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ORIGINAL RESEARCH ARTICLE

Ceftaroline Fosamil for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Bacteremia: A Real-World Comparative Clinical Outcomes Study

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Abstract

Background and Objective Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia results in substantial morbidity and mortality. As current treatments often lead to unsatisfactory outcomes, evidence guiding alternative treatment options is needed. This study evaluated real-world clinical outcomes of ceftaroline fosamil for the treatment of MRSA bacteremia.

Methods This retrospective study included adults hospitalized with MRSA bacteremia between 2011 and 2019. Patients were classified according to treatment with ceftaroline fosamil (ceftaroline), vancomycin, or daptomycin: Group 1, ceftaroline; Group 2, vancomycin or daptomycin (without ceftaroline); Group 3, combination therapy with ≥ 2 of these three agents. Clinical outcomes were compared using propensity-score-adjusted odds ratios (ORs) from logistic regression models.

Results Overall, 24,479 patients were included (Group 1, $n = 532$; Group 2, $n = 21{,}555$; Group 3, $n = 2392$). Mean age was 59.6, 60.8, and 57.4 years in Groups 1, 2, and 3, respectively. Mean post-index treatment length of stay was 8.8, 8.8, and 8.0 days, respectively. The most frequent line of therapy was ceftaroline first-line (42.1%), vancomycin or daptomycin first-line (95.4%), and combination therapy third-line or later (67.8%) in Groups 1, 2, and 3, respectively. Compared with Group 2, Groups 1 and 3 had similar favorable clinical responses {odds ratio [OR] = 1.18 [95% confidence interval (CI) 0.98–1.44], $p = 0.08$; OR = 1.20 [95% CI 0.97–1.47], $p = 0.09$, respectively} and were less likely to switch treatment (both $p < 0.001$). Compared with Group 2, Group 1 was more likely to undergo 30-day all-cause readmission [OR = 1.38 (95% CI 1.06–1.80), $p = 0.02$], whereas this was less likely for Group 3 [OR = 0.77 (95% CI 0.58–1.00), $p = 0.05$].

Conclusions Patients receiving ceftaroline more often had favorable clinical responses than those receiving vancomycin or daptomycin monotherapy. In the absence of large-scale randomized controlled trials, these real-world data provide insights into the potential role of ceftaroline for treating MRSA bacteremia.

Key Points

In this large real-world study, patients with MRSA bacteremia receiving ceftaroline fosamil monotherapy more often had favorable clinical responses than those receiving vancomycin or daptomycin monotherapy.

Combination therapy with two or more of the antibiotics ceftaroline fosamil, vancomycin, and daptomycin was generally associated with improved outcomes versus any agent as monotherapy in patients with MRSA bacteremia.

These hypothesis-generating results provide real-world insights into ceftaroline fosamil as a potential MRSA bacteremia treatment option.

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1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to represent a significant public health challenge, estimated to result in more than 80,000 invasive infections and 11,000 deaths every year in the USA alone [1]. MRSA bacteremia is associated with substantial morbidity and mortality, and compared with methicillin-susceptible *S. aureus* (MSSA) bacteremia, MRSA bacteremia is associated with an increased risk of 30-day readmission for bacteremia recurrence, in-hospital mortality, and longer hospitalization [2].

Vancomycin and daptomycin are currently recommended as first-line therapies for treating MRSA bacteremia [3]. However, limitations have been reported for both agents. Increasing reports of vancomycin failures, attributed to elevated vancomycin minimum inhibitory concentrations (MICs), and the emergence of reduced-vancomycin-susceptibility phenotypes have led to increased utilization of newer agents for the treatment of MRSA bacteremia [4, 5]. Daptomycin is often the preferred therapy choice for MRSA bacteremia caused by strains with elevated MICs to vancomycin (> 2 mg/L). However, rising daptomycin MICs have also been observed on treatment [6, 7].

The Infectious Diseases Society of America (IDSA) is currently developing new guidelines for *S. aureus* bacteremia [8]. Based on the existing IDSA guidelines, if MRSA bacteremia persists for approximately 7 days, it is recommended that patients be assessed to determine whether a change in therapy is appropriate [3]. However, no clear alternative or salvage regimen is proposed. Therefore, there is a clear need for evidence guiding alternative therapy options.

Several studies have demonstrated improved outcomes in the treatment of MSSA bacteremia with beta(β)-lactams versus vancomycin [9–13]. Clinical superiority of β-lactams compared with vancomycin in MSSA bacteremia may be partially explained by the observed pharmacodynamic synergy of β-lactams with the innate immune system—a synergy that seems to be absent among the non-β-lactam agents typically used for the treatment of MRSA [12, 14, 15].

