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MAJOR ARTICLE

The Relationship Between Antibiotic Agent and Mortality in Patients With Febrile Neutropenia due to Staphylococcal Bloodstream Infection: A Multicenter Cohort Study

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Background. Methicillin-susceptible *Staphylococcus aureus* (MSSA) is a common cause of bloodstream infection (BSI) in patients with febrile neutropenia, but treatment practices vary, and guidelines are not clear on the optimal regimen.

Methods. We conducted a multicenter retrospective cohort study of MSSA BSI in febrile neutropenia. We divided patients into 3 treatment groups: (1) broad-spectrum beta-lactams (ie, piperacillin-tazobactam, cefepime, meropenem); (2) narrow-spectrum beta-lactams (ie, cefazolin, oxacillin, nafcillin); and (3) combination beta-lactams (ie, both narrow- and broad-spectrum). We used multivariable logistic regression to compare 60-day mortality and bacteremia recurrence while adjusting for potential confounders.

Results. We identified 889 patients with MSSA BSI, 128 of whom had neutropenia at the time of the index culture: median age 56 (interquartile range, 43–65) years and 76 (59%) male. Of those, 56 (44%) received broad-spectrum beta-lactams, 30 (23%) received narrow-spectrum beta-lactams, and 42 (33%) received combination therapy. After adjusting for covariates, including disease severity, combination therapy was associated with a significantly higher odds for 60-day all-cause mortality compared with broad spectrum beta-lactams (adjusted odds ratio [aOR], 3.39; 95% confidence interval [CI], 1.29–8.89; $P = .013$) and compared with narrow spectrum beta-lactams, although the latter was not statistically significant (aOR, 3.30; 95% CI, .80–13.61; $P = .071$).

Conclusions. Use of combination beta-lactam therapy in patients with MSSA BSI and febrile neutropenia is associated with a higher mortality compared with treatment with broad-spectrum beta-lactam after adjusting for potential confounders. Patients in this study who transitioned to narrow-spectrum beta-lactam antibiotics did not have worse clinical outcomes compared with those who continued broad-spectrum beta-lactam therapy.

Keywords. beta-lactams; bloodstream infections; febrile neutropenia; *Staphylococcus aureus*.

Staphylococcus aureus bloodstream infection (BSI) is a serious bacterial infection with a high frequency of metastatic infection and a high risk of mortality [1]. The frequency of BSI in hospitalized patients with chemotherapy-induced neutropenia is estimated to be 10%–25% [2], with *S aureus* being one of the most commonly isolated organisms (up to 8.4% of cases in a recent study) [3]. Mortality associated with *S aureus* BSI is estimated to be 27% in neutropenic patients with hematologic malignancies and 46% in neutropenic patients with solid malignancies [4].

The optimal treatment regimen for *S aureus* BSI in patients with fever in the context of neutropenia remains unclear. Methicillin-susceptible *S aureus* (MSSA) and penicillin-susceptible *S aureus* (PSSA) are optimally treated with narrow-spectrum beta-lactam antibiotics. Several studies demonstrate the noninferiority or superiority of cefazolin to oxacillin or nafcillin in the treatment of MSSA, and these agents remain the first-line therapy recommended in clinical practice guidelines for MSSA BSI [5–11]. In contrast, the recommended therapy for undifferentiated febrile neutropenia includes empiric broad-spectrum antibiotics with activity against *Pseudomonas aeruginosa* and Gram-negative bacilli, which are frequent causes of infection in patients with febrile neutropenia [1, 12]. In addition, neutropenic patients are at a higher risk for developing more than 1 infection and may require broader spectrum therapy to treat other infections that are not microbiologically diagnosed, such as typhlitis [13]. These contrasting clinical concerns pose a conundrum to clinicians caring for patients with febrile neutropenia and confirmed MSSA or PSSA BSI because some clinicians may prefer continuing broad-spectrum

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beta-lactam agents such as piperacillin/tazobactam, cefepime, or meropenem rather than de-escalating to narrower spectrum agents, because the former have activity against both MSSA/PSSA and Gram-negative organisms including *P aeruginosa* [14]. In some settings, clinicians may treat patients with MSSA/PSSA and febrile neutropenia with a combination of narrow- and broad-spectrum beta-lactams (ie, dual beta-lactam therapy) so that they use first-line therapy for MSSA/PSSA BSI and first-line therapy for febrile neutropenia. Although guidelines on febrile neutropenia recommend narrowing antibiotics once bacterial susceptibilities result and fever has resolved, many physicians opt to continue broad-spectrum antibiotics with antipseudomonal activity until neutrophil count recovery even after an infection source is identified [12]. Therefore, there is considerable variability in antibiotic practice patterns for patients with MSSA or PSSA BSI and febrile neutropenia.

