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MAJOR ARTICLE

A Comparison of Cefazolin Versus Ceftriaxone for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bacteremia in a Tertiary Care VA Medical Center

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Background. Cefazolin and ceftriaxone are frequently used to treat methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia, especially in the realm of outpatient parenteral antimicrobial therapy. Both antimicrobials have been associated with favorable clinical outcomes for mixed MSSA infections. However, limited published data exist specifically comparing the use of these agents for the treatment of MSSA bacteremia.

Methods. We conducted a retrospective cohort study of Veteran patients with MSSA bacteremia who received ≥14 days of cefazolin or ceftriaxone between 2009 and 2014. Rates of treatment failure were compared between both groups. Treatment failure was defined as therapy extension, incomplete therapy, unplanned oral suppressive therapy, relapse of infection, or hospital admission or surgery within 90 days.

Results. Out of 71 patients, 38 received treatment with cefazolin and 33 with ceftriaxone. The overall rate of treatment failure was 40.8%, with significantly more failures among patients receiving ceftriaxone (54.5% versus 28.9%; $P = .029$). Factors associated with treatment failure included longer duration of parenteral therapy, heart failure, and treatment in an external skilled nursing facility as compared with treatment in the Department of Veterans Affairs attached Community Living Center.

Conclusions. Ceftriaxone had a higher rate of treatment failure than cefazolin for the treatment of MSSA bacteremia in a Veteran population. Potential reasons for this could include the higher protein binding of ceftriaxone, ultimately resulting in lower serum concentrations of free drug, or other unknown factors. Further studies are warranted to confirm these results.

Keywords. bacteremia; cefazolin; ceftriaxone; methicillin-susceptible *Staphylococcus aureus*; MSSA.

Staphylococcus aureus is one of the most common pathogens of both community and hospital-acquired bacteremia [1]. The high rate of recurrence of *S. aureus* bacteremia after completion of antistaphylococcal therapy, ranging from 5% to 23%, necessitates an extended duration of parenteral therapy to reduce the potential for recurrence and subsequent morbidity and mortality [2, 3]. Due to the extended duration of parenteral therapy that is required to effectively treat bacteremia, outpatient parenteral antimicrobial therapy (OPAT) has become popular to reduce hospital length of stay and treatment costs [4]. Compared with antistaphylococcal penicillins for the management of methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, cefazolin and ceftriaxone have found similar rates of treatment failure and low numbers of adverse events, thus making them viable alternatives [5–12]. Although cefazolin has been reported in vitro to be subject to an inoculum effect due to hydrolysis by *S. aureus* beta-lactamases, limited data exist regarding effects on clinical outcomes associated with this phenomenon [13–16]. Cefazolin and ceftriaxone also offer more convenient dosing than antistaphylococcal penicillins, which makes them an attractive option in the realm of OPAT [4]. Limited data exist comparing cefazolin and ceftriaxone for MSSA infections, and to the authors' knowledge, this is the first study that compares cefazolin versus ceftriaxone head-to-head specifically for the treatment of MSSA bacteremia. We compared the rates of treatment failure between cefazolin and ceftriaxone when used for the treatment of MSSA bacteremia. Secondary objectives included rates of overall 90-day mortality, *Clostridium difficile* infection, adverse events, and the cost of parenteral therapy.

METHODS

Study Design and Participants

A retrospective, observational cohort study was performed at the Louis Stokes Cleveland Department of Veterans Affairs (VA) Medical Center. This VA medical center is a tertiary care teaching hospital in Cleveland, Ohio, with approximately 600 licensed beds for acute and long-term care.

Received 19 December 2017; editorial decision 11 April 2018; accepted 15 May 2018.

