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Outcomes of outpatient parenteral antimicrobial therapy with ceftriaxone for methicillin-susceptible Staphylococcus aureus bloodstream infections—a single-center observational study

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Outcomes of Outpatient Parenteral Antimicrobial Therapy With Ceftriaxone for Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections—A Single-Center Observational Study

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Background. *Staphylococcus aureus* bloodstream infections (BSIs) are associated with significant morbidity and mortality. Ceftriaxone is convenient for outpatient parenteral antimicrobial therapy (OPAT), but data for this indication are limited.

Methods. Adult patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) BSI discharged on OPAT with cefazolin, oxacillin, or ceftriaxone for at least 7 days were included. We compared outcomes of ceftriaxone vs either oxacillin or cefazolin. Ninety-day all-cause mortality, readmission due to MSSA infection, and microbiological failure were examined as a composite outcome and compared among groups. Rates of antibiotic switches due to intolerance were assessed.

Results. Of 243 patients included, 148 (61%) were discharged on ceftriaxone and 95 (39%) were discharged on either oxacillin or cefazolin. The ceftriaxone group had lower rates of intensive care unit care, endocarditis, and shorter duration of bacteremia, but higher rates of cancer diagnoses. There was no significant difference in the composite adverse outcome in the oxacillin or cefazolin group vs the ceftriaxone group (18 [19%] vs 31 [21%]; $P = .70$), comprising microbiological failure (6 [6.3%] vs 9 [6.1%]; $P = .94$), 90-day all-cause mortality (7 [7.4%] vs 15 [10.1%]; $P = .46$), and readmission due to MSSA infection (10 [10.5%] vs 13 [8.8%]; $P = .65$). Antibiotic intolerance necessitating a change was similar between the 2 groups (4 [4.2%] vs 6 [4.1%]; $P = .95$).

Conclusions. For patients with MSSA BSI discharged on OPAT, within the limitations of the small numbers and retrospective design we did not find a significant difference in outcomes for ceftriaxone therapy when compared with oxacillin or cefazolin therapy.

Keywords. cefazolin; ceftriaxone; MSSA bacteremia; OPAT; oxacillin.

Staphylococcus aureus is a leading cause of both community-onset and hospital-acquired bloodstream infections (BSIs) [1]. *S. aureus* BSI is often associated with complications such as dissemination to distant sites and endocarditis, consequently leading to morbidity and mortality [2]. Due to the risk of recurrence, prolonged parenteral therapy with a beta-lactamase-resistant penicillin (nafcillin or oxacillin) or cefazolin is the guideline-suggested care to treat methicillin-susceptible *S. aureus* (MSSA) BSI [3]. Ceftriaxone has been shown to be an effective treatment for serious MSSA infections in previous studies and has a Food and Drug Administration–labeled indication for MSSA septicemia [4, 5]. A retrospective study of 124 patients with MSSA bone and joint infections at our institution comparing ceftriaxone vs oxacillin found that ceftriaxone had similar rates of success and was better tolerated than oxacillin [6]. Few studies have compared ceftriaxone with either nafcillin or cefazolin in MSSA BSIs. In a study by Patel et al., clinical and microbiological cure rates were similar among 51 patients treated with nafcillin or cefazolin and 42 patients treated with ceftriaxone [7]. Carr et al. reported more adverse outcomes in 33 patients with MSSA BSI treated with ceftriaxone compared with 38 treated with cefazolin, but the 2 groups were different, with many of the patients in the ceftriaxone group being sent to skilled nursing facilities that had higher readmission rates [8].

The optimal choice of beta-lactam therapy for MSSA bloodstream infection is unclear. When compared with nafcillin, oxacillin, or cefazolin, ceftriaxone has benefits in terms of lower costs, once- or twice-daily administration, and a favorable long-term side effect profile, making it an attractive drug for outpatient parenteral antibiotic therapy (OPAT) [4, 6]. Whether once- or twice-daily ceftriaxone therapy results in acceptable outcomes for patients with MSSA BSI is an open question [9, 10]. This study compared outcomes of MSSA BSI among patients discharged on ceftriaxone compared with oxacillin or cefazolin.