Ceftaroline fosamil is the pro-drug of ceftaroline, a fifth-generation cephalosporin (β-lactam), which has potent in vitro activity against MRSA [16]. Ceftaroline fosamil was the first widely approved β-lactam agent with activity against MRSA. It is approved in Europe and several other countries for the treatment of adults and children with complicated skin and soft tissue infections (cSSTI), including those caused by MRSA, and for community-acquired pneumonia (CAP; MSSA only) [17]; with similar approved indications in the USA [18].

Studies evaluating clinical outcomes with ceftaroline fosamil in patients with MRSA bacteremia, either as monotherapy [19] or combination therapy [15, 20, 21], suggest that it may be a useful treatment option for MRSA bacteremia, including refractory cases and those who have failed prior antimicrobial therapy, but most investigations have been limited by small sample sizes. Owing to the frequently severe disease status and poor outcomes of MRSA bacteremia, there is also interest in combinations of anti-MRSA treatments in this setting. A recent retrospective matched cohort study of 171 patients with MRSA bacteremia reported a lower 30-day mortality rate in patients receiving ceftaroline fosamil plus daptomycin within 72 h of index culture (8.3%), versus those receiving standard care (vancomycin or daptomycin; 14.2%) [22].

Geriak et al. (2019) prospectively investigated outcomes in MRSA bacteremic patients treated with ceftaroline fosamil plus daptomycin versus standard of care vancomycin or daptomycin monotherapy [15]. Results for the small numbers of patients studied showed that initial therapy with ceftaroline fosamil plus daptomycin was associated with reduced in-hospital mortality compared with vancomycin or daptomycin monotherapy in patients with MRSA bacteremia. However, the unexpected higher mortality incidence in the monotherapy treatment groups resulted in early termination of the study.

The objective of this large retrospective, observational study was to explore the outcomes of patients treated for MRSA bacteremia with ceftaroline fosamil, vancomycin, or daptomycin, according to whether they were administered separately or in combination.

2 Methods

2.1 Study Design and Patients

This retrospective observational study utilized US hospital services and discharge data from the Premier Healthcare Database from July 2011 to March 2019. Premier is the largest hospital-based database in the USA, with data from more than 208 million unique patients. It is geographically diverse, with hospitals in the database representing the four US Census geographic regions and their respective divisions, and includes both teaching and non-teaching institutions, as well as urban and rural facilities [23]. Ethics committee approval was not required, as this was a retrospective secondary database study.

Adult patients who were hospitalized with MRSA bacteremia; were treated with intravenous ceftaroline fosamil, vancomycin, or daptomycin; and had a hospital stay longer than 1 day were included. Patients transferred from other healthcare facilities or in a hospice and those with a hospital stay longer than 3 months were excluded; this criterion was chosen to exclude patients with persistent or recurrent infections.

Patients were classified into three mutually exclusive treatment groups (Fig. 1): Group 1, ceftaroline fosamil (no concurrent vancomycin or daptomycin, but therapy could be accompanied by any other treatment); Group 2, vancomycin or daptomycin (no concurrent ceftaroline fosamil or ceftobiprole, and vancomycin could not be administered concurrently with daptomycin, but therapy could be accompanied by any other treatment); or Group 3, combination therapy with at least two of the following agents: ceftaroline fosamil, vancomycin, or daptomycin (therapy could be accompanied by any other treatment). For patients who received both ceftaroline fosamil monotherapy and combination therapy, the treatment that was given first (of the two regimens) determined treatment group assignment. Patients who received either vancomycin or daptomycin but did not receive ceftaroline fosamil monotherapy or combination therapy at any time during the hospital stay were classified as Group 2. This approach was used, as studies have shown that ceftaroline fosamil alone or in combination with vancomycin or daptomycin may represent a promising salvage therapy for MRSA bacteremia [15, 19–21]. Vancomycin plus daptomycin combination therapy was also included so that all possible treatment combinations for eligible patients were incorporated into the analysis.

The index hospitalization was defined as the last hospitalization with a diagnosis of bacteremia and MRSA infection in which a patient had no prior hospitalization with MRSA bacteremia during the preceding 30 days. The index date was defined as the date of intravenous treatment with one or more of the three anti-MRSA agents of interest during the index hospitalization. Assignment of the index date used a hierarchy approach in which Group 1 and Group 3 were prioritized equally, as vancomycin and daptomycin are the

