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Comparison of Cefazolin versus Oxacillin for Treatment of Complicated Bacteremia Caused by Methicillin-Susceptible *Staphylococcus aureus*

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Contrary to prior case reports that described occasional clinical failures with cefazolin for methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, recent studies have demonstrated no difference in outcomes between cefazolin and antistaphylococcal penicillins for the treatment of MSSA bacteremia. While promising, these studies described low frequencies of high-inoculum infections, such as endocarditis. This retrospective study compares clinical outcomes of cefazolin versus oxacillin for complicated MSSA bacteremia at two tertiary care hospitals between January 2008 and June 2012. Fifty-nine patients treated with cefazolin and 34 patients treated with oxacillin were included. Osteoarticular (41%) and endovascular (20%) sources were the predominant sites of infection. The rates of clinical cure at the end of therapy were similar between cefazolin and oxacillin (95% versus 88%; $P = 0.25$), but overall failure at 90 days was higher in the oxacillin arm (47% versus 24%; $P = 0.04$). Failures were more likely to have received surgical interventions (63% versus 40%; $P = 0.05$) and to have an osteoarticular source (57% versus 33%; $P = 0.04$). Failures also had a longer duration of bacteremia (7 versus 3 days; $P = 0.0002$), which was the only predictor of failure. Antibiotic selection was not predictive of failure. Rates of adverse drug events were higher in the oxacillin arm (30% versus 3%; $P = 0.0006$), and oxacillin was more frequently discontinued due to adverse drug events (21% versus 3%; $P = 0.01$). Cefazolin appears similar to oxacillin for the treatment of complicated MSSA bacteremia but with significantly improved safety. The higher rates of failure with oxacillin may have been confounded by other patient factors and warrant further investigation.

The comparative efficacy of various beta-lactams for the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia has not been clearly defined, particularly in infections with high bacterial burdens. Currently, antistaphylococcal penicillins (ASPs), such as nafcillin and oxacillin, are recommended as first-line agents in the treatment of MSSA infections, with cefazolin reserved as an alternative in patients intolerant of these agents or for dosing convenience (e.g., outpatient parenteral antibiotic therapy or hemodialysis) (1). *In vitro* data have identified that cefazolin may sometimes be subject to an inoculum effect, where cefazolin can be hydrolyzed by increased production of beta-lactamases (2–5). Type A beta-lactamases, in particular, have been hypothesized to contribute to cefazolin treatment failure since they efficiently hydrolyze cefazolin. These reports have demonstrated an increase in MICs for high inocula of MSSA isolates that produce type A beta-lactamases (6, 7). However, only isolated case reports have described clinical failures with cefazolin therapy for MSSA endocarditis, and the clinical relevance of this *in vitro* phenomenon is unclear. Cefazolin does have advantages over ASPs in that it is associated with lower rates of adverse drug events, particularly hepatotoxicity and bone marrow suppression, and is markedly less expensive than ASPs.

Prospective studies directly comparing treatment outcomes between cefazolin and ASPs for MSSA bacteremia are lacking, but data are emerging to support the role of cefazolin as a first-line agent for MSSA bacteremia. Recently, a retrospective, propensity score-matched, case-control study demonstrated no difference in clinical outcomes between the use of cefazolin or nafcillin in the treatment of MSSA bacteremia (8). While promising, only half of the subjects in this study had high bacterial burden infections, defined as MSSA bacteremia accompanied by endocarditis, unremovable vascular graft infection, osteomyelitis, pneumonia, deep-seated abscess, or metastatic infection. Additionally, the matched cohort analysis only included two patients with endocarditis. Therefore, the objective of this study was to compare clinical outcomes of cefazolin versus oxacillin in the treatment of complicated MSSA bacteremia.

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MATERIALS AND METHODS

Study design and participants. This retrospective cohort study was conducted between January 2008 and June 2012 at two tertiary care hospitals in San Antonio, TX. The study protocol was approved by the institutional review board at the University of Texas Health Science Center at San Antonio and the research departments at University Hospital and the South Texas Veterans Health Care System. As part of an antibiotic stewardship initiative at both hospitals, cefazolin has been increasingly recom-

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mended as the antibiotic of choice for MSSA infections since October 2009 (9, 10). Initial recommendations targeted milder infections, such as soft tissue infections, but were eventually extended to patients with more complicated infections. By mid-2010, oxacillin was mainly reserved for patients with central nervous system infections or intolerance to cefazolin.

