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Multicenter Cohort Study of Ceftaroline Versus Daptomycin for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection

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Background. Observational data suggest ceftaroline may be effective for methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI), but comparative data with standard of care are limited. This analysis compares the outcomes of MRSA BSI treated with ceftaroline or daptomycin.

Methods. Multicenter, retrospective, observational cohort study of adult patients with MRSA BSI from 2010 to 2017. Patients treated with ≥72 hours of ceftaroline or daptomycin were included. Those clearing BSI before study drug and those with a pneumonia source were excluded. The primary outcome was composite treatment failure, defined as 30-day mortality, BSI duration ≥7 days on study drug, and 60-day MRSA BSI recurrence. Inverse probability of treatment weighted risk difference in composite failure between daptomycin and ceftaroline groups was computed and 15% noninferiority margin applied.

Results. Two hundred seventy patients were included; 83 ceftaroline and 187 daptomycin. Ceftaroline was noninferior to daptomycin with respect to composite failure (39% daptomycin, 32.5% ceftaroline; weighted risk difference, 7.0% [95% confidence interval, −5.0% to 19.0%]). No differences between treatment groups was observed for 30-day mortality or other secondary efficacy outcomes. Creatine phosphokinase elevation was significantly more common among daptomycin patients (5.3% vs 0%, *P* = .034). Rash was significantly more common among ceftaroline patients (10.8 vs 1.1%, *P* = .001).

Conclusions. No difference in treatment failure or mortality was observed between MRSA BSI treated with ceftaroline or daptomycin. These data support future study of ceftaroline as a primary MRSA BSI treatment and current use of ceftaroline when an alternative to vancomycin and daptomycin is required.

Keywords. bacteremia; β-lactam; infective endocarditis; lipoglycopeptide; MRSA.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious public health threat resulting in thousands of infections and deaths annually [1]. A major contributor to the associated morbidity and mortality is MRSA bloodstream infection (BSI) [2, 3]. Vancomycin has been the treatment of choice for MRSA BSI for decades, but treatment failure rates are in excess of 30% [4–6]. This, along with emergence of reduced-vancomycin-susceptibility phenotypes and vancomycin-associated adverse drug reactions, necessitates alternative treatment options. Despite availability of newer alternative anti-MRSA antibiotics, none have been shown to be conclusively more effective than vancomycin [6–11]. Daptomycin is currently the vancomycin alternative with the most available clinical evidence and the only US Food and Drug Administration (FDA) alternative for *S aureus* BSI and right-sided infective endocarditis

[12, 13]. However, the use of daptomycin for MRSA BSI is not without limitation. Similar to vancomycin, daptomycin failure is common and nonsusceptibility, although rare, has emerged [14–17]. Data suggest that as *S aureus* becomes less susceptible to vancomycin, susceptibility to daptomycin may also decrease [18]. Interactions with pulmonary surfactant also render daptomycin ineffective for BSI secondary to pneumonia source, which is an important subpopulation of MRSA BSI [19].

Ceftaroline fosamil, the prodrug of ceftaroline, is an advanced-generation cephalosporin with potent bactericidal gram-positive activity including against MRSA and many strains exhibiting reduced vancomycin susceptibility and daptomycin nonsusceptibility [20]. Observational data suggest that ceftaroline may be effective for MRSA BSI, but data comparing ceftaroline to standard of care are limited, and ceftaroline is not FDA approved for this indication. Without additional comparative data, clinicians may be hesitant to use ceftaroline, even when alternatives to vancomycin are required. Considering that vancomycin and/or daptomycin alternatives are frequently necessary for MRSA BSI management, these data are urgently needed. Because daptomycin is the primary vancomycin alternative, the objective of this study was to compare clinical outcomes between patients treated with ceftaroline or daptomycin for MRSA BSI.

