppé E, Barbier F, et al. Bloodstream infections in critically ill patients: an expert statement. *Intensive Care Med.* 2020;46(2):266-284.
 46. Martinez ML, Ferrer R, Torrents E, et al. Impact of source control in patients with severe sepsis and septic shock. *Crit Care Med.* 2017;45(1):11-19.
 47. Austin PC, Latouche A, Fine JP. A review of the use of time-varying covariates in the Fine-Gray subdistribution hazard competing risk regression model. *Stat Med.* 2020;39(2):103-113.