Despite the high frequency of *S aureus* BSI in patients presenting with febrile neutropenia, data comparing different beta-lactam antibiotic strategies are currently lacking. The primary objective of this study is to evaluate the effectiveness of narrow-spectrum, broad-spectrum, and combination beta-lactam therapy in patients with MSSA/PSSA BSI and febrile neutropenia. We hypothesized that patients treated with broad-spectrum beta-lactam (ie, cefepime, piperacillin-tazobactam, or meropenem) monotherapy would be more likely to experience treatment failure compared with those who are treated with narrow spectrum beta-lactam monotherapy (eg, oxacillin, nafcillin, cefazolin, or penicillin) or combination therapy.

METHODS

Study Design

We conducted a multicenter, retrospective, observational cohort study of patients with MSSA/PSSA BSI and febrile neutropenia treated at Brigham and Women's Hospital (BWH), Dana-Farber Cancer Institute (DFCI), and Massachusetts General Hospital (MGH), all in Boston, Massachusetts.

Patient Consent Statement

The design of the study was approved by the Mass General Brigham Investigational Review Board with a patient consent exemption (protocol number 2019P002660).

Study Population

We used the Massachusetts General Brigham Research Patient Data Registry and the WHONET microbiology laboratory database [15] to identify patients with MSSA- or PSSA-positive blood cultures. We searched for patients hospitalized on the primary oncology or pulmonary critical care services of these hospitals to maximize the likelihood of detecting cases that were also associated with febrile neutropenia. We included patients hospitalized between January 1, 2010 and April 1, 2021 at BWH or DFCI and between April 1, 2016 and April 1, 2021 at MGH. We included patients aged ≥18 years old and with febrile neutropenia (absolute neutrophil count [ANC] <500 cells/L and temperature >100.4°F) within 24 hours of the documented MSSA or PSSA index blood culture, with time zero being the culture collection date. Patients were excluded if they received antibiotics for less than 72 hours, if they received broad-spectrum antistaphylococcal antibiotics (eg, ceftriaxone, vancomycin, linezolid, or daptomycin monotherapy for ≥48 hours) for definitive treatment of MSSA or PSSA BSI, or if they had a documented microbiological polymicrobial bacterial infection at the time of the positive index culture.

Exposures

We evaluated antibiotic therapy at the time of the index blood culture until neutrophil recovery. We divided subjects into 3 mutually exclusive exposure groups based on their antibiotic therapy: (1) broad-spectrum beta-lactam monotherapy (ie, therapy that primarily targets febrile neutropenia); (2) narrow-spectrum beta-lactam monotherapy (ie, anti-*Staphylococcal* beta-lactams); and (3) combination therapy (Figure 1). We categorized subjects in the broad-spectrum beta-lactam monotherapy arm if they received piperacillin/tazobactam, cefepime, meropenem, or imipenem-cilastatin during the time of the positive index culture for at least 72 hours. We categorized subjects in the narrow-spectrum beta-lactam monotherapy arm if they received cefazolin, nafcillin, oxacillin, or penicillin from the time of the index culture for at least 72 hours. We categorized patients in the combination therapy arm if they received concomitant therapy with broad-spectrum and narrow-spectrum beta-lactams for at least 72 hours from the time of the index culture. The choice of therapy was made by either the treating physician and/or the Infectious Diseases consultant involved with the patient's care. We did not include any patient receiving ceftazidime monotherapy for MSSA or PSSA BSI, but we categorized patients who received ceftazidime and a narrow-spectrum beta-lactam into the combination therapy group.

Covariates

We included the following prespecified covariates: receipt of corticosteroids, presence of acute graft-versus-host disease (GVHD), Pitt bacteremia score [16], Charlson comorbidity index [17], and the Multinational Association for Supportive Care in Cancer (MASCC) risk-index score (Supplementary Material) [18]. Based on a univariable analysis, we also included age and obesity (body mass index ≥30 kg/m^2) as additional covariates.