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DOI: 10.1093/ofid/ofy089

Subjects with a diagnosis of MSSA bacteremia from January 2009 to August 2014 were identified from the institution's OPAT registry. Subjects were eligible for inclusion if they were treated for MSSA bacteremia with cefazolin or ceftriaxone for ≥14 days. Patients were excluded if they received OPAT with another antistaphylococcal antimicrobial in addition to cefazolin or ceftriaxone (with the exception of patients with a prosthesis or mycotic aneurysm), if they had documented polymicrobial infection, if they had received empiric antimicrobials >72 hours after cultures were finalized, or if OPAT was not being used as a curative modality. Patient charts were reviewed through the VA's electronic medical record system, Computerized Patient Record System (CPRS). All patients were managed by an infectious diseases physician, who made the treatment decisions and determination of the source of infection. Data collected from each subject included patient demographics, source of infection, antimicrobial characteristics, duration of parenteral therapy, blood culture data, adverse events based on chart review at follow-up visits and additional hospital encounters, overall 90-day mortality, *Clostridium difficile* laboratory tests, treatment setting, and presence of medical comorbidities.

Definitions

MSSA bacteremia was defined as having at least one positive blood culture growing *S. aureus* susceptible to oxacillin performed using VITEK 2 (BioMérieux, Inc, Durham, NC). Cefazolin and ceftriaxone were considered susceptible if *S. aureus* was oxacillin-susceptible. Treatment failure was defined as unplanned extension of parenteral antimicrobial therapy, failure to complete the course of parenteral therapy, relapse of infection within 90 days of treatment completion, unplanned addition of suppressive oral antimicrobial therapy (with the exception of patients with a prosthesis or mycotic aneurysm, as this was considered planned), readmission or unanticipated surgical intervention related to the primary site of infection within 90 days of treatment completion, or the patient being lost to follow-up, as treatment success could not be validated. Persistent bacteremia was defined as bacteremia that persists for ≥7 days. Relapse was defined as a repeat blood culture positive for MSSA obtained after antimicrobial therapy was completed. Source control was defined as removal of central lines in the setting of catheter-related bloodstream infection, drainage of intra-abdominal abscesses if collections were present, valve replacement for patients with endocarditis, and amputation or debridement of skin and soft tissue or osteoarticular infections. Adverse events were defined as any injury that directly resulted from the use of cefazolin or ceftriaxone. Cost of parenteral therapy was defined as the total acquisition cost of the parenteral therapy per patient, after adjusting for the final duration of parenteral treatment.

Statistical Analysis

The primary outcome of interest was treatment failure. A chi-square test was used to compare differences in rates of treatment failure based on treatment with cefazolin or ceftriaxone. A power analysis was conducted for a chi-square analysis. It was determined that a sample size of 71 participants, with an alpha of .05 and a power of 80%, would be able to detect a medium effect size of 0.33. Secondary outcomes were rates of overall 90-day mortality, *Clostridium difficile* infection, adverse events, and the cost of parenteral therapy. Categorical outcome data were compared using the chi-square test, continuous outcome data were compared using a *t* test, and logistic regression was used to assess variables predictive of treatment failure. Statistical analysis was performed using SPSS, version 20 (IBM SPSS, Chicago, IL). The study was approved by the Louis Stokes Cleveland Department of Veterans Affairs Medical Center Institutional Review Board prior to data collection.

RESULTS

Baseline Demographics

From January 2009 to August 2014, 71 patients in the OPAT registry were treated with cefazolin or ceftriaxone for MSSA bacteremia. Thirty-eight (54%) received treatment with cefazolin, and 33 (46%) received treatment with ceftriaxone (Table 1). Patients receiving hemodialysis and the presence of a prosthesis were significantly more likely in the cefazolin group, but there were no other significant differences in baseline characteristics between the groups. Patients were predominantly male, and the mean age was 63 years for the cefazolin group and 64 years

Table 1. Baseline Characteristics of 71 Patients With MSSA Bacteremia Unless Noted