Patients with ≥1 positive blood culture for MSSA were identified through computerized records and screened for inclusion. Only the first episode of MSSA bacteremia per patient was included in our analysis. Patients were included if they were ≥18 years of age, received definitive treatment with either cefazolin or oxacillin, and met criteria for complicated MSSA bacteremia. Complicated bacteremia was defined as ≥1 positive blood culture and at least one of the following: positive follow-up blood cultures within 5 days of therapy initiation, evidence of metastatic spread, infected prostheses not removed within 4 days, and presence of endocarditis (1, 11). Subjects were required to have received at least 10 days of therapy with cefazolin or oxacillin to be considered for inclusion. Patients were excluded if they had uncomplicated or polymicrobial bacteremia, received empirical antibiotics for ≥72 h, or received other antibiotics active against MSSA during treatment. Primary sources of infection were identified by concurrent microbiologic specimens positive for MSSA from the suspected site of infection or clinical signs and symptoms and radiographic evidence consistent with the suspected site of infection. The primary source of infection was determined by one investigator (J. Li). Time to surgery was defined as the number of days between first positive culture and day of first removal, debridement, or drainage of the primary source of infection.

Although cefazolin became the preferred antibiotic for the treatment of MSSA bacteremia, oxacillin may still have been reserved for more severe infections. To help control for this, a subgroup analysis of matched patients was also conducted. Cefazolin-treated patients were matched to oxacillin-treated patients based on age, intensive care unit (ICU) admission, source, receipt of surgical intervention, and presence of metastatic foci of infection.

Outcomes. The primary outcome was the rate of clinical cure at the end of therapy (CEOT), which was defined as clearance of bacteremia with defervescence and resolution of signs and symptoms of infection. Secondary outcomes included overall treatment failure, duration of bacteremia, time to defervescence, 30-day and 90-day all-cause mortality, rates of adverse drug events (ADEs), and discontinuation of therapy due to ADE. Overall treatment failure was evaluated through 90 days after completion of intravenous therapy and included persistent bacteremia, development of metastatic spread or progression of infection while on definitive therapy, relapse of infection, or death. Duration of bacteremia was defined as the number of days from first positive blood culture to first negative blood culture, with persistent bacteremia defined as ≥7 days of bacteremia. Blood cultures were repeated every 48 h, at minimum, until the first negative blood culture was obtained. Time to defervescence was determined by the number of days between first positive culture and first day without fever. Temperatures were measured daily, at minimum, at least until the patients defervesced. For the safety analysis, adverse events were considered to be drug related if they occurred while the patient was on cefazolin or oxacillin therapy. Acute kidney injury was defined as an increase in serum creatinine of ≥0.5 mg/dl or a 50% increase from baseline, and liver function test results were considered to be elevated if the aspartate transaminase or alanine aminotransferase exceeded 5 times the upper limit of normal.

Statistical analysis. Data were analyzed using JMP 9.0.2 (SAS Institute, Cary, NC). Descriptive statistics were used to summarize patient demographics and outcomes. Data are presented as means and standard deviations, medians and interquartile ranges, or percentages, as appropriate. Continuous variables were tested for normality by use of the Shapiro-Wilk W test. Normally distributed continuous data were analyzed with Student's *t* test, while non-normally distributed continuous data were analyzed by the Wilcoxon rank sum test. A chi-square or Fisher's exact test was used to compare nominal data as appropriate. An *a priori* alpha level of less than or equal to 0.05 was used to determine statistical significance for all comparisons. Multivariate analysis was used to identify any predictors of overall treatment failure. Any baseline characteristic with a *P* value of ≤0.2 was included in the analysis. Antibiotic treatment was included in the analysis regardless of *P* value.

RESULTS

Clinical characteristics. Of the 582 patients with MSSA bacteremia, 93 patients met the criteria for inclusion in this investigation. The primary reasons for exclusion were receipt of more than 72 h of empirical antibiotics (34%), receipt of other antibiotics active against MSSA (23%), receipt of less than 10 days of definitive antibiotics with cefazolin or oxacillin (15%), and uncomplicated bacteremia (10%). Of the 93 patients included in the study, 34 were treated with oxacillin and 59 were treated with cefazolin. A comparison of clinical characteristics between the two treatment groups is presented in Table 1. The mean age of the overall study population was 51 years. Most of the patients were male (77%), and 31% of patients were current or past intravenous drug users. Sources of bacteremia were largely osteoarticular (41%) or endovascular (20%). Of the 19 patients with endovascular sources, endocarditis was considered the primary source in 17 patients. One patient in each group had a septic thrombus identified as the primary source.

Baseline demographics were generally similar between both groups, but cefazolin-treated subjects were more likely to have end-stage renal disease (25% versus 0%; $P < 0.001$) and be admitted to a medical service (86% versus 68%; $P = 0.04$). More oxacillin-treated patients were admitted to intensive care units (18% versus 7%; $P = 0.16$), but the difference was not significant. One patient in each group required the use of vasopressor support. Rates of catheter removal, removal of other foreign material, and surgical interventions were not different between the two groups. The primary source of bacteremia in oxacillin-treated patients was predominantly osteoarticular (59%), while cefazolin-treated patients had mostly osteoarticular (31%) or endovascular (25%) sources, including 14 cases of endocarditis. Although the source of bacteremia differed between the groups, the percentage of patients having metastatic spread was nearly identical.