METHODS

Study Design and Population

This was a multicenter, retrospective, observational cohort study of adult patients with MRSA BSI from 2010 to 2017 in 10 acute-care hospitals: Detroit Medical Center and Henry Ford Hospital in Detroit, Michigan; University of Florida Health, Shands Hospital in Gainesville, Florida; Lee Memorial Hospital in Fort Myers, Florida; University of Tennessee Medical Center in Knoxville, Tennessee; University of Maryland Medical Center in Baltimore, Maryland; San Diego Veterans Affairs Medical Center in San Diego, California; Huntsville Hospital in Huntsville, Alabama; HonorHealth John C. Lincoln Medical Center in Phoenix, Arizona; and Our Lady of the Lake Regional Medical Center in Baton Rouge, Louisiana. Patients aged ≥18 years with ≥1 positive blood culture for MRSA who received ≥72 hours of ceftaroline or daptomycin for MRSA BSI treatment were eligible for inclusion [21]. Patients who received ≥96 hours of MRSA BSI therapy prior to first dose of study therapy, cleared BSI prior to first dose of study therapy, had a suspected pneumonia BSI source, or had a polymicrobial BSI were excluded. Patients receiving ≥24 hours of concomitant MRSA-active therapy during the initial 96 hours of study drug were also excluded.

Patient Consent Statement

This study was approved by the institutional review board at each study site and at Wayne State University (WSU). Waiver of patient informed consent was granted.

Patient Data Elements and Collection

Eligible patients were identified for inclusion by screening a list of patients who received either ceftaroline or daptomycin during the study period. Patient data were extracted from the medical record by trained reviewers using a structured data collection form within the REDCap (Research Electronic Data Capture, Vanderbilt University) data capture tool hosted at WSU [22]. Data elements included demographics, past medical history, comorbid conditions, antibiotic therapy and associated laboratory parameters, infectious diseases consult, and pursuit of source control. The degree of patient comorbidity was quantified using the Charlson Comorbidity Index [23]. Severity of illness was quantified using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score using the worst physiological parameters within 24 hours of index MRSA blood culture [24]. Source of MRSA BSI and/or metastatic foci of infection was based on treating physicians' notes and available clinical/diagnostic data. Microbiologic data including antibiotic susceptibilities by Microscan (Siemens Healthcare Diagnostics), Vitek-2 (bioMérieux), Phoenix (BD), and/or Etest (bioMérieux) were collected from the medical record.

Outcomes

The primary outcome was composite treatment failure, defined as any of the following: mortality within 30 days of first dose of study therapy, BSI duration ≥7 days after first dose of study therapy [12], or MRSA BSI recurrence within 60 days of the end of MRSA BSI therapy. Secondary efficacy outcomes included each single component of composite failure, 60-day readmission related to MRSA bacteremia defined as presence of positive blood cultures on readmission, BSI duration post–study drug initiation, and length of stay post–study drug initiation.

Multiple safety outcomes of interest were included. Creatine phosphokinase (CPK) elevation was defined as an increase to >600 U/L or >1000 U/L if baseline CPK was >200 U/L [25]. Neutropenia was defined as a decrease in absolute neutrophil count (ANC) to <1500 cells/mm^3 or ≥50% decline from initiation of study medication if baseline ANC <1500 cells/mm^3 [26]. *Clostridioides difficile* infection was defined as signs/symptoms along with positive laboratory test at least 48 hours after initiation of study therapy. Any adverse event apart from those defined above (eg, nausea, vomiting, rash) that was attributed to a study medication in the medical record by the treating physician was also recorded.

Data Analysis

The primary analysis focused on comparing composite treatment failure between patients receiving ceftaroline and daptomycin. We hypothesized that composite failure would be approximately equal between ceftaroline and daptomycin based on previously published data. Thus, the primary analysis

was designed to test noninferiority of ceftaroline compared to daptomycin. Assuming a 25% incidence of composite treatment failure in both treatment groups, a noninferiority margin of 15%, and a 2:1 daptomycin to ceftaroline allocation ratio, a minimum of 156 and 78 patients was required in the daptomycin and ceftaroline groups, respectively, to yield a statistical power of 80% and an α = 2.5% [13, 27, 28]. Actual and weighted risk differences with 95% confidence intervals (CIs) were computed for composite failure between the daptomycin and ceftaroline groups (ie, daptomycin minus ceftaroline). Ceftaroline was considered noninferior if the lower bound of the 95% CI for this risk difference did not cross −15%.