Primary and Secondary Outcomes

Our primary outcome was a composite clinical failure defined as 60-day all-cause mortality and/or 60-day bacteremia recurrence

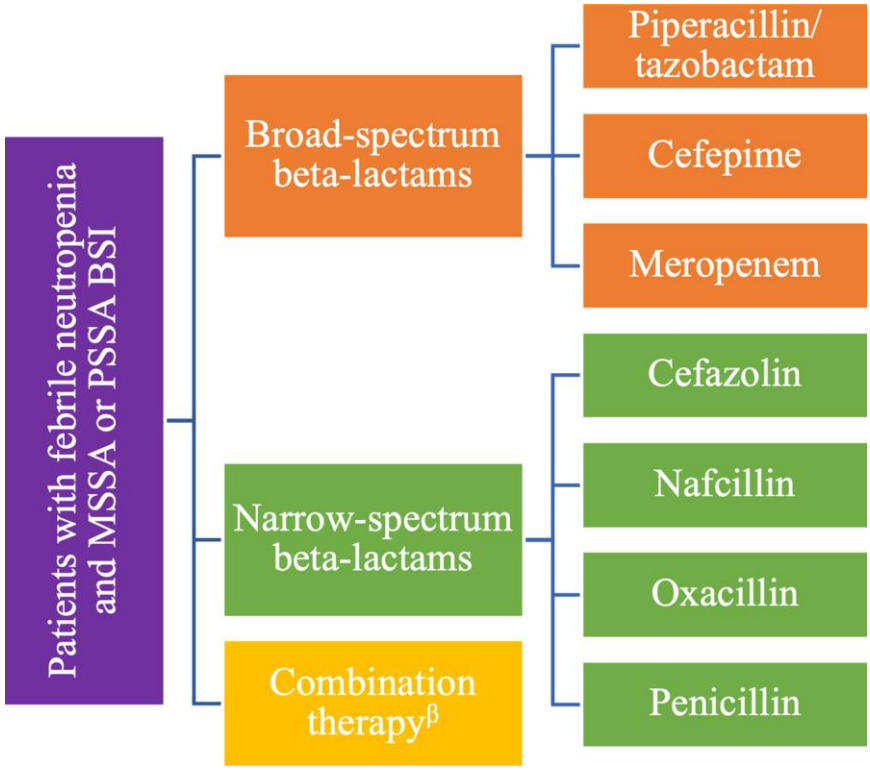

Figure 1. Categorization of treatment groups for patients *Staphylococcus aureus* bloodstream infection (BSI) and febrile neutropenia. No patient received ceftazidime monotherapy for treatment of *S aureus*. Combination antibiotics included the following: ceftazidime + nafcillin, cefepime + nafcillin, cefepime + oxacillin, ceftazidime + oxacillin, cefepime + cefazolin, ceftazidime + penicillin G, ceftazidime + cefazolin, cefepime + penicillin G, meropenem + cefazolin, piperacillin/tazobactam + nafcillin. MSSA, methicillin-susceptible *S aureus*; PSSA, penicillin-susceptible *S aureus*.

(analyzed as a binary outcome). Bacteremia recurrence was defined as any isolation of MSSA or PSSA in blood cultures after clearance within 60 days of the index blood culture. Secondary outcomes included the time to bacteremia clearance (defined as first negative blood culture collected after the index blood culture), time to mortality, 60-day all-cause mortality, 60-day bacteremia recurrence, inpatient mortality, 60-day hospital readmission, and hospital and intensive care unit (ICU) length of stay. Safety outcomes included the incidence of *Clostridioides difficile* infections (defined by a positive glutamate dehydrogenase/toxin and/or positive polymerase chain reaction), the incidence of hepatotoxicity (defined as an alanine aminotransferase or aspartate aminotransferase $\geq$3 times the upper limit of normal), the incidence of acute kidney injury (defined by the RIFLE criteria) [19], and the incidence of hypersensitivity reactions related to antibiotic therapy within 60 days of index culture. We reviewed the clinical documentation from treating physicians to determine the association of these safety events with antibiotics. We chose 60 days as the time point for outcome ascertainment consistent with prior studies evaluating clinical outcomes in *S aureus* bacteremia [20].

Statistical Analysis

We used χ^2 or Fisher's exact test for comparisons of categorical variables and Kruskal-Wallis test for continuous variables. We analyzed the incidence of the primary outcome using multivariable logistic regression with robust standard errors to account for clustering within treating physicians. We also performed sensitivity analyses: (1) we excluded subjects who changed therapy after 72 hours; (2) we excluded subjects who never achieved neutrophil recovery (ANC >500 cells/L for 72 hours); and (3) we excluded subjects who had a separate microbiologically confirmed bacterial infection within 14 days of the index culture. We evaluated the models' calibration using Hosmer-Lemeshow test and the models discrimination using receiver operating characteristic curve. We used STATA version 14.2 to carry out these analyses.