Almost all oxacillin-treated patients (94%) received 12 g/day, with two patients receiving oxacillin at 10 g/day. Oxacillin was administered by continuous infusions in 33 (97%) patients. Of the 44 patients treated with cefazolin that were not on hemodialysis, 41 (93%) patients were given 6 g/day and one patient was given 8 g/day. Two patients received a reduced dose of 4 g/day after adjusting for renal function. Cefazolin was given by continuous infusion in 33 of the 44 (75%) patients not on hemodialysis. Of the 15 patients receiving cefazolin on hemodialysis, 12 were treated with 2 g of cefazolin after every dialysis session. The other 3 patients received 3 g of cefazolin following the dialysis session that preceded the 72-hour interdialytic period. The median duration of therapy was 31 days (interquartile range [IQR], 21 to 42 days) for the oxacillin group and 39 days (IQR, 28 to 44 days) for the cefazolin group ($P = 0.18$). Synergistic gentamicin was used in 4 (11%) patients in the oxacillin arm and 5 (8%) patients in the cefazolin arm. Rifampin was also added in addition to gentamicin in 1 oxacillin-treated subject and 3 cefazolin-treated subjects. Prolonged courses of oral antibiotics following completion of intravenous therapy were prescribed for 4 (12%) patients in the oxacillin arm and 7 (12%) patients in the cefazolin arm. In these

TABLE 1 Clinical characteristics of 93 patients treated with cefazolin or oxacillin for complicated MSSA bacteremia

Characteristic	Value[a] for patients treated with:			*P* value
	Overall ($n = 93$)	Oxacillin ($n = 34$)	Cefazolin ($n = 59$)	
Mean age (yr) ± SD	51 ± 12	51 ± 14	51 ± 10	0.75
Male gender	72 (77)	28 (82)	44 (75)	0.45
Mean wt (kg) ± SD	81 ± 17	77 ± 18	83 ± 16	0.13
Mean body mass index (kg/m^2) ± SD	29 ± 6	28 ± 7	30 ± 6	0.15
History of intravenous drug use	29 (31)	10 (30)	19 (32)	0.60
History of alcohol use	50 (54)	21 (62)	29 (49)	0.21
Comorbidities				
Diabetes mellitus	47 (51)	16 (47)	31 (53)	0.67
End-stage renal disease	15 (16)	0 (0)	15 (25)	<0.001
Cirrhosis	19 (20)	6 (18)	13 (22)	0.79
Cancer	6 (6)	1 (3)	5 (9)	0.41
Other immunosuppression	6 (6)	2 (6)	4 (7)	1.0
Admission status				
Medical	74 (80)	23 (68)	51 (86)	0.04
Surgical	9 (10)	5 (15)	4 (7)	0.28
Intensive care unit	10 (11)	6 (18)	4 (7)	0.16
Median Pitt bacteremia score[b]	0 (0–1)	0 (0–1)	0 (0–1)	0.88
Mean white blood cell count (1,000/mm^3) ± SD	14 ± 7	15 ± 8	13 ± 7	0.28
Mean serum creatinine (mg/dl) ± SD	1.2 ± 0.7	1.1 ± 0.5	1.2 ± 0.9	0.80
Presence of fever	54 (58)	18 (53)	36 (61)	0.52
Presence of catheters	12 (13)	1 (3)	11 (19)	0.05
Catheter removal	11/12 (92)	1/1 (100)	10/11 (91)	1.0
Presence of other foreign material	19 (20)	3 (9)	16 (27)	0.06
Foreign material removal	6/19 (32)	1/3 (33)	5/16 (31)	1.0
Received surgical intervention	44 (47)	19 (56)	25 (42)	0.28
Multiple surgical procedures	18/44 (41)	8/19 (42)	10/25 (40)	0.79
Median time to surgery (days)[b]	4 (2–6)	3 (2–5)	4 (2–7)	0.13
Metastatic spread of infection	32 (34)	12 (35)	20 (34)	0.82
Multiple sites of metastasis	9/32 (28)	5/12 (41)	4/20 (20)	0.42
Primary source				
Catheter	7 (8)	1 (3)	6 (10)	0.42
Pneumonia	4 (4)	2 (6)	2 (4)	0.62
Endovascular[c]	19 (20)	4 (12)	15 (25)	0.18
Possible endocarditis	4/17 (24)	1/3 (33)	3/14 (21)	
Right-sided endocarditis	4/17 (24)	1/3 (33)	3/14 (21)	
Left-sided endocarditis	7/17 (41)	1/3 (33)	6/14 (43)	
Right- and left-sided endocarditis	2/17 (12)	0/3 (0)	2/14 (14)	
Osteoarticular	38 (41)	20 (59)	18 (31)	0.009
Soft tissue	9 (10)	1 (3)	8 (14)	0.15
Urinary tract	6 (6)	4 (12)	2 (3)	0.19
Unknown	10 (11)	2 (6)	8 (14)	0.32