Weighted risk differences were based on inverse probability of treatment weighting (IPTW). This was employed to address the high likelihood of confounding and treatment selection bias introduced by the fact that treatment assignment was not random. Logistic regression was used to estimate each patient's probability of receiving ceftaroline (ie, a propensity score). The model included a priori–identified covariates known to be associated with mortality and/or microbiologic failure in patients with MRSA BSI including age, BSI source/foci of infection, Charlson Comorbidity Index, APACHE II score, infectious diseases consult, and source control [5, 29–34]. Stabilized weights for each subject were generated from the inverse of the propensity score. A pseudo-cohort was then generated using these stabilized weights, and the standardized difference between treatment groups of each a priori–identified covariate of importance was examined to ensure balance was achieved. A threshold of >25% standardized difference was used to assess the need for a respecified propensity score model, and a threshold of >10% was used to assess the need for further adjustment of a covariate in outcome analysis [35–37].

Secondary analyses were also conducted to compare secondary efficacy and safety outcomes between treatment groups and using actual and weighted risk differences in a manner consistent with the primary analysis. Secondary analyses evaluating composite failure between treatment groups in both a priori–specified and post hoc subgroups of interest were also conducted. These subgroups included infective endocarditis BSI source/foci, skin and soft tissue BSI source/foci, bone/joint BSI source/foci, patients with chronic kidney disease stage 3 or greater, patients on intermittent hemodialysis, and patients with acute kidney injury (Acute Kidney Injury Network stages 1–3).

When comparing patient characteristics and outcomes between those receiving ceftaroline or daptomycin, the χ^2 or Fisher exact test was used for categorical variables and the Mann-Whitney U test was used for continuous and numeric ordinal variables. All statistical tests were 2-sided; P values ≤ .05 were considered statistically significant. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 270 patients were included. A full description of demographics, clinical characteristics, and outcomes of the cohort is available in Supplementary Table 1. The cohort was predominantly African American (52.6%) and White (42.2%), majority male (64.8%), and had a median age of 58 (interquartile range [IQR], 46–66.5) years. Common comorbidities were diabetes (38.5%), moderate/severe renal disease (40.0%), chronic hemodialysis (20.0%), heart failure (24.1%), injection drug use (24.1%), and liver disease (21.1%). The median Charlson Comorbidity Index and APACHE II scores were 2.5 (IQR, 1.0–5.0) and 14.0 (IQR, 9.0–19.0), respectively. The most common MRSA BSI sources/foci were endovascular (34.8%), bone/joint (31.1%), skin and soft tissue (20.4%), and intravenous catheter (19.3%). Composite failure occurred in 100 (37%) patients: 32 (11.9%) with 30-day mortality, 50 (18.5%) with BSI duration ≥7 days on study therapy, and 38 with (14.1%) 60-day MRSA BSI recurrence.

Eighty-three patients (30.7%) were in the ceftaroline group while 187 (69.3%) were in the daptomycin group. The majority of patients in both the ceftaroline group (71.1%) and daptomycin group (66.3%) initially received vancomycin therapy prior to study therapy. The most common ceftaroline dose was 600 mg (68.7%) and the most common dosing frequencies were every 12 hours (56.6%) and every 8 hours (42.2%). The median daptomycin dose was 600 mg (IQR, 500–700 mg), which equates to 7.7 (IQR, 6.1–9.3) mg/kg of total body weight and 8.5 (IQR, 6.9–10.1) mg/kg of adjusted body weight. Using total body weight for nonobese (body mass index [BMI] <30 kg/m^2) daptomycin patients, and adjusted body weight for obese daptomycin patients (BMI ≥30 kg/m^2), only 5 (2.7%) daptomycin patients had a dose <6 mg/kg, whereas 63 (33.7%) had a dose ≥10 mg/kg. The median duration of inpatient ceftaroline and daptomycin was 10 (IQR, 5–18) days and 9 (IQR, 6–15) days, respectively.