RESULTS

We identified 889 hospitalized oncology patients with MSSA or PSSA BSI, 136 of whom (15.3%) had febrile neutropenia and 128 (14.4%) met our inclusion criteria (Supplementary Figure 1). The median age of this cohort was 56 (interquartile

Table 1. Baseline Characteristics Among Patients Treated for *Staphylococcus aureus* Bloodstream Infection and Febrile Neutropenia

Characteristics	Broad-Spectrum Beta-Lactam ($n=56$)	Narrow-Spectrum Beta-Lactam ($n=30$)	Combination Therapy[a] ($n=42$)
Male, *n* (%)	33 (58.9)	18 (60)	25 (59.5)
Age, median (IQR)	57 (43–65)	53 (22–62)	58 (44–66)
BMI, *n* (%)			
<30 kg/m^2	47 (83.9)	22 (73.3)	31 (73.8)
≥30 kg/m^2	9 (16.1)	8 (26.7)	11 (26.2)
Race, *n* (%)			
White	41 (73.2)	20 (66.7)	37 (88.1)
Non-White	15 (26.8)	10 (33.3)	5 (11.9)
Smoking, *n* (%)	2 (3.6)	5 (16.7)	2 (4.8)
Alcohol use, *n* (%)	14 (25.0)	7 (23.3)	8 (19.0)
Charlson Comorbidity Index score, *n* (%)			
<3	24 (42.9)	9 (30)	13 (31)
≥3	32 (57.1)	21 (70)	29 (69.0)
Immunocompromising Condition, *n* (%)			
Chemotherapy	50 (96.1)	23 (76.7)	36 (85.7)
HSCT	16 (28.6)	8 (26.7)	14 (33.3)
Corticosteroid[b]	21 (37.5)	9 (30.0)	7 (16.7)
Source of Malignancy, *n* (%)			
Hematologic	44 (78.6)	24 (80)	35 (83.3)
Solid tumor	10 (17.9)	6 (20)	4 (9.5)
Both	2 (3.6)	0 (0)	3 (7.1)
Acute GVHD grade 2 or higher at the time of the index culture, *n* (%)*	1 (1.9)	7 (23.3)	1 (2.4)
Duration of Neutropenia After Index Culture, *n* (%)*			
<7 days	36 (64.3)	10 (33.3)	17 (40.5)
≥7 days	20 (35.7)	20 (66.7)	25 (59.5)
Central line not removed, *n* (%)	2 (3.6)	1 (3.33)	0 (0)
ID consult, *n* (%)	47 (83.9)	26 (86.7)	33 (78.6)
Time to ID consult from index culture, days, median (IQR; range)	1 (1–2; 0–7)	1 (1–2; 0–11)	1 (1–4; 0–12)
Empiric vancomycin use, *n* (%)	54 (96.4)	29 (96.7)	40 (95.2)
Multinational Association for Supportive Care in Cancer Risk-Index Score, *n* (%)			
<18	21 (37.5)	15 (50)	18 (42.9)
≥18	35 (62.5)	15 (50)	24 (57.1)

Abbreviations: BMI, body mass index; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ID, Infectious Diseases; IQR, interquartile range.

NOTE: See Figure 1 for categorization of narrow spectrum, broad spectrum, and combination beta-lactam therapy groups.

[a]Combination antibiotics included the following: ceftazidime + nafcillin ($n=16$), cefepime + nafcillin ($n=8$), cefepime + oxacillin ($n=4$), ceftazidime + oxacillin ($n=4$), cefepime + cefazolin ($n=3$), ceftazidime + penicillin G ($n=2$), ceftazidime + cefazolin ($n=2$), cefepime + penicillin G ($n=1$), meropenem + cefazolin ($n=1$), piperacillin/tazobactam + nafcillin ($n=1$).

[b]Prednisone ≥20 mg or equivalent for at least 21 days.

*$P < .05$.

range [IQR], 43–65) years and 59.4% were male (Table 1). A majority of patients had a hematologic malignancy (80.5%) and were receiving chemotherapy (85.2%) at the time of the hospitalization. The median duration of neutropenia after the index culture was 7 days (IQR, 3–14) and 82.8% received an infectious diseases service consultation. In this cohort, 56 (43.8%) received broad-spectrum beta-lactam monotherapy, 30 (23.4%) received narrow-spectrum beta-lactam monotherapy, and 42 (32.8%) received combination therapy for at least 72 hours. The majority of *Staphylococcal* BSIs were due to MSSA (75.8%) and were catheter-related (64.8%) (Supplementary Table 1). All but 3 patients had their central venous catheters removed until bacteremia clearance.