[a] Values are numbers (with percentages in parentheses) unless indicated otherwise.
[b] Values are medians (with interquartile ranges in parentheses).
[c] Endocarditis was the primary source of infection in 17 of 19 patients. For one patient in each group, a septic thrombus was identified as the primary source. One patient in each group also had involvement of an intracardiac device. Two patients in the cefazolin arm had prosthetic valve endocarditis (one right-sided and one left-sided).

patients, CEOT was evaluated at the end of intravenous antibiotic therapy.

Treatment outcomes. Cefazolin-treated patients had rates of CEOT similar to oxacillin-treated patients (95% versus 88%; $P = 0.25$) (Table 2). Overall treatment failure was higher in the oxacillin arm (47%) than in the cefazolin arm (24%; $P = 0.04$), but reasons for overall treatment failure were similarly distributed among failures in both groups. The primary reasons for treatment failure were persistent bacteremia (43%) and progression of infection on therapy (30%), followed by relapse of infection (23%). Treatment discontinuation due to failure occurred in one patient. Cefazolin was replaced with oxacillin after 28 days of therapy due

TABLE 2 Treatment outcomes with cefazolin and oxacillin for complicated MSSA bacteremia

Outcome or parameter	Value[a] for patients treated with:			*P* value
	Overall ($n = 93$)	Oxacillin ($n = 34$)	Cefazolin ($n = 59$)	
Clinical cure at end of therapy	86 (92)	32 (88)	56 (95)	0.25
Duration of bacteremia (days)[b]	4 (2–6)	4 (3–7)	4 (2–5)	0.20
Time to defervescence (days)[b]	2 (1–3)	2 (1–3)	2 (1–4)	0.33
Median no. of blood cultures drawn[b]	4 (4–8)	5 (4–9)	4 (3–8)	0.21
Median no. of blood cultures positive[b]	4 (3–7)	4 (3–10)	4 (2–6)	0.28
Overall treatment failure	30 (32)	16 (47)	14 (24)	0.04
Persistent bacteremia	13/30 (43)	7/16 (44)	6/14 (43)	0.55
Progression of infection on therapy	9/30 (30)	5/16 (31)	4/14 (29)	0.16
Relapse of infection	7/30 (23)	3/16 (19)	4/14 (29)	1.0
Death	1/30 (3)	1/16 (6)	0/14 (0)	0.37
Antibiotic discontinuation due to failure	1 (1)	0 (0)	1 (2)	0.30
Infection-related 90-day readmission	13 (14)	8 (24)	5 (9)	0.06
Recurrence of bacteremia	3 (3)	2 (6)	1 (2)	0.55
30-day mortality	1 (1)	1 (3)	0 (0)	0.37
90-day mortality	1 (1)	1 (3)	0 (0)	0.37

[a] Values are numbers (with percentages in parentheses) unless indicated otherwise.
[b] Values are medians (with interquartile ranges in parentheses).

to progression of disease. The patient had an undrained paraspinal abscess which decreased in size, but follow-up radiography demonstrated progression to vertebral osteomyelitis. One death occurred during the study in the oxacillin arm, in which a patient had an infected intracardiac device that was not removed. Of the patients receiving oral antibiotics after completion of intravenous therapy that failed treatment, 3 were in the cefazolin group and 1 patient was in the oxacillin group. Only one patient, in the cefazolin group, that received oral antibiotics failed therapy due to relapse of infection. The median duration of bacteremia and time to defervescence were similar between both groups at 4 days and 2 days, respectively. In the matched analysis ($n = 15$ per group), both baseline characteristics and treatment outcomes, including rates of CEOT and overall failure, were similar to those for the overall cohort (data not shown).

The safety profiles of both treatments were also compared and are listed in Table 3. ADEs were documented in 10 (30%) oxacillin-treated patients and 2 (3%) cefazolin-treated patients ($P = 0.0006$). The most common ADE was elevated transaminases, which occurred in 6 (18%) patients on oxacillin and no patients on cefazolin ($P = 0.002$). Other ADEs included rash, increased serum creatinine, and diarrhea. Treatment was interrupted due to ADEs in 9 (10%) patients, with a median treatment duration of 21 days (IQR, 17 to 30 days) before discontinuation. Rates of treatment discontinuation due to ADEs were 21% and 3% in the oxacillin group and cefazolin group, respectively ($P = 0.01$). One patient in each group had therapy discontinued after 36 days of therapy and was not continued on further intravenous antibiotics. Of the remaining 6 patients for which oxacillin was discontinued, 2 were switched to vancomycin and 4 were switched to cefazolin. Reasons for discontinuation in the oxacillin group were increased transaminases ($n = 4$), rash ($n = 1$), leukopenia ($n = 1$), and to reduce sodium load ($n = 1$). Cefazolin was discontinued in one patient due to a rash, and the patient was switched to vancomycin.