A complete bivariate comparison of patient characteristics between the ceftaroline and daptomycin groups in the unadjusted cohort is displayed in Table 1. While select comorbidities were significantly different between groups, the distribution of Charlson Comorbidity Index was similar. A similar proportion of patients had acute kidney injury at index culture and the distribution of APACHE II scores was similar between groups. A similar proportion of patients in each group had an endovascular BSI source/foci. However, skin/soft tissue source/foci was significantly more common in the ceftaroline group whereas intravenous catheter source/foci was significantly more common in the daptomycin group. Median time from index blood culture to study drug was similar in both groups (42 [IQR, 20–71] hours for ceftaroline vs 44 [IQR, 21–71] hours for daptomycin). However, daptomycin was significantly more likely to be the first MRSA BSI treatment compared to ceftaroline.

Table 1.   Bivariate Comparisons of Demographic and Clinical Characteristics Between Patients Receiving Daptomycin or Ceftaroline

Covariate	Daptomycin (n = 187)	Ceftaroline (n = 83)	*P* Value
Demographics			
Age, y, median (IQR)	58 (48–68)	56 (40–63)	.248
Male sex	117 (62.6)	58 (69.9)	.246
Race/ethnicity			
African American	120 (64.3)	22 (26.5)	<.001
White	57 (30.5)	57 (35.0)	<.001
Asian	3 (1.6)	1 (1.2)	1.000
Hispanic	1 (0.5)	1 (1.2)	.521
Other/unknown	6 (5.5)	2 (2.4)	1.000
Study site			
Detroit Medical Center	122 (65.2)	12 (14.5)	<.001
UF Health–Shands Hospital	24 (12.8)	11 (13.3)	.925
Henry Ford Hospital	23 (12.3)	7 (8.4)	.351
University of Tennessee Medical Center	0	17 (20.5)	<.001
Lee Memorial Hospital	15 (8.0)	1 (1.2)	.027
University of Maryland Medical Center	3 (1.6)	10 (12.0)	.001
VA San Diego Healthcare System	0	11 (13.3)	<.001
Huntsville Hospital	0	9 (10.8)	<.001
HonorHealth John C. Lincoln Medical Center	0	3 (3.6)	.028
Our Lady of the Lake Medical Center	0	2 (2.4)	.094
Comorbidities and past medical history			
Myocardial infarction	17 (9.1)	11 (13.3)	.301
Heart failure	47 (25.1)	18 (21.7)	.541
Peripheral vascular disease	37 (19.8)	8 (9.6)	.039
Cerebrovascular disease	25 (13.4)	10 (12.0)	.766
Dementia	8 (4.3)	3 (3.6)	.799
Chronic pulmonary disease	42 (22.5)	15 (18.1)	.415
COPD	29 (15.5)	12 (14.5)	.824
Asthma	19 (10.2)	3 (3.6)	.070
Connective tissue disease	25 (13.4)	4 (4.8)	.036
Peptic ulcer disease	0	0	
Liver disease	34 (18.2)	23 (27.7)	.077
Mild[a]	28 (15.0)	19 (22.9)	.113
Moderate/severe[b]	6 (3.2)	4 (4.8)	.502
Diabetes	74 (39.6)	30 (36.1)	.593
Without end-organ damage	17 (9.1)	10 (12.0)	.455
With end-organ damage	57 (30.5)	20 (24.1)	
Hemiplegia	9 (4.8)	0	.061
Moderate/severe renal disease[c]	82 (43.9)	26 (31.3)	.053
Chronic hemodialysis	44 (23.5)	10 (12.0)	.030
Solid tumor without metastasis	6 (3.2)	2 (2.4)	1.000
Leukemia	1 (0.5)	3 (3.6)	.088
Lymphoma	1 (0.5)	0	1.000
Metastatic solid tumor	2 (1.1)	2 (2.4)	.589
HIV	7 (3.7)	2 (2.4)	.726
AIDS	0	2 (2.4)	.094
Charlson Comorbidity Index, median (IQR)	3 (1–5)	2 (1–5)	.275
Intravenous drug use	37 (19.8)	28 (33.7)	.013
Prior hospitalization (90 d)	76 (40.6)	25 (30.1)	.099
Prior MRSA infection (1 y)	51 (27.3)	20 (24.1)	.584
Prior IV vancomycin (90 d)	33 (17.6)	14 (16.9)	.876
Prior daptomycin (90 d)	22 (11.8)	5 (6.0)	.189
Prior ceftaroline (90 d)	0	3 (3.6)	.028
Clinical data			
Admitted from:			.471
Home	137 (73.7)	66 (62.6)	
Transferred from another hospital	24 (12.9)	10 (12.0)	
Nursing facility	25 (13.4)	7 (9.9)	
Weight, kg, median (IQR)	79.8 (68.0–96.0)	83.6 (72.6–99.5)	.235
BMI, kg/m^2, median (IQR)	26.6 (23.4–32.6)	27.2 (23.7–32.4)	.614
Obesity[d]	60 (32.1)	29 (34.9)	.645