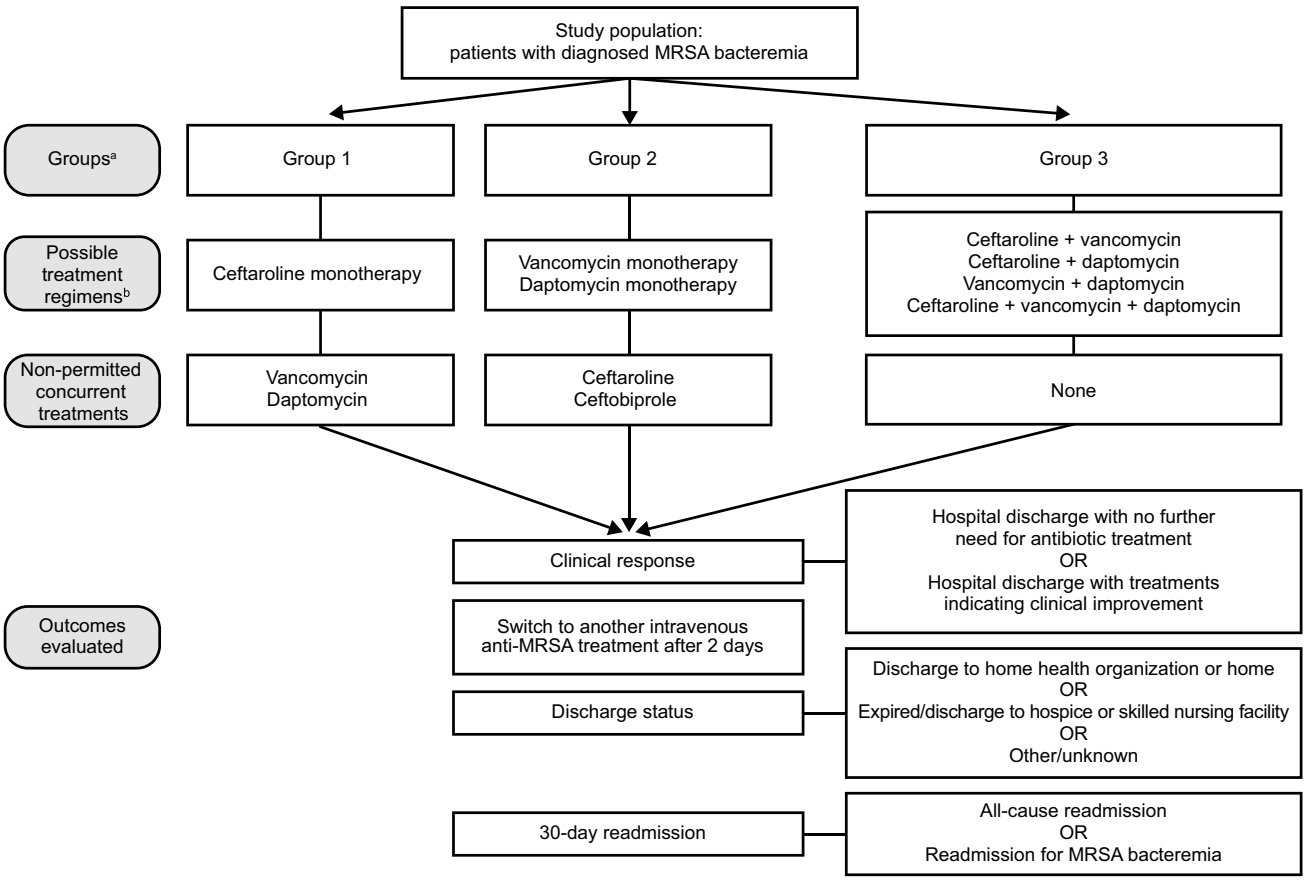

Fig. 1 Study design and outcomes assessed. [a]For patients who received both ceftaroline fosamil monotherapy and combination therapy, the treatment regimen that was given first determined treatment group assignment. Patients who did not receive ceftaroline fosamil monotherapy or combination therapy at any time during the hospital stay, but did receive vancomycin monotherapy or daptomycin monotherapy, were assigned to Group 2. [b]Group 1, ceftaroline fosamil (no concurrent vancomycin or daptomycin, but therapy could be accompanied by any other treatment); Group 2, vancomycin or daptomycin (no concurrent ceftaroline fosamil or ceftobiprole, and vancomycin could not be administered concurrently with daptomycin, but therapy could be accompanied by any other treatment); or Group 3, combination therapy with at least two of the following agents: ceftaroline fosamil, vancomycin, or daptomycin (therapy could be accompanied by any other treatment)

only two agents recommended for MRSA bacteremia in the IDSA guidelines [3].

Outcomes assessed included clinical response, switch to another intravenous anti-MRSA therapy, discharge status, and 30-day readmission (Fig. 1). Clinical response was defined as a composite measure of hospital discharge with no further need for antibiotic treatment or with specific treatments indicating clinical improvement (i.e., oral antibiotics, or intravenous treatment with dalbavancin or oritavancin on day of discharge). Discharge endpoints were combined on the basis of clinical equivalence.