TABLE 3 Adverse drug events with cefazolin or oxacillin for complicated MSSA bacteremia

Outcome or parameter	No. (%) among patients treated with:			*P* value
	Overall ($n = 93$)	Oxacillin ($n = 34$)	Cefazolin ($n = 59$)	
All adverse drug events	12 (13)	10 (30)	2 (3)	0.0006
Rash	2 (2)	1 (3)	1 (2)	1.0
Elevated transaminases	6 (6)	6 (18)	0 (0)	0.002
Elevated serum creatinine	1 (1)	1 (3)	0 (0)	0.37
Leukopenia	1 (1)	1 (3)	0 (0)	1.0
Diarrhea	1 (1)	0 (0)	1 (2)	0.37
Other	1 (1)	1 (3)	0 (0)	0.37
Discontinued due to adverse drug event	9 (10)	7 (21)	2 (3)	0.01

Clinical characteristics of overall treatment failures. Clinical characteristics were compared between treatment failures ($n = 30$) and treatment successes ($n = 63$) (Table 4). Treatment failures were more likely to have surgical intervention (63% versus 40%; $P = 0.05$) with a longer median duration of bacteremia (7 versus 3 days; $P = 0.0002$). Treatment failures were also more likely to have osteoarticular sources (57% versus 33%; $P = 0.04$) than the treatment successes. Metastatic spread of infection was more common in treatment failures (50%) than in treatment successes (27%), as was metastasis to multiple sites of infection (40% versus 17%), but the differences were not significant ($P = 0.10$ for both comparisons). Additional details of the individual treatment failures are reported in Table 5. The only significant predictor of treatment failure in the multivariate analysis was duration of bacteremia ($P < 0.001$). All other variables were not predictors of treatment failure, including selection of antibiotic (Table 6).

DISCUSSION

The results of our study suggest that cefazolin is similar to oxacillin in terms of clinical outcomes at the end of therapy for the

TABLE 4 Characteristics of overall treatment failure and treatment success for complicated MSSA bacteremia

Outcome or parameter	Value[a] for patients with:		
	Failure ($n = 30$)	Success ($n = 63$)	*P* value
Length of therapy (days)[b]	38 (27–44)	39 (25–44)	0.75
Less than 28 days	8 (27)	17 (27)	0.55
Received surgical interventions	19 (63)	25 (40)	0.05
Time to first surgery (days)[b]	4 (2–8)	3 (2–5)	0.37
Multiple surgeries	7/19 (37)	11/25 (44)	0.65
Duration of bacteremia (days)[b]	7 (3–8)	3 (2–4)	0.0002
Evidence of metastasis	15 (50)	17 (27)	0.10
Multiple sites of metastasis	6/15 (40)	3/17 (17)	0.10
Primary source			
Catheter	1 (3)	6 (10)	0.42
Pneumonia	1 (3)	3 (5)	1.0
Endovascular	4 (13)	15 (24)	0.28
Osteoarticular	17 (57)	21 (33)	0.04
Soft tissue	4 (13)	5 (8)	0.46
Urinary tract	2 (7)	7 (4)	1.0
Unknown	1 (3)	9 (14)	0.16

[a] Values are numbers (with percentages in parenthese) unless indicated otherwise.
[b] Values are medians (with interquartile ranges in parentheses).

treatment of complicated MSSA bacteremia (95% versus 88%; $P = 0.25$). Cefazolin was also similar to oxacillin in terms of median duration of bacteremia ($P = 0.20$) and median time to defervescence ($P = 0.33$). The rate of overall treatment failure at 90 days of follow-up was higher in oxacillin-treated patients than in cefazolin-treated patients (47% versus 24%; $P = 0.04$). The worse longer-term outcomes in the oxacillin group may be explained by inadequate source control of osteoarticular infections, including the need for multiple surgical interventions and longer time to surgery, as well as higher rates of metastatic spread of infection. These factors may have prolonged the duration of bacteremia in the treatment failures, which was the only predictor of failure in the multivariate analysis.