METHODS

Study Design and Patient Population

We performed a retrospective cohort study of adults with MSSA BSI who were discharged from Barnes-Jewish Hospital on OPAT and followed by the Washington University Infectious Disease service over a 4.5-year period from December 1, 2014, to April 30, 2019. Barnes-Jewish Hospital is a 1350-bed tertiary care medical center located in St. Louis, Missouri. Patients were identified from the OPAT registry, which includes all patients who are seen by Infectious Disease physicians and discharged on parenteral antibiotics. Patients were included if they had ≥1 positive blood culture for MSSA and were discharged on 1 of the 3 antibiotics of interest: ceftriaxone 2–4 g daily, oxacillin 2 g every 4 hours, or cefazolin 2 g every 8 hours or equivalent, adjusted for renal injury (of note, nafcillin is not on the hospital formulary). If the patient had multiple admissions for MSSA BSI, the first admission was included as the index admission. Patients were excluded if they had polymicrobial bloodstream infections, had <7 days of OPAT, or had end-stage renal disease (ESRD) on hemodialysis (HD). HD patients were excluded as they could have been preferentially treated with either cefazolin due to the ease of dosing or ceftriaxone, given that its main route of excretion is not renal. Patients were identified from the Washington University Infectious Diseases OPAT database. All patients were seen by Infectious Disease providers during the index hospitalization.

Clinical Data Collection

Clinical data were collected through review of inpatient and outpatient electronic medical records using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Washington University in St Louis. REDCap is a secure, Web-based software platform designed to support data capture for research studies [11]. Clinical data abstracted by 3 authors (L.C., Y.H., I.A.G.) included demographic characteristics, patient comorbidities, clinical presentation, diagnostic evaluations (including laboratory results, microbiology results, and imaging studies), antibiotics used, and planned duration of treatment. In addition, outpatient clinical parameters assessed in infectious diseases (at 2–3 weeks after discharge and/or at the end of therapy) and surgical subspecialty clinics included signs and symptoms of infection noted during the follow-up visit(s), documentation of adverse events related to antibiotic administration, laboratory data, imaging studies, change or extension of intravenous (IV) antibiotics, and oral suppressive antibiotic recommendations. These data were used to determine whether there was evidence of successful treatment or treatment failure. Outcomes were compared between the 2 groups—those who received oxacillin or cefazolin vs those who received ceftriaxone on discharge.

Variable Definitions

Ninety-day all-cause mortality was defined as death occurring within 90 days of discharge determined by electronic medical record review. Clinical failure was defined as unanticipated readmission or surgical intervention related to MSSA infection within 90 days of discharge from the index admission. Microbiological failure was defined as subsequent isolation of MSSA from any sterile site within 90 days of completion of treatment. The composite outcome for treatment failure was defined by death or clinical or microbiological failure within the specified periods above.

Comorbid conditions were evaluated using the Elixhauser Comorbidity Index, which is based on the *International Classification of Diseases, 9th and 10th Revisions, Clinical Modification* (ICD-9-CM and ICD-10-CM), codes. ICD codes were supplemented by chart review to identify concurrent infections including skin and soft tissue infections, endocarditis, and osteomyelitis, as well as ESRD, central line–associated bloodstream infections (CLABSIs), intravenous drug use, and the presence of prosthetic materials. The primary source of infection was identified from concurrent positive microbiologic specimens for MSSA or based upon consistent clinical signs and symptoms and radiographic evidence. Endocarditis was defined by evidence of a vegetation on cardiac valves identified by echocardiography, along with concomitant MSSA bacteremia, or if the ID physician suspected infective endocarditis and a decision was made to treat as infective endocarditis. The Elixhauser Comorbidity Index (ECI), incorporating comorbidities to predict inpatient mortality, was used as a composite variable to associate risk factors for the composite outcome [12]. Source control was felt to be achieved if the reviewing physician ascertained that the focus of infection had been removed (eg, abscess drained, central venous catheter removed).

Statistical Analysis

Descriptive statistics were used for the demographic and clinical characteristics of the study population. Categorical data were compared using the chi-square test or Fisher exact test, and continuous variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Patients with proven or suspected endocarditis were evaluated as a subgroup, as these were potentially sicker patients. Potential risk factors for treatment failure were analyzed for the 2 groups using univariable and multivariable Cox proportional hazards models. The proportional hazards assumption was evaluated for the outcome variables using visual inspection of log-log survival curves [13]. For the multivariable model, variables were specified by selecting clinically meaningful factors that could potentially be associated with treatment failure, which included comorbidity indices, choice of antibiotics, discharge destination, source control, and evidence of endocarditis. Patients were censored at

the time of last follow-up or 90 days post-treatment, whichever came first.