Table 1. Continued

Covariate	Daptomycin (n = 187)	Ceftaroline (n = 83)	*P* Value
Creatinine clearance[e,f], mL/min, median (IQR)	61.7 (35.7–95.4)	62.6 (35.8–104.9)	.861
>50 mL/min	89 (47.6)	47 (56.6)	.350
30.01–50 mL/min	30 (16.0)	14 (16.9)	
15–30 mL/min	21 (11.2)	9 (10.8)	
<15 mL/min or ESRD	47 (25.1)	13 (15.7)	
Acute kidney injury[f]	61 (32.6)	29 (34.9)	.709
APACHE II score[f], median (IQR)	14 (9–20)	14 (9–19)	.527
Neutropenia[f]	3 (1.6)	1 (1.2)	1.000
Infection data			
Endovascular	65 (34.8)	29 (34.9)	.977
Infective endocarditis	55 (29.4)	27 (32.5)	.607
Other endovascular	11 (5.9)	2 (2.4)	.356
Intra-abdominal	4 (2.1)	2 (2.4)	1.000
Lower respiratory tract	0	0	
Bone/joint	56 (29.9)	28 (33.7)	.535
Invasive prosthetic device	20 (10.7)	4 (4.8)	.117
Skin/soft tissue	32 (17.1)	23 (27.7)	.046
Deep tissue abscess	13 (7.0)	9 (10.8)	.281
Intravenous catheter	42 (22.5)	10 (12.0)	.045
Urinary	5 (2.7)	1 (1.2)	.670
Unknown	8 (4.3)	5 (6.0)	.546
Treatment data			
Infectious diseases consult	173 (93.0)	82 (98.8)	.071
Source control pursued	97 (52.4)	36 (43.9)	.198
Study drug line of therapy[g]			.014
First-line	62 (33.2)	16 (19.3)	
Second-line	124 (66.3)	64 (77.1)	
Third-line	1 (0.5)	3 (3.6)	
Preceding MRSA BSI therapy			
Vancomycin	122 (65.2)	59 (71.1)	.346
Daptomycin	0	6 (7.2)	.001
Ceftaroline	1 (0.5)	0	1.000
Linezolid	3 (1.6)	6 (7.2)	.026
Time to study drug, h, median (IQR)	44 (21–71)	42 (20–71)	.964
Ceftaroline dose (n = 83)	…		
600 mg		57 (68.7)	
400 mg		12 (14.5)	
300 mg		11 (13.3)	
200 mg		3 (3.6)	
Ceftaroline dose interval (n = 83)	…		
Every 8 h		35 (42.2)	
Every 12 h		47 (56.6)	
Every 24 h		1 (1.2)	
Daptomycin dose, mg, median (IQR)	600 (500–770)	…	
Daptomycin dose, mg/kg (actual body weight), median (IQR)	7.7 (6.1–9.3)	…	
Daptomycin dose, mg/kg (adjusted body weight), median (IQR)	8.5 (6.9–10.1)	…	
Daptomycin dose interval			
Every 24 h	120 (64.2)	…	
Every 48 h/posthemodialysis	67 (35.8)	…	
Inpatient study drug duration, d, median (IQR)	9 (6–15)	10 (5–18)	.545

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BSI, bloodstream infection; COPD chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; UF, University of Florida; VA, Veterans Affairs.

[a]Mild liver disease defined as chronic hepatitis without cirrhosis.

[b]Severe liver disease defined as portal hypertension or cirrhosis.

[c]Moderate/severe renal disease defined as chronic kidney disease stage 3 or greater or receiving chronic dialysis.