2.2 Statistical Analyses

Clinical outcomes were compared for patients with MRSA bacteremia treated with ceftaroline fosamil, vancomycin, and daptomycin.

Descriptive analyses were performed for all patient and hospital characteristics and all clinical outcome variables. Dichotomous and categorical measures were summarized as frequencies and percentages. Continuous measures were summarized using summary statistics.

Bivariate analyses were conducted to test for significant differences between the treatment groups. For dichotomous and categorical measures, Chi-squared tests or Fisher's exact tests (for any expected values below 5) were used to test for differences between groups. For continuous measures, *t*-tests or Wilcoxon rank sum tests were utilized to test for differences in two-sample comparisons.

Propensity scores were used to balance the distribution of patient characteristics in the treatment groups. Logistic regression was used to create separate propensity scores predicting the probability of treatment with a specific regimen were calculated from patient demographics, patient clinical characteristics and history, and hospital characteristics. Propensity score distributions were graphically examined for overlap between the treatment groups to verify that comparable cohorts with balanced characteristics were created. In addition, baseline characteristics were compared by stratifying the propensity score by quintiles. Each propensity score was included as a covariate in the relevant multivariable model. Clinical outcomes were compared using propensity-score-adjusted odds ratios (ORs) from logistic regression models; outcomes were compared separately for Group 1 versus Group 2, Group 3 versus Group 2, and Group 3 versus Group 1.

Additionally, two subgroup analyses were conducted. The first subgroup analysis evaluated all clinical outcomes for each of the four possible combination therapy regimens in Group 3 compared with Group 1 and Group 2, separately. The second subgroup analysis evaluated readmission outcomes (30-day readmission for any cause and for MRSA bacteremia) in Group 1 according to line of ceftaroline fosamil therapy. Analyses were repeated as described above.

As the time of administration of therapy was not recorded in the Premier database, sensitivity analyses were performed including only patients who receive ≥ 2 consecutive days of the same treatment regimen for treatment group assignment, and for all anti-MRSA therapies (for patients switching to another treatment and/or receiving combination treatment), to address potential misclassification of exposure and of line of therapy.

3 Results

In total, 24,479 patients with MRSA bacteremia were included (Group 1, $n = 532$; Group 2, $n = 21{,}555$; Group 3, $n = 2392$; Table 1). Of patients receiving combination therapy, 371 (15.5%) received ceftaroline fosamil plus vancomycin, 158 (6.6%) received ceftaroline fosamil plus daptomycin, and 1863 (77.9%) received vancomycin plus daptomycin. No patients were recorded as receiving all three treatments concurrently (Table 2). Demographic and clinical characteristics of patients with MRSA bacteremia are shown in Table 1. The majority of patients in all groups were male. Group 3 was, on average, younger, with fewer comorbidities compared with Groups 1 and 2. Endocarditis, diabetes mellitus, and chronic kidney disease were more common in patients in Group 1 than in Groups 2 and 3 (Table 1), and mean Charlson Comorbidity Index score was also higher in patients in Group 1. A larger proportion of patients in Group 1 had documented MRSA infection within the past year versus patients in Groups 2 and 3.

Treatment characteristics of patients included in the analysis are shown in Table 2. In Group 1, ceftaroline fosamil was administered as first-line therapy to 42.1% of patients and as third-line or later to 41.4% of patients, whereas in Group 2, vancomycin or daptomycin were administered as first-line to 95.4% and as third-line or later to 1.7% of patients. In Group 3, combination therapy was administered as third-line or later to most (67.8%) patients.

3.1 Primary Analyses

Clinical outcomes are shown in Table 3. No difference was observed in clinical response when comparing the ceftaroline fosamil group or combination therapy group to the vancomycin/daptomycin group (OR = 1.18 (95% CI 0.98–1.44), $p = 0.08$ and OR = 1.20 (95% CI 0.97–1.47), $p = 0.09$, respectively]. However, the ceftaroline fosamil group and combination therapy group were less likely to switch treatment (both $p < 0.001$) compared with the vancomycin/daptomycin group. Compared with the vancomycin/daptomycin

Table 1 Demographic and baseline clinical characteristics of patients with MRSA bacteremia