Statistical significance was set at $P < .05$. All analyses were performed using SAS 9.4 software (Cary, NC, USA).

Patient Consent Statement

The Washington University School of Medicine Human Research Protection Office (HRPO) approved this study. Informed consent was not required for this study according to the HRPO regulations given its minimal risk and retrospective study design.

RESULTS

During the study period, 243 patients with MSSA BSI received 1 of the 3 antibiotics of interest for at least 7 days as part of OPAT. Of these, 148 (61%) received ceftriaxone while 95 (39%) patients received either oxacillin (56) or cefazolin (39). The mean age was 59.6 years, and patients were predominantly male (63%) and White (77%). The most common comorbidities were diabetes mellitus (59 [24%]), solid tumor (51 [21%]), valvular heart disease (50 [21%]), and congestive heart failure (49 [20%]). Over a third of patients (89 [37%]) required intensive care unit care during the index hospitalization, including 40 (16%) who required mechanical ventilation (Table 1). There were 15 (6.2%) patients who were lost to follow-up during the course of the study, 8 (5.4%) in the ceftriaxone group and 7 (7.4%) in the oxacillin-cefazolin group.

Endocarditis complicated many of the BSIs, occurring in 83 (34%) patients. MSSA bacteremias were associated with central venous catheters (CVCs) in 70 (29%) patients and bone and

Table 1. Clinical Characteristics and Outcomes of 243 Patients in the Ceftriaxone and Oxacillin-Cefazolin Treatment Groups

Variable, No. (%) or Median (IQR)	Total (n = 243)	Oxacillin-Cefazolin (n = 95 [39%])	Ceftriaxone (n = 148 [61%])	P Value
Age, y	59.6 (47.8–70)	57.1 (46.4–68.2)	61.3 (48.9–71.5)	.08
Sex (male)	154 (63.4)	61 (64.2)	93 (62.8)	.83
Race (White)	187 (77.4)	73 (76.8)	115 (77.7)	.88
Body mass index, kg/m^2	29.1 (23.5–35.6)	29.1 (24.2–32.9)	27.3 (23.5–33.3)	.84
AIDS	5 (2.1)	1 (1.1)	4 (2.7)	.27
CHF	49 (20.6)	20 (21.7)	29 (19.9)	.73
Diabetes	59 (24.3)	20 (21.1)	39 (26.4)	.35
Acute renal failure in the past year	43 (18.1)	16 (17.4)	27 (18.5)	.83
Solid tumors	51 (21)	8 (8.4)	43 (29.1)	<.01
Hematological malignancies	14 (5.9)	6 (6.5)	8 (5.5)	.74
Valvular heart disease	50 (21)	31 (33.7)	19 (13)	<.01
Length of stay after positive blood culture	9.9 (6.6–16.2)	15.3 (9.9–20.8)	7.4 (5.5–12.2)	<.01
Intensive care unit stay	89 (36.6)	46 (48.4)	43 (29.1)	<.01
Recent hospitalization in the last 30 d	43 (17.7)	18 (19)	25 (16.9)	.68
Ventilator support	40 (16.5)	20 (21.1)	20 (13.5)	.12
Presence of CIED	23 (9.5)	12 (12.6)	11 (7.4)	.18
CIED explanted	7 (30.4)	4 (33.3)	3 (27.3)	.99
LVAD	6 (2.5)	2 (2.1)	4 (2.7)	.32
Transthoracic echocardiography	228 (93.8)	86 (90.5)	142 (95.6)	.09
Transesophageal echocardiography	93 (38.3)	56 (59)	37 (25)	<.01
Source control not achieved	23 (9.5)	9 (9.5)	14 (9.5)	.99
Total IV antibiotic course duration	42 (34–44)	42 (42–44)	42 (28–43)	.01
Inpatient IV antibiotic duration	6 (4–11)	9 (5–15)	5 (4–9)	<.01
OPAT duration	34 (24–39)	34 (27- 39)	34 (24–39)	.70
Discharge to post–acute care facility	83 (34.2)	32 (33.7)	51 (34.5)	.90
Bacteremia duration, d	1.5 (1–2.4)	1.7 (1–2.9)	1.3 (1–2.2)	.04
CVC present	72 (29.6)	21 (22.1)	51 (34.5)	.04
Percentage of CVC removed	67 (93.1)	21 (100)	46 (90.2)	.31
Source/site of infection				
Primary bacteremia	40 (16.5)	13 (13.7)	27 (18.2)	.35
Central line–associated bacteremia	70 (28.8)	22 (23.2)	48 (32.4)	.12
Infection of prosthetic material	26 (10.7)	11 (11.6)	15 (10.1)	.72
Skin & soft tissue infection	33 (13.6)	9 (9.5)	24 (16.2)	.13
Surgical site infections	16 (6.6)	3 (3.2)	13 (8.8)	.05
Osteomyelitis	40 (16.5)	20 (21.1)	20 (13.5)	.12
Septic arthritis/prosthetic joint infection	28 (11.5)	12 (12.6)	16 (10.8)	.66
Epidural abscess	13 (5.4)	6 (6.3)	7 (4.7)	.59
Endocarditis	83 (34.2)	41 (43.2)	42 (28.4)	.02