[d]Defined as BMI ≥30 kg/m^2.

[e]Calculated using Cockcroft-Gault formula using actual body weight for BMI <30 kg/m^2 and adjusted body weight for BMI ≥30 kg/m^2.

[f]At time of index MRSA blood culture.

[g]Reasons for switch to daptomycin or ceftaroline, when documented, included elevated vancomycin minimum inhibitory concentration, concern for failure or previous therapy, concern for adverse reaction on previous therapy, and perceived improved target site penetration.

Table 2 shows the actual and weighted risk differences between the daptomycin and ceftaroline groups for treatment outcomes. No significant difference in composite treatment failure was observed between daptomycin and ceftaroline patients (39% daptomycin, 32.5% ceftaroline; weighted risk difference, 7.0% [95% CI, –5.0 to 19.0%]). This met the definition of noninferiority of ceftaroline compared to daptomycin for composite treatment failure. No statistically significant difference in any of the secondary efficacy outcomes was observed between daptomycin and ceftaroline patients, including 30-day mortality. No significant difference in BSI duration post–study drug initiation was observed between treatment groups (daptomycin, 3 [IQR, 2–5] days vs ceftaroline, 4 [IQR, 2–6] days; *P* = .134). Similarly, length of stay post–study drug initiation was not different between groups (daptomycin, 11 [IQR, 7–18] days vs ceftaroline, 13 [IQR, 7–24] days; *P* = .095). With respect to safety outcomes, creatine phosphokinase elevation was significantly more common among daptomycin patients whereas rash was significantly more common among ceftaroline patients (Table 2). No significant difference was noted in any other safety outcome. *Clostridioides difficile* infection occurred numerically more frequently in the ceftaroline group. There were no cases of study drug–associated neutropenia in either group. There were 2 cases of eosinophilic pneumonia in the daptomycin group.

The results of the a priori secondary subgroup analyses are displayed in Table 3. The results were consistent with primary analyses. No statistically significant association was observed between treatment group and composite failure in any of the subgroups of interest. The results of the post hoc subgroup analyses evaluating composite failure by study drug line of therapy are displayed in Supplementary Table 2. No statistically significant association was observed between treatment group and composite failure when study therapy was used as first-line or second-line therapy.

DISCUSSION

This study sought to compare the effectiveness and safety of ceftaroline and daptomycin for the treatment of MRSA BSI. Patients receiving ceftaroline and daptomycin had similar treatment outcomes in both unadjusted and IPTW-adjusted analysis designed to mitigate the influence of treatment selection bias and confounding. This was also true in the prespecified subgroup analysis, most notably patients with an infective endocarditis source/foci and those with moderate/severe renal impairment. The only notable differences in outcome observed between the 2 treatment groups was with respect to safety outcomes. Not surprisingly, patients treated with ceftaroline were more likely to develop a rash whereas patients treated with daptomycin were more likely to experience a CPK elevation.

Table 2. Actual and Inverse Probability of Treatment Weighted Risk Differences Between Daptomycin and Ceftaroline for the Primary and Secondary Outcomes

Outcome	Daptomycin (n = 187)	Ceftaroline (n = 83)	Risk Difference (95% CI)	*P* Value[a]	Weighted Risk Difference (95% CI)	*P* Value[b]
Composite failure	73 (39.0)	27 (32.5)	6.5 (–5.8 to 18.8)	.307	7.0 (–5.0 to 19.0)	.264
30-d mortality	20 (10.7)	12 (14.5)	–3.8 (–12.5 to 5.0)	.377	–5.2 (–13.8 to 3.5)	.215
BSI duration ≥7 d	36 (19.3)	14 (16.9)	2.4 (–7.5 to 12.2)	.642	5.4 (–3.8 to 14.5)	.273
60-d MRSA BSI recurrence	31 (16.6)	7 (8.4)	8.1 (.001–16.2)	.076	7.8 (–.002 to 15.9)	.085
60-d MRSA BSI-related readmission	17 (9.1)	6 (7.2)	1.9 (–5.1 to 8.8)	.613	1.3 (–5.8 to 8.4)	.718
Adverse drug reaction[c]	24 (12.8)	17 (20.5)	–7.7 (–17.6 to 2.3)	.106	–6.3 (–15.7 to 3.1)	.164
CPK elevation[d]	10 (5.4)	0	5.4 (2.1–8.6)	.034	5.0 (1.9 to 8.1)	.034
Rash	2 (1.1)	9 (10.8)	–9.8 (–16.6 to –2.9)	.001	–8.0 (–14.3 to –1.8)	.001
Neutropenia[e]	0	0	...		...	
Clostridioides difficile infection[f]	2 (1.1)	4 (4.8)	–3.8 (–8.6 to 1.1)	.074	–3.3 (–7.8 to 1.2)	.076