Characteristic	Ceftaroline fosamil monotherapy (Group 1) $n = 532$	Vancomycin or daptomycin monotherapy (Group 2) $n = 21{,}555$	Combination therapy (Group 3) $n = 2392$
Mean (SD) age, years	59.6 (17.0)	60.8 (17.5)	57.4 (17.4)[a,b]
Gender, *n* (%)			
Male	320 (60.2)	12,496 (57.7)	1489 (62.3)[b]
Female	212 (40.0)	9127 (42.3)	903 (37.8)
Unknown	0 (0)	2 (0.01)	0 (0)
Race, *n* (%)			
White	364 (68.4)	15,260 (70.8)	1728 (72.2)
Black	99 (18.6)	3813 (17.7)	369 (15.4)[a,b]
Other	61 (11.5)	2324 (10.8)	283 (11.8)
Unknown	8 (1.5)	158 (0.7)	12 (0.5)
MRSA infection in past year, *n* (%)	201 (37.8)[c]	4241 (19.7)	574 (24.0)[a,b]
Treatment with ceftaroline fosamil in past 3 months, *n* (%)	100 (18.8)[c]	0 (0)	49 (2.1)[a,b]
Treatment with vancomycin or daptomycin in past 3 months, *n* (%)	133 (25.0)	5499 (25.5)	642 (26.8)
In ICU during hospitalization, *n* (%)	99 (18.6)	3632 (16.9)	426 (17.8)
Inpatient admission through ER, *n* (%)	398 (74.8)	17,160 (79.6)	1874 (78.3)
CCI score, mean (SD)	3.0 (3.2)[c]	2.3 (3.0)	2.0 (2.8)[a,b]
Cancer, *n* (%)	26 (5.0)	1405 (6.5)	132 (5.5)
CKD, *n* (%)	244 (45.9)[c]	7535 (35.0)	712 (29.8)[a,b]
COPD, *n* (%)	71 (13.4)	2529 (11.7)	214 (9.0)[a,b]
Diabetes mellitus, *n* (%)	223 (41.9)[c]	6404 (29.7)	643 (26.9)[a,b]
Endocarditis, *n* (%)	42 (7.9)[c]	637 (3.0)	102 (4.3)[a,b]
Hemodialysis, *n* (%)	59 (11.1)	2043 (9.5)	132 (5.5)[a,b]
HIV, *n* (%)	6 (1.1)	159 (0.7)	23 (1.0)
Liver disease, *n* (%)	47 (8.8)	1493 (6.9)	178 (7.4)
Neutropenia, *n* (%)	3 (0.56)	237 (1.1)	28 (1.2)
Opioid use, *n* (%)	33 (6.2)	1030 (4.8)	137 (5.7)[a]
Osteomyelitis, *n* (%)	78 (14.7)[c]	1725 (8.0)	243 (10.2)[a,b]
Pneumonia, *n* (%)	90 (16.9)[c]	2923 (13.6)	257 (10.7)[a,b]

CCI Charlson Comorbidity Index, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disorder, *ER* emergency room, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *MRSA* methicillin-resistant *Staphylococcus aureus*, *SD* standard deviation

[a] $p \leq 0.05$ (Group 3 versus 1)

[b] $p \leq 0.05$ (Group 3 versus 2)

[c] $p \leq 0.05$ (Group 1 versus 2)

group, patients in the ceftaroline fosamil group were more likely to require 30-day all-cause readmission [OR = 1.38 (95% CI 1.06–1.80), $p = 0.02$; Table 3].

Compared with the ceftaroline fosamil group, patients in the combination therapy group were more likely to achieve clinical response [OR = 1.38 (95% CI 1.27–1.51), $p < 0.001$], and compared with the ceftaroline fosamil group and vancomycin/daptomycin group, were less likely to switch treatment [OR = 0.09 (95% CI 0.08–0.10), $p < 0.001$ and OR = 0.23 (95% CI 0.19–0. 29), $p < 0.001$, respectively; Table 3]. Compared with the ceftaroline fosamil group, patients in the combination therapy group were also less likely to be discharged to a hospice or skilled nursing facility, or expire in hospital (Table 3).

Sensitivity analyses including only patients who received 2 or more consecutive days of the same treatment regimen included a total of 18,826 patients (Group 1, $n = 440$; Group 2, $n = 17{,}982$; Group 3, $n = 404$). Demographic characteristics were generally similar between patients included in the sensitivity and main analyses. Sensitivity analyses indicated that, for each treatment group, the relative proportions of patients with clinical response and 30-day readmission