Table 1. Continued

Variable, No. (%) or Median (IQR)	Total (n = 243)	Oxacillin-Cefazolin (n = 95 [39%])	Ceftriaxone (n = 148 [61%])	*P* Value
Valve replaced	17 (7)	15 (15.8)	2 (1.4)	<.01
Inpatient antibiotics received >48 h				
Ceftriaxone	80 (32)	0	80 (53)	<.01
Oxacillin	53 (21)	40 (41)	13 (9)	<.01
Cefazolin	33 (13)	23 (24)	10 (7)	<.01
Cefepime	3 (1)	0	3 (2)	.28
Meropenem	12 (5)	3 (3)	9 (6)	.38
Piperacillin-tazobactam	8 (3)	2 (2)	6 (4)	.49
Vancomycin	25 (10)	7 (7)	18 (12)	.24
Linezolid	4 (2)	3 (3)	1 (1)	.30
Inpatient laboratory values at discharge				
CRP	145 (68–223)	131 (54–199)	156 (71–234)	.32
ESR	71 (45–95)	71 (38–94)	71 (53–97)	.24
White blood count	7.9 (5.7–10.6)	7.9 (5.6–10)	8 (5.7–10.9)	.75
Platelets	262 (157–367)	295 (159–393)	245 (154–332)	.11
Creatinine clearance	97 (66–132)	88 (54–128)	102 (73–134)	.10
Oral antibiotic suppression after OPAT	44 (18.1)	25 (26)	19 (13)	<.01
Outcomes				
Change in antibiotics due to toxicity	11 (4.5)	4 (4.2)	6 (4.1)	.95
Microbiological failure	15 (6.2)	6 (6.3)	9 (6.1)	.94
90-d all-cause mortality	22 (9.1)	7 (7.4)	15 (10.1)	.46
Readmitted due to MSSA infection	23 (9.5)	10 (10.5)	13 (8.8)	.65
Composite	49 (20.2)	18 (19)	31 (21)	.70

Abbreviations: CHF, congestive heart failure; CIED, cardiovascular implantable electronic device; CRP, C-reactive protein; CVC, central venous catheter; ESR, erythrocyte sedimentation rate; IQR, interquartile range; IV, intravenous; LVAD, Left ventricular assist device; MSSA, methicillin-susceptible *Staphylococcus aureus*; OPAT, outpatient parenteral antimicrobial therapy.

joint infections in 40 (16%) patients and were determined to be primary bacteremia in 40 (16%) patients. Ninety-three percent (67) of CVCs were removed in patients with concurrent bacteremia, and 7 (30%) cardiac implantable electronic devices (CIEDs) were removed. Patients were treated for a median (interquartile range [IQR]) of 42 (34–44) days from the time of culture clearance or source control achievement (Table 1). One hundred thirty-nine patients (93.2%) on ceftriaxone received 2 g daily, while 10 patients (6.8%) received 2 g every 12 hours.