	Cefazolin (n = 38)	Ceftriaxone (n = 33)	*P* Value
Age, mean ± SD, y	63 ± 10.7	64 ± 13.6	.724
Male, n (%)	36 (95)	32 (97)	.641
Hemodialysis, n (%)	9 (24)	0 (0)	.003
Prosthesis, n (%)	20 (53)	8 (24)	.015
Race (n = 67),[a] n (%)			.457
African American	13 (35)	8 (27)	
Caucasian	24 (65)	22 (73)	
Comorbid disease states			
Hypertension	33 (87)	24 (73)	.136
Diabetes mellitus	23 (61)	18 (55)	.611
Peripheral vascular disease	9 (24)	7 (21)	.804
Coronary artery disease	14 (37)	8 (24)	.252
Heart failure	10 (26)	10 (30)	.71
Hematologic/oncologic disorder	8 (21)	9 (27)	.54
Psychiatric disorder	6 (16)	7 (21)	.556
Alcohol/tobacco use	18 (47)	14 (42)	.676
Intravenous drug use	5 (13)	0 (0)	.039

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

[a]Other/unknown race excluded from statistical analysis.

for the ceftriaxone group. Intravenous drug use was the only comorbid disease state that differed significantly between treatment groups as cefazolin was favored, 13% versus 0%.

Treatment and Infection Characteristics

Duration of parenteral therapy was similar between the cefazolin and ceftriaxone groups (37.8 days versus 38.1 days; P = .938) (Table 2). The majority of patients received 2-g doses of cefazolin and ceftriaxone, 95% and 88%, respectively. Significant differences in the primary source of bacteremia between the treatment groups was not evident; however, there was a trend toward more patients in the cefazolin group having an associated endovascular source of infection and more patients in the ceftriaxone group having skin and soft tissue infection. Overall, osteoarticular infection was the most common associated infection, followed by an endovascular source, with a total of 7 patients having presumed endocarditis, per the infectious diseases physician and echocardiogram. Rates for the achievement of source control did not differ significantly between cefazolin and ceftriaxone (20 [56%] versus 19 [58%], P = .631], respectively. Time to blood culture clearance was similar between cefazolin and ceftriaxone (2.8 days versus 3.5 days, P = .276). Additionally, there were no significant differences between treatment groups for the rate of blood culture clearance within 72 hours (cefazolin 26 [74%] versus ceftriaxone 21 [66%], P = .439) and persistent bacteremia (cefazolin 1 [3%] versus ceftriaxone 1 [3%], P = .949).

Outcomes

Of the 71 patients with MSSA bacteremia, there were 29 overall treatment failures (Table 3). Rates of treatment failure were higher in the ceftriaxone group than the cefazolin group (18 [55%] versus 11 [29%], P = .029). Of the reasons that accounted for treatment failure, only extension of parenteral therapy and incomplete course of parenteral therapy were significantly different between treatment groups. Extension of parenteral therapy (ceftriaxone 7 [21%] versus cefazolin 0 [0%], P = .003) was secondary to 2 patients who required additional source control and 5 patients who had persistent signs and symptoms of infection that required the duration to be extended. An incomplete course of parenteral therapy (ceftriaxone 0 [0%] versus cefazolin 5 [13%], P = .031) was secondary to 2 patients with adverse events that required change in therapy, 2 patients who died before therapy completion, and 1 patient who had therapy modified due to development of vancomycin-resistant *Enterococcus faecium* bacteremia. There was a trend toward greater overall 90-day mortality in the cefazolin-treated group compared with those treated with ceftriaxone (11% versus 3%). The rate of *C. difficile* infection between the treatment groups was not different. Adverse events were similar in the treatment groups. The ceftriaxone group did not have any changes in therapy due to an adverse event, whereas the cefazolin group had 1 patient change therapy due to rash and urticaria and another patient change therapy due to neutropenia. Ceftriaxone had a slightly higher cost for a complete course of parenteral therapy per patient than cefazolin ($868.72 versus $760.80).

The majority of the patients received OPAT in the home setting (Table 4). The only significant differences in treatment failures based on location were between those patients treated in the VA's attached Community Living Center (CLC) and external skilled nursing facilities (SNFs), 17% and 71% (P = .008), respectively. Other factors that were found to be predictive of treatment failure included longer duration of parenteral therapy (OR, 1.05; 95% CI, 1.01–1.1; P = .015) and heart failure (OR, 7.93; 95% CI, 2.43–25.92; P < .001) (Table 5).