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; CPK, creatine phosphokinase; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] *P* value for χ² or Fisher exact test of actual risk differences.

[b] *P* value for χ² test of weighted risk differences.

[c] Includes CPK elevation, neutropenia, rash, *Clostridioides difficile* infection (data presented in table), and additional adverse reactions occurring while on study drug or attributed to study drug by treating clinicians, such as acute kidney injury, thrombocytopenia, fever, hypotension and bradycardia, and eosinophilic pneumonia.

[d] Increase to >600 U/L or >1000 U/L if baseline CPK >200 U/L.

[e] Decrease in absolute neutrophil count (ANC) to <1500 cells/mm³ or ≥50% decline from initiation of study medication if baseline ANC <1500 cells/mm³.

[f] *Clostridioides difficile* infection defined as signs/symptoms along with positive laboratory test at least 48 hours after initiation of study drug.

Table 3. Actual and Inverse Probability of Treatment Weighted Risk Differences Between Daptomycin and Ceftaroline for the Composite Treatment Failure in A Priori–Specified Subgroups of Interest

Subgroup	Daptomycin	Ceftaroline	Risk Difference (95% CI)	PValue[a]	Weighted Risk Difference (95% CI)	PValue[b]
Infective endocarditis source/foci (n = 82)	25/55 (45.5)	9/27 (33.3)	12.1 (−10.0 to 34.2)	.295	12.2 (−10.2 to 34.7)	.299
Skin/soft tissue source/foci (n = 55)	11/32 (34.4)	7/23 (30.4)	3.9 (−21.1 to 28.9)	.759	−2.8 (−30 to 24.5)	.840
Bone/joint source/foci (n = 84)	25/56 (44.6)	8/28 (28.6)	16.1 (−5.1 to 37.3)	.155	19.8 (−1.9 to 41.4)	.095
Moderate/severe renal disease (n = 108)	37/82 (45.1)	11/26 (42.3)	2.8 (−19 to 24.7)	.801	−0.6 (−21.3 to 20)	.951
Chronic hemodialysis (n = 54)	18/44 (40.9)	3/10 (30)	10.9 (−21 to 42.8)	.723	2.5 (−27.1 to 32.1)	.870
Acute kidney injury (n = 90)	29/61 (47.5)	10/29 (34.5)	13.1 (−8.3 to 34.4)	.243	13.2 (−9.1 to 35.5)	.260

Data are presented as no./No. (%) unless otherwise indicated.

Abbreviation: CI, confidence interval.

[a]P value for χ^2 or Fisher exact test of actual risk differences.

[b]P value for χ^2 test of weighted risk differences.

The results of this study contribute to a growing body of clinical evidence suggesting that ceftaroline may be a viable treatment option for MRSA BSI. Numerous noncomparative observational studies have demonstrated the potential utility of ceftaroline for MRSA BSI. These data are the first clinical data comparing ceftaroline to daptomycin, a standard-of-care therapy for MRSA BSI. Although observational in nature, and thus unable to firmly establish ceftaroline as noninferior to daptomycin, these data do represent an increase in the level and quality of the evidence to support the use of ceftaroline for MRSA BSI. Ceftaroline should be a priority for inclusion into future randomized clinical trials evaluating novel treatments for MRSA BSI in order to fully delineate its place in therapy.