Three other studies have also demonstrated similar efficacies between cefazolin and ASPs in the treatment of MSSA bacteremia (8, 12, 13). A single-center retrospective cohort study examined the comparative efficacy of several different beta-lactams, including cloxacillin ($n = 281$) and cefazolin ($n = 72$) (12). Mortality at 90 days was not significantly different between the two groups when both agents were used as definitive therapy. However, baseline characteristics differed significantly between the two groups, possibly reflecting preferential use of cloxacillin in patients with more severe MSSA infections. A retrospective, multicenter observational study comparing oxacillin ($n = 32$) and cefazolin ($n = 95$) for the treatment of MSSA bacteremia also demonstrated no difference between the two treatment groups (13). However, treatment with oxacillin was unexpectedly a predictor for failure in the overall analysis (odds ratio [OR], 4.9; 95% confidence interval [CI], 1.44 to 1.63). A recent propensity score-matched, case-control study minimized the potential for bias by comparing nafcillin use with cefazolin use during periods of limited nafcillin supply (8). No differences in either mortality or cure at the end of therapy were documented between the two groups, but the study was limited by small sample size ($n = 41$ in each group) and low numbers of patients with endocarditis ($n = 2$).

Similarly, selection bias was minimized at our institutions through the implementation of an antimicrobial stewardship initiative recommending cefazolin as the beta-lactam of choice for MSSA infections. Oxacillin use decreased from 21.1 daily defined doses (DDD) to 4.8 DDD per 1,000 bed-days at one institution ($P = 0.006$) and from 546 DDD to 46 DDD per quarter at the other institution (9, 10). No other formal programs or changes were implemented during this time that could have impacted the study. Due to the retrospective nature of the study, there is potential for unrecognized changes to have impacted the outcomes. Although stewardship initiatives may have minimized treatment bias at our institutions, oxacillin may still have been reserved for patients with more severe MSSA infections. Therefore, we also conducted a matched analysis to further control for any confounders. The subgroup analysis was small ($n = 15$ per group), but baseline characteristics and treatment outcomes were no different from the overall cohort.

This study also demonstrated better tolerability of cefazolin over oxacillin, with overall ADE rates of 30% versus 3% ($P = 0.0006$), respectively. Elevated transaminases were the most commonly observed ADE with oxacillin (18%). Discontinuation rates due to ADEs were also higher in the oxacillin group (21% versus 3%, $P = 0.01$). Although ASPs have been associated with higher rates of adverse drug reactions, such as elevated liver enzymes, rash, and acute kidney injury, there are few studies that have directly compared ADEs between ASPs and cefazolin (14–16). Our findings are consistent with other studies that have demonstrated higher rates of ADEs and treatment discontinuation with ASPs than with cefazolin (8, 17). A recent retrospective cohort analysis of patients receiving nafcillin or cefazolin for outpatient parenteral antimicrobial therapy demonstrated higher rates of rash (14% versus 4%; $P = 0.002$), renal dysfunction (11% versus 3%; $P = 0.006$), and elevated liver enzymes (8% versus 2%; $P = 0.01$) with nafcillin (17). Furthermore, fewer patients completed prespecified treatment courses with nafcillin than did those treated with cefazolin (overall discontinuation rate, 34% versus 7%; $P < 0.0001$). ASPs are also more commonly associated with other untoward reactions, such as phlebitis and neutropenia (18, 19). Other pharmacologic advantages of cefazolin over ASPs include lower sodium content and dosing convenience in patients on hemodialysis. Additionally, ASPs are more costly than cefazolin, and we previously demonstrated an annualized cost avoidance of at least $37,000 and up to $243,000 based on antibiotic expenditures alone with the conversion of ASPs to cefazolin for MSSA infections (9, 10). Other studies have also demonstrated significant cost savings with a conversion of treatment with an ASP to treatment with cefazolin (20, 21).

Concerns regarding reports of clinical failures with cefazolin in high inoculums have limited the preferential use of cefazolin over ASPs for MSSA infections (2–7). MSSA isolates from high-burden infections, such as endocarditis, are thought to hyperproduce beta-lactamases, which could increase inactivation of cefazolin and result in therapeutic failures. Recent studies characterizing the incidence of the inoculum effect with cefazolin and MSSA have reported rates as low as 4% and up to 36% (6, 7, 22). However, the inoculum effect alone may not be sufficient to explain cefazolin clinical failures. Other factors that may affect clinical

TABLE 5 Description of overall failures in patients receiving cefazolin or oxacillin for complicated MSSA bacteremia