Table 2. Treatment and Infection Characteristics

	Cefazolin (n = 38)	Ceftriaxone (n = 33)	*P* Value
Duration of parenteral therapy, mean ± SD, d	37.8 ± 8.3	38.1 ± 18.8	.938
Duration of empiric therapy, mean ± SD, d	3.7 ± 2.5	3.9 ± 2.2	.734
Primary source, n (%)			.086
Osteoarticular	16 (42)	12 (36)	
Endovascular	12 (32)	5 (15)	
Presumed endocarditis[a]	5 (13)	2 (6)	
Skin and soft tissue infection	3 (8)	11 (33)	
Urinary tract	2 (5)	1 (3)	
Unknown	5 (13)	4 (12)	
Achievement of source control, n (%)	20 (56)	19 (58)	.631
Duration of bacteremia, mean ± SD, d	2.8 ± 1.8	3.5 ± 3.3	.276
Blood culture clearance within 72 h, n (%)	26 (74)	21 (66)	.439
Bacteremia that persists ≥7 d, n (%)	1 (3)	1 (3)	.949

[a]Presumed endocarditis based on echocardiogram and suspicion of infectious diseases physician.

Table 3. Clinical Outcomes of 71 Patients With MSSA Bacteremia

	Cefazolin (n = 38), n (%)	Ceftriaxone (n = 33), n (%)	*P* Value[a]
Treatment failure	11 (29)	18 (55)	.029
Extension of parenteral therapy	0 (0)	7 (21)	.003
Incomplete course	5 (13)	0 (0)	.031
Relapse after treatment	2 (5)	4 (12)	NS
Readmission	5 (13)	6 (18)	NS
Unplanned surgical intervention	1 (3)	5 (15)	NS
Unplanned oral antimicrobials	2 (5)	4 (12)	NS
Lost to follow-up	2 (5)	4 (12)	NS
Mortality	4 (11)	1 (3)	NS
Clostridium difficile infection	2 (5)	1 (3)	NS
Adverse events	2 (5)	1 (3)	NS
Change of therapy due to adverse event	2 (5)	0 (0)	NS

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; NS, nonsignificant.
[a]Not significant ($P \geq .05$).

Table 4. Treatment Failure According to OPAT Setting

	Home (n = 39), n (%)	CLC (n = 18), n (%)	SNF (n = 14), n (%)	*P* Value	Significant Setting Differences
Treatment failure	16 (41)	3 (17)	10 (71)	.008	SNF > CLC

Abbreviations: CLC, Community Living Center (Department of Veterans Affairs nursing home); OPAT, outpatient parenteral antimicrobial therapy; SNF, skilled nursing facility.

DISCUSSION

Our hospital and many others frequently use cefazolin and ceftriaxone for MSSA bacteremia due to more convenient dosing and perceived lower number of adverse events than antistaphylococcal penicillins. Additionally, previous studies have found similar favorable treatment outcomes with cefazolin or ceftriaxone as an alternative to antistaphylococcal penicillins for MSSA infections [4–6]. To our knowledge, this is the first trial that has compared cefazolin versus ceftriaxone head-to-head specifically for the treatment of MSSA bacteremia [10, 11].

We found higher rates of treatment failure with ceftriaxone, whereas multiple previously published retrospective studies have not described differences in treatment failure rates between cefazolin and ceftriaxone for various MSSA infections. Winans et al. showed similar favorable clinical outcomes for cefazolin and ceftriaxone in 122 patients treated for various types of MSSA infections (67.9% and 79.5%, $P = .17$, respectively) [10]. In another evaluation, Patel et al. described similar clinical cure rates comparing ceftriaxone with standard of care therapy, which included cefazolin, vancomycin, and nafcillin, in 93 Veteran patients treated for various types of MSSA infections (83.3% and 74.5%, $P = .303$, respectively) [11]. Higher rates of treatment failure with third-generation cephalosporins, ceftriaxone, and cefotaxime for MSSA bacteremia have been reported, but these data by Paul et al. included both cefazolin and cloxacillin as a single comparator [12]. In this study, higher 30-day mortality rates with third-generation cephalosporins were found when compared with cloxacillin/cefazolin therapy (OR, 2.24; 95% CI, 1.23–4.08; $P = .008$). Our study had similar rates of treatment failure in the cefazolin treatment group compared with previous studies.