Our primary composite outcome occurred in 11 patients (19.6%) in the broad-spectrum beta-lactam monotherapy group, 8 patients (26.7%) in the narrow-spectrum beta-lactam monotherapy group, and 14 (33.3%) in the combination group ($P=.306$) (Table 2). Of these, 1 patient in the broad-spectrum beta-lactam had a retained central venous catheter. The 60-day all-cause mortality occurred 9 patients (16.1%) in the broad-spectrum beta-lactam monotherapy group, 8 patients (26.7%) in the narrow-spectrum beta-lactam monotherapy group, and 13 (30.9%) in the combination group ($P=.203$). Bacteremia recurrence occurred in 3 patients (5.4%) in the broad-spectrum beta-lactam group, zero patients in the narrow-spectrum beta-lactam, and 2 patients (4.8%) in the combination group ($P=.611$). Hospital readmission within 60 days occurred in 27 patients (48.2%) in the broad-spectrum beta-lactam group, 15 patients (50%) in the narrow-spectrum beta-lactam, and 17 patients (40.5%) in the combination group ($P=.735$).

Table 2. Primary and Secondary Outcomes

Outcomes	Broad-Spectrum Beta-Lactam ($n=56$)	Narrow-Spectrum Beta-Lactam ($n=30$)	Combination Therapy ($n=42$)	*P* Value
Composite clinical failure, *n* (%)	11 (19.64)	8 (26.67)	14 (33.33)	.306
60-day all-cause mortality, *n* (%)	9 (16.1)	8 (26.67)	13 (30.9)	.203
Inpatient mortality, *n* (%)	7 (12.5)	6 (20.0)	11 (26.2)	.859
Time to mortality, days, median (IQR)	11 (8–23)	16.5 (10.75–23.25)	17 (9–29)	.605
60-day bacteremia recurrence, *n* (%)	3 (5.4)	0 (0.0)	2 (4.8)	.611
60-day re-admission, *n* (%)	27 (48.2)	15 (50.0)	17 (40.5)	.735
Infection status 60 days after the last dose of antibiotics, *n* (%)				.575
Documented or presumed resolution of infection signs and symptoms[a]	47 (83.9)	22 (73.3)	30 (71.4)	
Documented or presumed persistent infection signs and symptoms	3 (5.4)	2 (6.7)	4 (9.5)	
Lack of data	6 (10.7)	6 (20.0)	8 (6.25)	
Microbiological status 60 days after the last dose of antibiotics, *n* (%)*				.351
Documented or presumed microbiological cure	51 (91.1)	24 (80.0)	39 (92.9)	
Documented or presumed microbiological failure	3 (5.4)	2 (6.7)	2 (4.8)	
Lack of data	2 (3.6)	4 (13.3)	1 (2.4)	
Hospital length of stay from index culture, median, day (IQR)	22.5 (12.5–33.5)	21 (7–31)	24.5 (18–30)	.4377
Hospital length of stay, median, day (IQR)	11 (6.5–21.4)	11 (6–20)	12.5 (8–24)	.4274
ICU admission, *n* (%)	12 (21.4)	7 (23.3)	14 (33.3)	.387
ICU length of stay, median, days (IQR)	3.5 (1.5–9; 1–22)	4 (1–9;1–11)	6.5 (4–13; 1–81)	.2328
Duration of bacteremia, median, hours (IQR)	28.7 (23.94–41.94)	35.15 (23.83–43.18)	28.02 (23.5–48)	.8712
Antibiotics days of therapy, days, median (IQR)	26.5 (16–30.5)	24 (16–30)	24 (16–30)	.8734

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a]Resolution of fevers and hemodynamic instability.

*Microbiological cure was defined as at least 3 consecutive negative methicillin-susceptible *Staphylococcus aureus* or penicillin-susceptible *S aureus* blood culture.

Documented or presumed resolution of infection signs and symptoms occurred in 47 patient (83.9%) in the broad-spectrum beta-lactam group, 22 patients (73.3%) in the narrow-spectrum beta-lactam, and 30 (71.4%) in the combination group ($P=.575$). Microbiologic cure, defined as negative blood cultures after the index culture, occurred in 51 patients (91.1%) in the broad-spectrum beta-lactam group, 24 patients (80%) in the narrow-spectrum beta-lactam, and 39 (92.9%) in the combination group ($P=.351$).