Table 2 Treatment characteristics of patients with MRSA bacteremia

Characteristic	Ceftaroline fosamil monotherapy (Group 1) $n = 532$	Vancomycin or daptomycin monotherapy (Group 2) $n = 21,555$	Combination therapy (Group 3) $n = 2392$
Ceftaroline fosamil monotherapy (Group 1), *n* (%)	532 (100.0)	N/A	N/A
Vancomycin or daptomycin monotherapy (Group 2), *n* (%)	N/A	21,555 (100.0)	N/A
Vancomycin monotherapy	N/A	20,146 (93.5)	N/A
Daptomycin monotherapy	N/A	1409 (6.5)	N/A
Combination therapy (Group 3), *n* (%)	N/A	N/A	2392 (100.0)
Ceftaroline fosamil + vancomycin	N/A	N/A	371 (15.5)
Ceftaroline fosamil + daptomycin	N/A	N/A	158 (6.6)
Vancomycin + daptomycin	N/A	N/A	1863 (77.9)
Ceftaroline fosamil + vancomycin + daptomycin	N/A	N/A	0
Line of therapy, *n* (%)			
1	224 (42.1)	20,566 (95.4)	431 (18.0)
2	88 (16.5)	630 (2.9)	339 (14.2)
3+	220 (41.4)	359 (1.7)	1622 (67.8)
Treatment with vancomycin monotherapy prior to receiving index treatment in same hospitalization, *n* (%)	231 (43.4)	N/A	1804 (75.4)
Treatment with daptomycin monotherapy prior to receiving index treatment in same hospitalization, *n* (%)	80 (15.0)	N/A	290 (12.1)
Mean (SD) duration of treatment, days	6.7 (6.9)	6.9 (6.0)	1.9 (3.1)
Mean (SD) overall length of stay: overall, days	13.8 (11.4)	11.2 (9.8)	14.4 (11.8)
Mean (SD) length of stay prior to treatment initiation, days	4.0 (5.6)	1.4 (3.4)	5.5 (6.6)
Mean (SD) length of stay post index treatment, days	8.8 (9.2)	8.8 (8.9)	8.0 (9.5)
Mean (SD) duration of previous MRSA therapy (with vancomycin or daptomycin monotherapy) prior to receiving index treatment, days	4.0 (4.1)	N/A	4.7 (4.7)

N/A not applicable, *MRSA* methicillin-resistant *Staphylococcus aureus*, *SD* standard deviation

(all-cause and for MRSA bacteremia) were similar to those of the original analyses. The proportions of patients who switched treatment were numerically slightly lower in each group in the sensitivity analysis compared with the main analysis (Table S1).

When sensitivity analysis criteria were applied, patients in the combination therapy group had a lower probability of clinical response compared with both the ceftaroline fosamil group and the vancomycin/daptomycin group (both $p < 0.05$; Table S1). Additionally, while the original analysis results showed patients in the ceftaroline fosamil group to be more likely to require 30-day all-cause readmission versus the vancomycin/daptomycin group, results of the sensitivity analyses did not support an association (all $p > 0.05$; Table S1).

3.2 Subgroup Analyses

Results of the subgroup analyses are provided in Tables S2 and S3. Subgroup analysis of 30-day all-cause and MRSA bacteremia-related readmission outcomes in the ceftaroline fosamil group indicated that readmissions were not significantly affected by the ceftaroline fosamil line of therapy. Results of the sensitivity subgroup analyses were broadly consistent with those of the main subgroup analyses, although there were occasional instances where results which previously met significance criteria were no longer significant once sensitivity analyses criteria were applied (data not shown).

4 Discussion

This retrospective study compared outcomes in patients with MRSA bacteremia treated with ceftaroline fosamil versus the non-β-lactam anti-MRSA agents, vancomycin and daptomycin; to our knowledge it is the largest real-world MRSA bacteremia study on this topic to date. Ceftaroline fosamil monotherapy was shown to result in a similar probability of favorable clinical outcomes to those of vancomycin or daptomycin monotherapy, with patients receiving ceftaroline fosamil monotherapy less likely to switch antibiotic

Table 3 Clinical outcomes for patients with MRSA bacteremia: propensity-score-adjusted models

Characteristic	Ceftaroline fosamil monotherapy (Group 1) $n = 532$	Vancomycin or daptomycin monotherapy (Group 2) $n = 21{,}555$	Combination therapy (Group 3) $n = 2392$	Group 1 versus 2		Group 3 versus 1		Group 3 versus 2	
				Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Clinical response[a], *n* (%)	239 (44.9)	10,500 (48.7)	928 (38.8)	1.18 (0.98, 1.44)	0.08	1.38 (1.27, 1.51)	< 0.0001	1.20 (0.97, 1.47)	0.09
Treatment switch, *n* (%)	187 (35.2)	3430 (15.9)	1661 (69.4)	0.34 (0.28, 0.42)	< 0.0001	0.09 (0.08, 0.10)	< 0.0001	0.23 (0.19, 0.29)	< 0.0001
30-day readmission: all-cause, *n* (%)	88 (16.5)	4240 (19.7)	467 (19.5)	1.38 (1.06, 1.80)	0.02	0.98 (0.88, 1.10)	0.77	0.77 (0.58, 1.00)	0.05
30-day readmission: for MRSA bacteremia, *n* (%)	7 (1.3)	278 (1.3)	45 (1.9)	0.95 (0.42, 2.18)	0.91	0.73 (0.53, 1.0)	0.07	0.81 (0.35, 1.87)	0.62
Discharge status									
Expired/discharge to hospice or to skilled nursing facility	162 (30.5)	7416 (34.4)	668 (27.9)	1.00 (0.80, 1.24)	0.98	0.88 (0.80, 0.98)	0.01	1.03 (0.81, 1.31)	0.80
Other/unknown	109 (20.5)	3670 (17.0)	449 (18.8)	1.15 (0.89, 1.49)	0.28	1.03 (0.92, 1.16)	0.62	0.93 (0.71, 1.22)	0.60
Discharge to HHO/home	261 (49.1)	10,469 (48.6)	1275 (53.3)	Ref	Ref	Ref	Ref	Ref	Ref