There are a number of considerations to bear in mind when interpreting these findings. First and foremost, although we conducted noninferiority testing on the primary outcome of composite treatment failure, the observational nature of this study precludes the ability to conclude that ceftaroline is truly noninferior to daptomycin for MRSA BSI. That would require one or more robustly designed randomized controlled trials. The noninferiority testing was conducted due to the fact that we wanted to power the study under the hypothesis that there would be no difference in failure between ceftaroline and daptomycin. A noninferiority margin of 15% was selected a priori due to the anticipated difficulty in obtaining a large enough sample of ceftaroline monotherapy–treated patients to use a stricter margin and the fact that a less-strict noninferiority margin of 20% was used to conclude daptomycin was noninferior to vancomycin for MRSA BSI [6]. Readers should note that a noninferiority margin of 10% would have been ideal considering that a 10% difference in treatment failure is clinically meaningful. Although the primary analysis suggests that it is statistically unlikely the incidence of failure is more than 5% greater in the ceftaroline group, noninferiority at any threshold <15% cannot be concluded because the study was not powered to do so.

It is also important to note that the study therapy was not the initial MRSA BSI therapy for the majority of the patients in this study, particularly those in the ceftaroline group. It is unclear whether the results would be similar if more patients had been given ceftaroline or daptomycin as first-line therapy. It is encouraging that the majority of patients in both treatment groups received study therapy within 48 hours of index culture. This is similar to currently published randomized clinical trials where the transition from standard of care to experimental therapy often takes up to 48 hours [6]. However, this similarity with published clinical trials does not nullify the potential impact that studying sequential therapy could have. Data suggest that the initial 24–48 hours of MRSA BSI therapy is most strongly associated with outcome [34, 38]. Ideally, the comparison of 2 MRSA BSI treatments would occur during this early timeframe to best capture treatment effect and minimize the potential bias and confounding imparted by prior treatment.

Due to the observational nature of the study and in the absence of pharmacokinetic sampling, we were unable confirm pharmacodynamically optimized dosing in either treatment group. The majority of patients received daptomycin at doses that exceed the FDA-approved dosage for bloodstream infections including right-sided endocarditis of 6 mg/kg. However, only one-third of daptomycin patients received daptomycin doses of at least 10 mg/kg. Although in vitro data suggest that 10 mg/kg is the optimal dose for serious staphylococcal infections, data derived from patients with MRSA BSI suggest that fixed doses of 500–750 mg provide similar probability of effective exposures as 10 mg/kg [39]. At least 75% of the patients in this study received a daptomycin dose of at least 500 mg. Moreover, clinical data suggest success with daptomycin doses ≥7 mg/kg daily [40]. Evaluating adequacy of ceftaroline exposure is more complicated as the optimal dosing for serious infection is unknown. Less than half of the ceftaroline patients were given ceftaroline every 8 hours, a frequency often used for serious infections [10]. However, no clinical data indicate increased effectiveness of this more aggressive dosing, and pharmacokinetic simulation studies suggest it would be most beneficial for infections caused by isolates with a ceftaroline minimum inhibitory concentration ≥1 mg/L, accounting for only 4 (4.8%) of the ceftaroline group in the present study [41].

It is also important to note that the generalizability of the study may be limited. Patients with a pneumonia BSI source/foci were excluded given the lack of daptomycin efficacy for pulmonary infections. As such, these data are unable to demonstrate the comparative effectiveness of ceftaroline for BSI with a pneumonia source. It should also be noted that although adverse drug reactions were evaluated, the study was not specifically designed for this purpose. Many of the adverse reactions did not have an objective definition (eg, rash) and relied upon the diagnosis and documentation in the electronic medical record by treating clinicians. As such, the results should be interpreted with caution. Last, it is possible that some misclassification of BSI recurrence could have occurred. Although the 60-day threshold for an infection to be considered recurrence rather than reinfection is commonly used, data indicate that it is not a perfect threshold.

In conclusion, ceftaroline was noninferior to daptomycin for MRSA BSI in this observational study. Notable safety differences were observed; ceftaroline patients were more likely to develop a rash and daptomycin patients were more likely to have a CPK elevation. These data lend further evidence for the use of ceftaroline in patients with MRSA BSI who have failed treatment or cannot receive vancomycin or daptomycin and suggest that evaluating ceftaroline for MRSA BSI via randomized controlled trial should be a priority.

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.

Notes

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