We did not observe any significant differences in other secondary outcomes (Table 2). Safety outcomes were also similar across the groups (Supplementary Table 2). Treatment-emergent *C difficile* occurred in 4 patients (7.1%) in the broad-spectrum beta-lactam group, 2 patients (6.7%) in the narrow-spectrum beta-lactam, and 3 patients (7.5%) in the combination group ($P=1$). Treatment-emergent acute kidney injury occurred in 13 patients (30.9%) in the broad-spectrum beta-lactam group, 6 patients (20%) in the narrow-spectrum beta-lactam group, and 11 patients (26.2%) in the combination group ($P=.802$). Treatment-emergent hepatotoxicity occurred in 8 patients (14.3%) in the broad-spectrum beta-lactam group, 5 patients (16.7%) in the narrow-spectrum beta-lactam group, and 8 patients (19.0%) in the combination group ($P=.827$). Only 1 patient (2.4%) in the combination group developed a rash or hypersensitivity reaction related to antibiotics.

In a multivariable logistic regression adjusting for possible confounding variables, combination therapy was associated with a significantly higher odds of 60-day all-cause mortality (adjusted odds ratio [aOR], 3.39; 95% confidence interval [CI], 1.29–8.89; $P=.013$) compared with broad-spectrum antibiotics (Table 3). The aOR for 60-day all-cause mortality for combination therapy compared with narrow-spectrum antibiotics was a similar point estimate, but it did not reach statistical significance (aOR, 3.30; 95% CI, .8–13.61; $P=.071$). Our model demonstrated the following risk factors for clinical failure: age >55 years (aOR, 2.91; 95% CI, 1.01–8.35; $P=.047$), obesity (aOR, 3.21; 95% CI, 1.01–10.22; $P=.049$), corticosteroid use (aOR, 2.44; 95% CI, 1.02–5.80; $P=.043$), GVHD (aOR, 7.89; 95% CI, 2.01–31.06; $P=.003$), and Pitt bacteremia score ≥4 (aOR, 5.6; 95% CI, 1.08–28.48; $P=.040$) (Figure 2). All of the multivariable logistic regression models demonstrated adequate calibration (Hosmer-Lemeshow test $P>.05$) and excellent discrimination (C-statistics >0.8).

Sensitivity Analyses

In a sensitivity analysis excluding subjects who changed therapy after 72 hours ($n=9$), combination therapy was associated with a significantly higher odds for 60-day all-cause mortality compared with broad-spectrum therapy (aOR, 4.73; 95% CI, 1.67–13.36; $P=.003$) and narrow-spectrum therapy (aOR, 5.34; 95% CI, 1.11–25.72; $P=.037$) (Supplementary Table 3). In a second sensitivity analysis excluding subjects who never achieved neutrophil recovery ($n=18$), combination therapy was still associated with a significantly higher odds of 60-day

Table 3. Composite Clinical Failure and 60-Day All-Cause Mortality Calculated With the Use of a Multivariable Logistic Regression

	Unadjusted OR (95% CI; *P* Value) (*n* = 128)	Adjusted OR (95% CI; *P* Value) (*n* = 128)
Composite Clinical Failure		
Narrow spectrum vs broad spectrum	1.49 (.64–3.48; *P* = .36)	0.77 (.22–2.66; *P* = .68)
Combination therapy vs broad spectrum	2.04 (.77–5.46; *P* = .15)	2.47 (.87–7.04; *P* = .09)
Combination therapy vs narrow spectrum	1.37 (.49–3.86; *P* = .55)	3.22 (.89–11.59; *P* = .074)
60-Day All-Cause Mortality		
Narrow spectrum vs broad spectrum	1.90 (.87–4.17; *P* = .11)	1.03 (.30–3.49; *P* = .97)
Combination therapy vs broad spectrum	2.61 (1.04–6.52; *P* = .04)	3.39 (1.29–8.89; *P* = .013)
Combination therapy vs narrow spectrum	1.38 (.47–4.04; *P* = .58)	3.30 (.80–13.61; *P* = .071)

Abbreviations: CI, confidence interval; OR, odds ratio.