Patient no.	Antibiotic[a]	Primary reason for failure	Primary source[b]	Treatment duration (days)	Duration of bacteremia (days)	Metastasis?	Received surgical intervention?	Time to surgery (days)	Multiple surgeries needed?	Hardware removal?
1	CFZ 2 g post-HD	Persistence	Septic knee and elbow	26	8	Y	Y	14	N	
2	CFZ 6 g (CI)	Persistence	Right and left-sided IE	36	10	Y	N			
3	CFZ 6 g (CI)	Persistence	Septic shoulder	46	7	N	Y	4	Y	
4	CFZ 6 g (II)	Persistence	Septic phlebitis	42	8	Y	N			
5	CFZ 6 g (CI)	Persistence	Renal abscess	42	8	N	Y	2	N	
6	CFZ 6 g (CI)	Persistence	Paraspinal abscess	69	10	Y	Y	13	Y	N
7	CFZ 6 g (II)	Progression	Paramediastinal abscess with OM	28	1	N	N			
8	CFZ 6 g (II)	Progression	Psoas abscess	26	3	Y	N			
9	CFZ 2 g post-HD	Progression	AV graft infection	42	3	N	Y	4	N	N
10	CFZ 8 g (CI)	Progression	Epidural and psoas abscess with OM	96	17	N	Y	9	Y	N
11	CFZ 4 g (II)	Relapse	Lumbar abscess	12	2	N	Y	1	Y	
12	CFZ 6 g (CI)	Relapse	Possible endocarditis	35	1	Y	N			
13	CFZ 6 g (II)	Relapse	Septic knee	39	1	N	Y	1	N	
14	CFZ 6 g (CI)	Relapse	Left-sided endocarditis	44	3	Y	N			
15	OX 12 g (CI)	Death	Right-sided endocarditis with ICD infection	30	9	N	N			N
16	OX 12 g (CI)	Persistence	Septic knee, ankle, and subclavian joints	42	9	Y	Y	4	Y	
17	OX 12 g (CI)	Persistence	Septic knee and shoulder	42	8	N	Y	10	N	
18	OX 12 g (CI)	Persistence	Renal and prostate abscess	28	8	Y	Y	2	N	
19	OX 12 g (CI)	Persistence	Septic elbow and knees	30	9	Y	Y	7	N	
20	OX 12 g (CI)	Persistence	Humerus muscle abscess	46	7	N	Y	1	Y	
21	OX 12 g (CI)	Persistence	Vertebral OM	17	9	Y	N			
22	OX 12 g (CI)	Persistence	Hip OM	15	7	N	Y	8	N	
23	OX 10 g (CI)	Progression	Pleural abscess	14	4	N	N			
24	OX 12 g (CI)	Progression	Epidural abscess	42	8	N	Y	6	N	
25	OX 12 g (CI)	Progression	Septic subclavian joint with vertebral OM	45	4	Y	Y	4	N	
26	OX 12 g (CI)	Progression	Septic ankle and epidural abscess with vertebral OM	55	8	Y	Y	5	Y	
27	OX 12 g (CI)	Progression	Craniotomy bone flap infection	37	4	N	N			
28	OX 12 g (CI)	Relapse	Vertebral OM	42	2	N	N			
29	OX 12 g (CI)	Relapse	Unknown	14	3	Y	N			
30	OX 12 g (II)	Relapse	Foot abscess with OM	58	5	N	Y	3	N	

[a] The total daily dose is reported for patients not on hemodialysis. CFZ, cefazolin; OX, oxacillin; CI, continuous infusion; II, intermittent infusion; HD, hemodialysis.
[b] IE, infective endocarditis; OM, osteomyelitis; AV, arteriovenous; ICD, intracardiac device.

outcomes include degree of the inoculum effect, dose of cefazolin used, bacterial load and antibiotic penetration at infection site, and the host immune system (23). Additionally, adequate source control likely plays an important role by reducing bacterial burdens, thereby diminishing the inoculum effect. Studies evaluating the clinical impact of the cefazolin inoculum effect are limited, and a relationship between these strains and adverse clinical outcomes has not been clearly established. A recent multicenter, retrospective cohort study examining the effects of MSSA isolates with and without the inoculum effect found no association between inoculum effect and overall treatment failure at 12 weeks in patients treated with cefazolin for MSSA bacteremia (24). However, the inoculum effect was associated with early treatment failure (OR, 4.89; 95% CI, 1.00 to 22.23; $P = 0.04$). The most common sites of infection were skin and soft tissue (35%), primary bacteremia (20%), and catheter-related infections (18%), and only 33% of patients had eradicated foci of infection. The association between inoculum effect and early treatment failure was primarily driven by persistent bacteremia defined as bacteremia for ≥72 h (9% versus 0%; $P = 0.04$). Time to eradication of foci of infection and persistence of bacteremia at 7 days or later were not reported. More importantly, in patients with serious infections, such as endocarditis, pneumonia, and osteomyelitis, that demonstrated an inoculum effect, higher rates of failure (47% versus 25%) and bacteremia-related mortality (12 versus 0%) were observed, but the differences were not significant. Multivariate analysis identified endocarditis (OR, 22.7; 95% CI, 1.53 to 335.86; $P = 0.02$) and pneumonia (OR, 7.19; 95% CI, 1.33 to 42.31; $P = 0.03$)

TABLE 6 Results of multivariate logistic fit for overall treatment failure

Variable[a]	*P* value
Antibiotic treatment	0.36
Duration of bacteremia	0.0001
Pitt bacteremia score	0.06
BMI	0.39
ESRD	0.29
Admission to ICU	0.30

[a] BMI, body mass index; ESRD, end-stage renal disease; ICU, intensive care unit.

as the only significant risk factors for treatment failure. Inoculum effect and type A beta-lactamase were not significantly associated with treatment failure. Severity of infection was suggested as a more important factor than inoculum effect for overall treatment outcome.