CI confidence interval, *HHO* home health organization, *MRSA* methicillin-resistant *Staphylococcus aureus, Ref* reference group, *SD* standard deviation

[a]Defined as a composite measure of hospital discharge with no further need for antibiotic treatment or with specific treatments indicating clinical improvement (i.e., oral antibiotic(s) or specific intravenous agents)

treatment. Patients receiving ceftaroline fosamil monotherapy were shown to be more likely to require 30-day all-cause readmission, compared with those receiving vancomycin or daptomycin monotherapy. However, when sensitivity analysis criteria were applied (analysis included only patients who received 2 or more consecutive days of the same treatment regimen), there was a similar probability of 30-day all-cause readmission both in patients receiving ceftaroline fosamil monotherapy and in patients receiving any combination therapy, compared with vancomycin or daptomycin monotherapy. Of note, ceftaroline fosamil was more frequently used as third-line or later therapy than vancomycin or daptomycin (41.4% versus 1.7%, respectively); however, subgroup analysis showed that 30-day readmission outcomes in Group 1 were not significantly affected by the ceftaroline fosamil line of therapy.

Combination therapy with two of the three antibiotics assessed was generally associated with improved outcomes versus any agent as monotherapy; patients receiving any combination therapy were more likely to achieve clinical response and were less likely to switch treatment. Furthermore, subgroup analyses of the specific Group 3 combinations that patients received indicated that, compared with vancomycin or daptomycin monotherapy, each of the combination regimens had generally consistent associations with improved clinical response. Statistical significance of this result was borderline for the ceftaroline fosamil plus daptomycin combination; however, this is not unexpected given that patients receiving this regimen consisted of the smallest sample size in the study. In contrast, patients receiving ceftaroline fosamil plus vancomycin were more likely to achieve a clinical response than those receiving ceftaroline fosamil monotherapy. For those receiving vancomycin

plus daptomycin or ceftaroline fosamil plus daptomycin, the likelihood of clinical response was generally similar versus ceftaroline fosamil monotherapy.

Possible reasons for the overall improved outcomes with combination versus monotherapy include synergy between the agents used in combination, potentially as a result of an increase in penicillin-binding protein inhibition. The activity of daptomycin against MRSA has been shown to be enhanced in the presence of β-lactam antibiotics [24, 25]. Additionally, synergistic mechanisms have been observed in vitro when ceftaroline fosamil is added to daptomycin [26]. Indeed, a previous retrospective, comparative cohort study found that combination therapy with daptomycin and a β-lactam, including ceftaroline fosamil, resulted in improved clinical outcomes versus daptomycin alone, in patients with MRSA bacteremia [27]. However, of note in the present study, no significant improvement in clinical response was observed with ceftaroline fosamil plus daptomycin combination therapy versus ceftaroline fosamil alone.

There has been an emergence of clinical MRSA isolates with reduced vancomycin susceptibility, considered to be due in part to increased vancomycin use [28, 29]. Combination therapy may therefore offer an alternative option for treating these infections. In vitro data have shown enhanced antibacterial activity of vancomycin and cephalosporin combinations against MRSA strains with decreased susceptibility to vancomycin versus vancomycin alone [30].

Combination therapy with vancomycin and a β-lactam has also been shown to lead to significantly fewer treatment failures than vancomycin monotherapy for MRSA bacteremia [31]. However, some studies have found no significant advantages in microbiologic or clinical efficacy as a result of using vancomycin in combination with other antibiotics [32].

Our study, investigating outcomes of ceftaroline fosamil, daptomycin, or vancomycin, alone or in combination, is conducted on a far larger scale than other real-world studies, analyzing data for just under 25,000 patients. Furthermore, unlike some other retrospective studies, the present study compares a number of clinical outcomes (including response, treatment switch, and 30-day readmission rates) for more than two treatment groups, thus further adding to published data.