NOTES: Composite clinical failure defined as 60-day all-cause mortality and/or 60-day bacteremia recurrence. Covariates included in the model: age >55, body mass index ≥30 kg/m^2, receipt of corticosteroids, presence of acute graft-versus-host disease, Pitt bacteremia score, Charlson comorbidity index, and the Multinational Association for Supportive Care in Cancer Risk-Index score.

all-cause mortality compared with broad-spectrum therapy (aOR, 4.40; 95% CI, 1.28–15.13; *P* = .019) but not compared with narrow-spectrum therapy (aOR, 2.49; 95% CI, .45–13.73; *P* = .29) (Supplementary Table 4). In a third sensitivity analysis excluding subjects who had a separate microbiologically confirmed bacterial infection within 14 days of the index culture, but not the day of the index culture (*n* = 23), combination therapy was still associated with a significantly higher odds of 60-day all-cause mortality compared with broad-spectrum therapy (aOR, 2.76; 95% CI, 1.18–6.42; *P* = .019) but not compared with narrow-spectrum therapy (aOR, 7.60; 95% CI, .78–78.98; *P* = .089) (Supplementary Table 5).

DISCUSSION

In this study assessing the effectiveness of MSSA/PSSA BSI treatment in hospitalized oncology (primarily hematologic malignancy) patients with febrile neutropenia, we found that subjects receiving combination therapy with both broad-spectrum and narrow-spectrum beta-lactam antibiotic therapy experienced a significantly higher odds of 60-day all-cause mortality, after adjusting for possible confounders. Subjects receiving a narrow-spectrum beta-lactam alone did not have significantly different outcomes compared with subjects receiving a broad-spectrum beta-lactam alone. As shown in this study, there are inconsistent practice patterns in treating patients with MSSA/PSSA BSI and febrile neutropenia, likely because narrow-spectrum beta-lactams are first-line agents recommended for treatment of MSSA/PSSA BSI and broad-spectrum beta-lactams are first-line agents for empiric treatment in patients

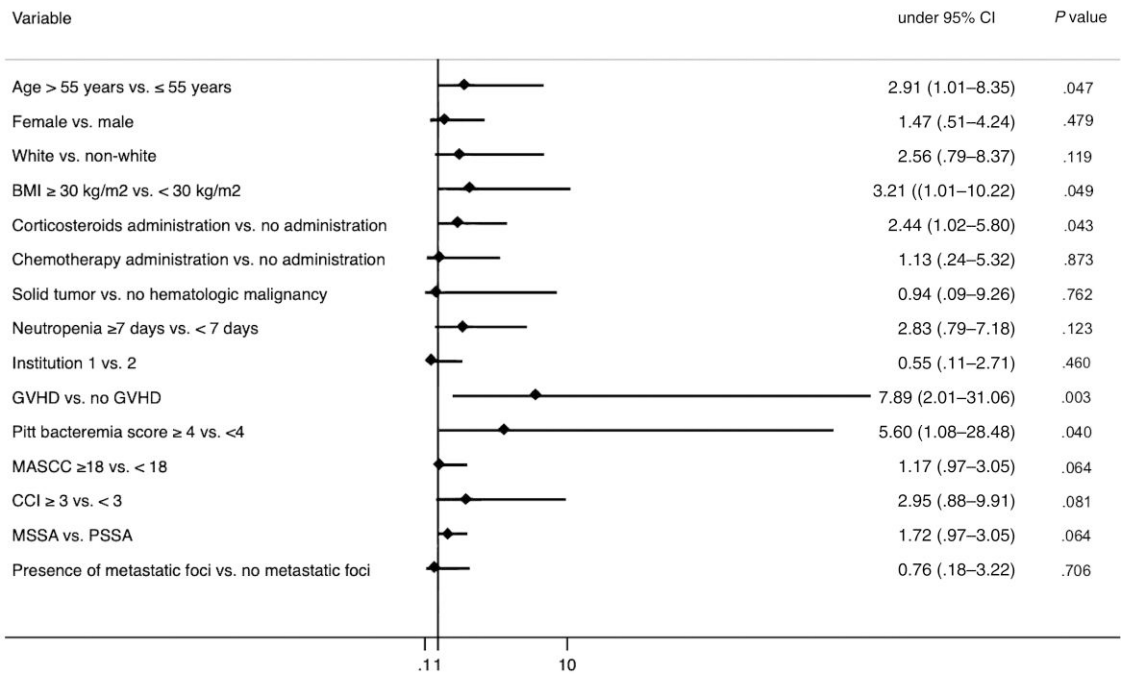

Figure 2. Risk factors for 60-day mortality and/or bacteremia recurrence among patients with *Staphylococcus aureus* bloodstream infection and febrile neutropenia. BMI, body mass index; CCI, Charlson comorbidity index; GVHD, graft-versus-host disease; MASCC, Multinational Association for Supportive Care in Cancer risk-index score; MSSA, methicillin-susceptible *S aureus*; PSSA, penicillin-susceptible *S aureus*.

with febrile neutropenia. To our knowledge, this is the first study to assess the effectiveness of different MSSA or PSSA BSIs treatment regimens in patients with febrile neutropenia and without other identified infections.