Comparison of the Treatment Groups

Patients in the ceftriaxone and oxacillin-cefazolin groups had similar overall baseline and clinical characteristics. However, the ceftriaxone group had lower rates of intensive care unit care (29.1% vs 48.4%; *P* < .01), shorter duration of bacteremia (1.3 vs 1.7 days; *P* = .04), and shorter intravenous antibiotic duration (median [IQR], 42 [28–43] vs 42 [42–44] days; *P* = .01). The ceftriaxone group also had lower rates of valvular heart diseases (13% vs 33.7%; *P* < .01), TEEs performed (25% vs 59%; *P* < .01), endocarditis (28.4% vs 43.2%; *P* = .02), and subsequent valve replacement surgeries (1.4% vs 15.8%; *P* < .01), but had more solid tumors (29.1% vs 8.4%; *P* < .01) (Table 1). Both groups had similar rates of discharge to post–acute care facilities (34.5% vs 33.7%; *P* = .90). Of patients discharged on IV ceftriaxone, 23 (16%) received oxacillin or cefazolin for more than 48 hours while inpatient. Patients in the oxacillin-cefazolin group were more likely to have received oral antibiotics for suppression

after the end of OPAT (25 [26%] vs 19 [13%]; *P* ≤ .01) (Table 1). The most common antibiotics used for suppression were doxycycline 26 (60%), cephalexin 11 (26%), and trimethoprim/sulfamethoxazole 3 (7%).

Outcomes

The primary composite outcome (death, readmission related to MSSA infection, or microbiological failure within 90 days of hospital discharge) occurred in 49 (20%) of patients. Microbiological failure occurred in 15 (6%), 90-day all-cause mortality occurred in 22 (9%), and hospital readmission due to MSSA infection occurred in 23 (10%) patients. Changes in antibiotics due to toxicity occurred in 11 (4.5%) patients, 6 (4.1%) in the ceftriaxone group and 4 (4.2%) in the oxacillin-cefazolin group (*P* = .95). Toxicities in the ceftriaxone group were skin rashes in 3 patients (1 with concomitant eosinophilia), acute kidney injury in 2, and nausea in 1, while in the oxacillin-cefazolin group, the reasons for switch were neutropenia in 2 patients and acute kidney injury and hepatotoxicity in 1 each. There were no significant differences in microbiological failure (6 [6.3%] vs 9 [6.1%]; *P* = .94), 90-day all-cause mortality (7 [7.4%] vs 15 [10.1%]; *P* = .46), readmission due to an MSSA infection (10 [10.5%] vs 13 [8.8%]; *P* = .65), or composite outcome (18 [19%] vs 31 [21%]; *P* = .70) among the oxacillin-cefazolin and ceftriaxone treatment groups, respectively (Table 1).

Table 2. Multivariable Risk Factors Associated With Treatment Failure (Composite of Death and Clinical/Microbiological Failure)

	Multivariate Analysis		
Variable	Hazard Ratio	95% CI	P Value
Age >65 y	0.907	0.484–1.700	.76
Elixhauser Comorbidity Index	1.015	0.993–1.039	.19
Endocarditis	0.884	0.471–1.660	.70
Lack of source control	1.080	0.426–2.737	.87
Discharged on ceftriaxone	0.994	0.537–1.841	.99
Discharge to post–acute care facility	1.769	0.974–3.214	.06

In the Cox regression model, the use of ceftriaxone was not associated with composite outcome of treatment failure in either univariate (hazard ratio [HR], 1.062; 95% CI, 0.594–1.898) or multivariate analysis (HR, 0.994; 95% CI, 0.537–1.841) (Table 2).

Endocarditis Subgroup

Most patients (228 [94%]) underwent transthoracic echocardiography (TTE), while 93 (38%) underwent transesophageal echocardiography (TEE) to evaluate for endocarditis. Endocarditis was suspected in 83 (34%) patients with concomitant MSSA BSI. Echocardiography confirmed the suspicion in 54 (65%) patients, while 29 (35%) did not have a TEE done and were treated for endocarditis. Forty-two (50.6%) were treated with ceftriaxone, while 41 (49.4%) were treated with oxacillin/cefazolin. When analyzing the endocarditis group, the ceftriaxone group had higher rates of 90-day all-cause mortality (6 [14.3%] vs 1 [2.4%]; P = .11) and composite outcome (11 [25.6%] vs 4 [10%]; P = .17). The risks of microbiological failure and hospital readmission due to MSSA infection did not differ between the 2 groups (Table 3).