In the CAMERA-1 pilot randomized controlled trial (RCT), a trend toward a reduction in the duration of MRSA bacteremia infection was observed in patients who received combination therapy of vancomycin plus flucloxacillin versus patients receiving vancomycin monotherapy, although the study was not powered for superiority [33]. In the larger, adequately powered, CAMERA-2 RCT, the addition of an anti-staphylococcal β-lactam (flucloxacillin, cloxacillin, or cefazolin) to vancomycin or daptomycin did not significantly reduce the primary composite end point of mortality, bacteremia, relapse, or treatment failure (35% versus 39%, respectively) [34]. Of note, this study was terminated early because of an increased risk of acute kidney injury in the combination therapy group. A subsequent analysis from the study found that increasing vancomycin exposure, even within the therapeutic range and regardless of concomitant anti-staphylococcal β-lactam use, was associated with an increasing probability of acute kidney injury [35]. As a result of the early termination of the main study, the study may not have been sufficiently powered to detect any improvement in the composite primary end point; however, the authors note that it is probable that any potential gains in efficacy with combination therapy would be offset by an increase in toxicity [34]. It is therefore important to consider that, while combination therapies may be beneficial, certain therapeutic combinations may lead to unexpected adverse events. The fact that these studies did not lead to conclusions on the value of combining a β-lactam with vancomycin also reiterates the need to supplement the available RCT data with evidence from real-world clinical settings.

Planned and currently ongoing studies, including the *Staphylococcus aureus* bacteremia Network Adaptive Platform (SNAP) RCT [36], which is evaluating a range of interventions in patients with *S. aureus* bacteremia, should also provide additional insights into the benefits of various treatment options in this patient population.

The high probability of a clinical response observed with ceftaroline fosamil in this study is consistent with previous observational studies of ceftaroline fosamil for the treatment of MRSA bacteremia, which have reported generally favorable outcomes, and highlighted that ceftaroline fosamil may be useful in the setting of salvage therapy after other antibiotic treatments have failed [19–21, 37–43].

A strength of this large database study is that the data obtained may be more representative of real-world use of these antibiotics in patients, compared with patients enrolled in controlled trials with restrictive study eligibility criteria. The retrospective design, intended for hypothesis generation, represents a limitation of this study; as this is a secondary database study, patients were not followed up for safety outcomes (including mortality) subsequent to hospital discharge, potentially resulting in underestimation of mortality and other adverse events. Underlying differences between the groups also limit outcomes comparisons in this observational study, as unlike in randomized clinical trials or case-control studies, matching the treatment groups for all baseline characteristics is not possible. Furthermore, it is an inherent limitation of observational data that there is no control over unmeasured potentially confounding factors, such as prior therapies received. Additionally, while Premier is one of the most comprehensive hospital discharge and services databases available, the database is nonetheless a

convenience sample, which could result in estimates with unknown biases. The patient inclusion criteria also have implications for bias. The requirement of patients to have certain characteristics to qualify for study inclusion may have resulted in potential selection bias, specifically immortal time bias (survivor bias), as patients must have survived or not have been transferred to another healthcare facility and received treatment to be included. Finally, no adjustments were made for multiplicity in this analysis, which could have implications for increased rate of Type I and type II errors.

An additional limitation is that the evaluated outcome of clinical improvement was based on patient outcomes and discharge status only, as patient clinical assessment information is not available in the Premier Healthcare Database. A further limitation is that the reason(s) for treatment regimen switch was not recorded and is therefore unknown; potential reasons may have included cost considerations, patient response, treatment , and/or other clinical factors, such as co-infections in addition to MRSA bacteremia.

5 Conclusion

The scope of this study focuses on three specific anti-MRSA agents for the treatment of MRSA bacteremia among hospitalized patients. Considerations outside of the scope of the current study include combination therapies consisting of agents other than ceftaroline fosamil, vancomycin, and daptomycin; polymicrobial infections; and patients treated in a hospice setting. Accordingly, any interpretations of these results are limited to the type of infection, treatments, and patient population covered in this study. While the findings are hypothesis-generating, in the absence of large-scale RCTs, these real-world observational data provide insights into the potential role of ceftaroline fosamil as a treatment option for MRSA bacteremia.

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Declarations

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Conflict of Interests Jennifer Hammond, Michael Benigno, Wajeeha Ansari, and Jennifer Nguyen are employees of, and shareholders in, Pfizer. Nataly Bleibdrey is a former employee of Pfizer.

Availability of Data and Material Data queries should be addressed to Premier Inc., which is an independent third party with rights to data availability in the Premier Healthcare Database. These data are proprietary, and the authors do not have permission to disseminate them; however, they can be obtained from the vendor at a cost. Please contact the vendor for additional information.

Ethics Approval Ethics committee approval was not required, as this was a retrospective secondary database study.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

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