Since the impact of the inoculum effect is likely seen in infections with high bacterial burdens, the probability for treatment failure with cefazolin is more likely with such infections, particularly endocarditis, where the inoculum may be as high as 10^{10} CFU/g of tissue. In the studies comparing cefazolin to ASPs for MSSA bacteremia, high bacterial burden infections, especially endocarditis, were infrequent sources of infection (8, 13). In the first study, 48% of patients had high-burden diseases in the overall study population. Similar to the inoculum effect study, endocarditis (OR, 8.6; 95% CI, 2.0 to 36.8; $P < 0.01$) and pneumonia (OR, 6.0; 95% CI, 1.5 to 23.2; $P = 0.02$) were the only predictors of treatment failure. Cefazolin therapy was not associated with failure at either 4 or 12 weeks. Site of infection was suggested as a more important prognostic factor than selection of cefazolin or nafcillin in predicting clinical outcomes of MSSA bacteremia (8). In the second study, the rate of these infections was 34% of cefazolin-treated patients and 25% of oxacillin-treated patients (13). Although high-burden infections were not clearly defined, the study included 20 (18%) patients with endocarditis, with 17 in the cefazolin group. No difference in outcomes was seen in the subgroup analysis of both high-burden infections and endocarditis.

We did not specifically investigate the prevalence of the inoculum effect in the patients in this study. However, this study maximized the inclusion of high-burden MSSA infections by only evaluating complicated MSSA bacteremia, including 19 (20%) patients with endovascular sources and 38 (41%) patients with deep-seated osteoarticular infections. No difference in efficacy was observed in these high-burden infections, but optimized dosing and pharmacodynamics may have mitigated the impact of the inoculum effect in this study. The majority of patients not on hemodialysis were administered cefazolin by continuous infusion (75%), with all patients receiving at least 6 g/day (adjusted for renal function). However, our study was not designed to evaluate any difference in the efficacy of continuous versus intermittent infusions.

The only predictor of treatment failure in our study was persistence of bacteremia, defined as positive blood cultures for ≥7 days. Treatment failures were more likely to have osteoarticular sources and have received surgical interventions, possibly indicating the severity and burden of these infections and thus necessitating source control. Several factors may lead to persistent bacteremia, including source of infection, retention of prosthetic material, and inability to remove foci of infection (25–27). An increased duration of bacteremia leads to poorer outcomes due to an increased risk of metastatic spread of infection of up to 45% with bacteremia for ≥10 days (27, 28). Adverse outcomes in the setting of persistent bacteremia without metastatic infection have also been described (29). One cohort study of 177 *S. aureus* bacteremia episodes identified persistent bacteremia as an independent predictor of mortality (OR, 17.5; 95% CI, 1.5 to 212; $P = 0.024$) (30).

There are several limitations to our study. First, this study included a limited number of patients, and our sample size may have been too small to detect any differences in outcomes. Second, this was a retrospective cohort study evaluating outcomes in patient populations from two different time periods. However, the study period was relatively short, and there were no significant medical advances or changes in practices in the management of MSSA bacteremia at our institutions over the two time periods other than the change from oxacillin to cefazolin. The retrospective nature of our study also prohibited us from controlling for biases between the two groups, but treatment bias may have been minimized through the extent of our stewardship initiatives. Third, we did not evaluate the prevalence of the inoculum effect, but its impact may have been mitigated by optimized pharmacodynamics through our predominant use of continuous infusions. Despite these limitations, this is the first study to our knowledge to evaluate the efficacy and tolerability of cefazolin and oxacillin in the setting of complicated MSSA bacteremia.

Our study suggests that cefazolin and oxacillin have similar efficacies in the treatment of complicated MSSA bacteremia, but cefazolin is better tolerated and has lower rates of treatment interruption. Preferential selection of cefazolin over ASPs for MSSA infections, including high-burden infections, based on consideration of tolerability, dosing convenience, and cost may not adversely affect clinical outcomes. Regardless of antibiotic selection, inadequate source control and site of infection may contribute to persistence of bacteremia and, in turn, portend a worse clinical outcome. More data, including prospective randomized trials, comparing cefazolin to ASPs for high-burden MSSA infections would be of value to help validate our findings.

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