DISCUSSION

Although widely accepted as standard treatment for MSSA BSI, the quality of evidence for preferential use of antistaphylococcal beta-lactam antibiotics like oxacillin, nafcillin, or cefazolin is poor and relies mostly on observational data [10]. At our institution, ceftriaxone is increasingly being used to treat MSSA infections. This practice, driven by practical implications of cost and convenience of outpatient treatment, was evaluated in a retrospective review done at our institution of 124 MSSA osteoarticular infections that documented favorable treatment outcomes with ceftriaxone [6, 14].

This study demonstrates that in selected patients discharged on OPAT, ceftriaxone is a viable option for MSSA BSI when compared with oxacillin and cefazolin. We did not detect a difference in the composite outcome for treatment failure (including mortality, readmissions due to infection, and microbiological failure) between the oxacillin/cefazolin group (19%) and the ceftriaxone group (21%; P = .70) (Table 1). These results were very similar to the retrospective study of 93 male patients with MSSA bacteremia by Patel et al., where there were no significant differences between patients treated with ceftriaxone (n = 42) compared with those treated with nafcillin or cefazolin (n = 51) in either microbiological (95.2% vs 94.1%; P = .81) or clinical cure rates (83.3% vs 74.5%; P = .30). Our results conflict with those of Carr et al., who reported significantly higher failure rates among patients with MSSA BSI receiving ceftriaxone (n = 33) compared with cefazolin (n = 38; 54.5% vs 28.9%; P = .029). However, in this study, there were more patients on ceftriaxone who were discharged to an external skilled nursing facility (SNF) as compared with an attached community living center (CLC), which was shown to be a risk factor for treatment failure. The authors argue that the difference could be due to closer monitoring and availability of ID physicians in the attached CLC compared with the SNF. In our study, the rates of discharge to post–acute care facilities (34.5% vs 33.7%; P = .90) were similar in both the comparison groups, but there was a trend for treatment failure in patients discharged to a post–acute care facility (HR, 1.769) (Table 2). Suboptimal outcomes (eg, unplanned hospitalizations or line-associated infections) have been described in patients discharged on OPAT to post–acute care facilities and could indicate a gap in the continuity of care and adequate laboratory monitoring of adverse events [15, 16].

Although there were no significant differences in the failure rates between the 2 groups in our study overall, among the subgroup of patients with endocarditis there was a trend toward more adverse events in the ceftriaxone group (25.6% vs 10%; P = .17). Possible reasons could be that the higher minimal inhibitory concentration distributions of ceftriaxone tend to be associated with a lower MSSA bactericidal

Table 3. Outcomes of the Ceftriaxone Group vs Oxacillin-Cefazolin Group in Patients Diagnosed With Endocarditis

Outcome Variables	Total (n = 83), No. (%)	Oxacillin-Cefazolin (n = 41), No. (%)	Ceftriaxone (n = 42), No. (%)	P Value
Microbiological failure	6 (7.2)	3 (7.3)	3 (7.1)	.99
90-d all-cause mortality	7 (8.4)	1 (2.4)	6 (14.3)	.11
Readmitted due to MSSA infection	6 (7.2)	3 (7.3)	3 (7.1)	.99
Composite	15 (18.1)	4 (10)	11 (25.6)	.17
Change in antibiotics due to toxicity after discharge	1 (1.2)	0	1 (2.4)	.99

Abbreviation: MSSA, methicillin-susceptible *Staphylococcus aureus*.

effect when compared with cefazolin in pharmacodynamics models, and such an effect might have greater implications in endocarditis patients [17]. Our microbiology laboratory tests for cefoxitin susceptibility as a surrogate for cefazolin, ceftriaxone, and oxacillin susceptibilities, consistent with the Clinical and Laboratory Standards Institute guidelines [18]. In a study evaluating pharmacokinetic/pharmacodynamic end points of commonly used antibiotics for *S. aureus*, 5% of MSSA isolates tested were ceftriaxone-nonsusceptible and in a modeling-based prediction tool; for ceftriaxone, only a higher dose of 2000 mg q12h produced a cumulative fraction of response (CFR) ≥90% [19]. Another pharmacologic argument is that ceftriaxone is highly protein bound (up to 95%) and hence has decreased free drug available to exhibit antibacterial activity, especially when maintaining a high serum level is needed to penetrate deeper tissues such as vegetations in endocarditis. However, cefazolin is around 80% protein bound, and oxacillin is around 94% protein bound, so this theory should affect all the 3 antibiotics of interest equally [20]. Although not statistically significant, given the trend for worse outcomes in patients with endocarditis and the plausible pharmacodynamic arguments to explain this, twice-daily ceftriaxone therapy should be further studied in this setting. The overall 90-day mortality (9%) in our cohort was lower when compared with studies in the United States that have reported 90-day mortality (25%–26%) in *S. aureus* bacteremias [17, 21]. This is likely due to the fact that we included patients who survived the inpatient stay and were well enough to be discharged on OPAT.