Although we found a significantly higher risk of 60-day mortality in the combination beta-lactam group compared with broad-spectrum beta-lactam, we did not find a significant difference in the planned primary outcome measure, which was a composite clinical outcome of 60-day mortality and/or bacteremia recurrence. The higher 60-day mortality in the combination beta-lactam group may be related to unmeasured effects of inappropriate antibiotic use, such as invasive fungal infections or antibiotics adverse reactions [21, 22]. In addition, beta-lactam-induced neurotoxicity could be more common in combination therapy, which may have contributed to the increased mortality [23]. Another possibility is that this exposure group is subject to confounding by indication, because patients who are sicker may be more likely to receive combination beta-lactam therapy. We attempted to control for this by including validated measures of comorbidity, bacteremia, and cancer severity in our regression model, but the possibility of unmeasured confounding persists. Although we excluded patients with documented evidence of polymicrobial infection, it is possible that more patients in the combination therapy group had undocumented polymicrobial infection. The combination therapy group also had a higher risk of 60-day mortality when compared with the narrow-spectrum group in one of our sensitivity analyses, whereas results of the other analyses demonstrated a similar point estimate but did not reach statistical significance. We did not find a significant difference between treatment groups with the secondary outcomes, including time to bacteremia clearance, hospital readmission, hospital or ICU length of stay, and antibiotic-days of therapy.

De-escalating therapy to narrow-spectrum antistaphylococcal beta-lactams was not associated with increased odds of clinical failure or 60-day all-cause mortality compared with maintaining broad-spectrum beta-lactam therapy. Although our study may be underpowered to detect significant differences between these treatment groups, the fact that there were no differences between the broad-spectrum and narrow-spectrum in any of the secondary clinical outcomes suggests that narrow-spectrum beta-lactams can be safely used in patients with neutropenia and documented MSSA or PSSA after resolution of fever and thorough evaluation for additional sources of infection. Here again, there may be unmeasured differences between the exposure groups that may affect both their prognosis and treatment choice, such as the presence of mucositis [24]. However, a separate observational study of neutropenic patients hospitalized in the ICU with severe sepsis also found that narrowing antibiotics after a microbiologic diagnosis was not associated with worse clinical outcomes [25]. The importance of narrowing antibiotics and targeting therapy based on microbiologic data is underscored by the rising incidence of multidrug resistance Gram-negative infections, particularly among the immunocompromised patient population [26, 27]. Other risks of antibiotic overuse include *C difficile* infection, renal toxicity, hepatotoxicity, and hypersensitivity reactions [28]. We did not find a difference in these safety outcomes between the treatment groups, but our study was likely underpowered to detect differences in these less frequent events.

Our study is limited by the small sample size and the retrospective nature that is subject to residual confounding. As noted above, we attempted to account for this in our regression model with available data, but the potential for unmeasured confounders means that these findings should be confirmed with larger, prospective studies and randomized trials where possible. In addition, clinical practice patterns may vary by the prescribing physician and/or infectious disease consultant, meaning that observations in our sample may not be truly independent. However, we used robust standard errors in our regression model to account for clustering within treating physicians in the sample. There may be some heterogeneity within treatment groups in terms of the final treatment regimen, because we assessed antibiotic exposure during the first 72 hours after source identification, which may not be reflective of the total treatment course in people who changed therapy. However, a sensitivity analysis excluding patients who changed therapy after 72 hours did not find different results.

CONCLUSIONS

In conclusion, we report that combination beta-lactam therapy was associated with a greater risk of 60-day all-cause mortality compared with broad-spectrum beta-lactams after adjusting for possible confounders. Transitioning to a narrow-spectrum beta-lactam before neutrophil recovery in febrile neutropenia patients with MSSA or PSSA BSIs could be considered based on these data in appropriate patients, given that this was not associated with greater incidence of clinical failure compared with broad-spectrum beta-lactams. Patients who (1) are critically ill, (2) have suspected polymicrobial infection, (3) have severe mucositis, or (4) have uncontrolled gastrointestinal or genitourinary sources of infection would likely need to maintain broad-spectrum therapy. Further prospective studies are needed to support antimicrobial stewardship initiatives in oncology patients.

Supplementary Data

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

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Potential conflicts of interests. J. S. has given presentations for Abbvie and provided consulting for Bristol Myers Squibb, outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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