There are several limitations to this study. This is a retrospective single-center study, and we are unable to prove noninferiority of ceftriaxone. We would need 332 patients in each treatment arm, with estimated 85% survival, accepting a 10% difference in outcomes, to have 95% power (with α = .025) to prove noninferiority [22]. There could be a difference in the treatment outcomes that we are unable to detect due to the relatively small numbers in our study. However, we feel that this reflects a pragmatic comparison of 2 concurrent treatment practices in our institution. We observed significant differences in the baseline characteristics between the 2 treatment groups, likely due to a selection bias of certain infectious disease physicians' preference of using oxacillin/cefazolin for complicated bacteremia. The oxacillin/cefazolin group had a higher proportion of patients with endocarditis (43.2% vs 28.4%; *P* = .02), longer length of stay (median days, 15.3 vs 7.4), and longer duration of bacteremia (median days, 1.7 vs 1.3). Oxacillin/nafcillin and cefazolin are recommended by treatment guidelines endorsed by the Infectious Diseases Society of America for treating MSSA endocarditis, and it is likely that physicians when treating endocarditis follow guideline-recommended antibiotic selection [23]. The ceftriaxone group had fewer cases of endocarditis, and this may have led to outcomes in the ceftriaxone

group being inherently better than in the comparator group. We did not see significant differences in outcomes between treatment groups even after adjusting for different factors including antibiotic choice and endocarditis in the multivariable model. Another limitation is that this study addresses the question of antibiotic choice after discharge from the hospital (OPAT) and does not compare the antibiotic choices made while inpatient. We felt that this was a more relevant question to answer, as ceftriaxone offers more convenient dosing and has a cost advantage, which makes it an attractive option for OPAT [6]. In the study by Wieland et al., the median cost estimate for the antibiotic course was significantly lower in the ceftriaxone group compared with the oxacillin group ($6720 vs $11 329; *P* < .001). We were also not able to make meaningful comparisons regarding the optimal dosing for use of ceftriaxone due to the sparse number of patients (<7%) receiving doses >2 g/d. There is a concern that the broader coverage of ceftriaxone compared with oxacillin and cefazolin would lead to antibiotic resistance and would be against good stewardship practice. Lastly, there is a possibility of poor adherence to OPAT therapy, and this was not measured for the study participants.

Despite these limitations, this is the largest study to date comparing ceftriaxone with other antibiotics of interest in MSSA bacteremia. Infectious Disease physicians saw all included patients, and hence there is some degree of homogeneity in the workup, management, and treatment duration of these patients. In a recent survey of OPAT patients at our institution, receiving a simpler regimen once or twice daily was significantly associated with better adherence when compared with more frequent dosing regimens (76% vs 17% of the adherent and nonadherent groups, respectively; *P* = .01) [24]. Thus, patients are more likely to adhere to ceftriaxone as compared with more frequent dosing regimens of oxacillin or cefazolin. Furthermore, once-daily regimens facilitate patients receiving therapy at an infusion center, which is the only outpatient option for Medicare patients without a significant out-of-pocket cost [22]. The results of this study would be encouraging especially for Medicare patients and for those centers that offer self-directed OPAT, where cost and ease of dosing are important considerations [25, 26].

CONCLUSIONS

Ceftriaxone might be a reasonable alternative for the treatment of patients with MSSA bacteremia discharged on OPAT, and when compared with oxacillin or cefazolin, no significant difference in outcomes was noted in this retrospective study. There was a trend toward adverse outcomes in patients with endocarditis, although it was not statistically significant. Further studies, possibly prospective comparisons, should be undertaken to further document clinical equivalence, optimal dosing, and cost effectiveness of ceftriaxone considering the advantages of ease of dosing and excellent tolerability.

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