Table 5. Risk Factors Predictive of Treatment Failure

	OR (95% CI)	*P* Value
Duration of parenteral therapy	1.05 (1.01–1.1)	.015
Hemodialysis	0.69 (0.16–3.03)	.624
Prosthesis	0.7 (0.26–1.87)	.478
Race	1.68 (0.57–4.93)	.343
Comorbid disease states		
Hypertension	0.9 (0.28–2.95)	.864
Diabetes mellitus	1.35 (0.52–3.55)	.54
Peripheral vascular disease	1.62 (0.53–4.97)	.397
Coronary artery disease	1.72 (0.62–4.77)	.293
Heart failure	7.93 (2.43–25.92)	<.001
Hematologic/oncologic disorder	0.36 (0.1–1.24)	.096
Psychiatric disorder	1.3 (0.39–4.38)	.667
Alcohol/tobacco use	1.24 (0.48–3.22)	.652

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

Although definitive conclusions regarding the reasons for higher treatment failure rates with ceftriaxone are not known, several possibilities exist. Firstly, although other studies have evaluated various types of MSSA infections with or without bacteremia, our study solely focused on the rates of treatment failure in MSSA bacteremia, thus reducing the variability in treatment between multiple disease states without a subsequent bacteremia. From a biological plausibility standpoint, it is possible that the differing MIC distributions between ceftriaxone and cefazolin [17] and/or the higher protein binding manifested by ceftriaxone resulting in lower serum-free drug concentration could contribute to treatment failure [18]. Secondly, another possibility is that there were more patients treated with cefazolin in the VA's attached CLC than those treated with ceftriaxone, 34% and 15%, respectively. Conversely, more patients in the ceftriaxone group were treated at an external SNF than those treated with cefazolin, 30% and 11%, respectively. Of those patients treated at an external SNF, there were 9 treatment failures in the ceftriaxone group and 1 treatment failure in the cefazolin group. The differences in treatment failure rates based on the location of treatment in the VA's attached CLC and external SNF could be due to closer monitoring of therapy and the availability of infectious diseases physicians in the VA's CLC.

Our study has several limitations. Firstly, our analysis is retrospective, and it is possible that unknown variables could have affected the results, for instance, the clinical factors that led to the choice between cefazolin and ceftriaxone by the infectious diseases physician, such as the source of infection. Although the predominant source of infection in both groups was osteoarticular infections, skin and soft tissue was the second most frequent source of infection in the ceftriaxone group, whereas endovascular infection was the second most frequent source in the cefazolin group. The differences in the source of infection could explain why the overall duration of parenteral therapy was similar between the groups despite ceftriaxone having the duration of parenteral therapy extended more often than cefazolin. This could illustrate the infectious diseases physicians' preference at our site to use ceftriaxone in patients with an uncomplicated bacteremia who would generally be able to receive a shorter duration of therapy. Secondly, although all patients had MSSA bacteremia, many patients may have had a metastatic foci

of infection as a result of bacteremia that could have resulted in a higher number of treatment failures. However, significant differences were not found in the primary source of infection or rate of source control between treatment groups that would have favored cefazolin over ceftriaxone, and the overall duration of parenteral therapy was similar between both groups. As the majority of patients met criteria for complicated bacteremia, the duration of therapy was similar to the recommended duration of therapy for complicated bacteremia of 4–6 weeks, per the Infectious Diseases Society of America methicillin-resistant *Staphylococcus aureus* guidelines [19]. Lastly, patients who were planned to have OPAT with ceftriaxone were occasionally given cefazolin until discharge from the hospital. Cefazolin is more commonly used for MSSA infections in acute care because the difference in convenience between once-daily and every-8-hour regimens are not as impactful; therefore, strictly looking at those who received ceftriaxone or cefazolin for the full duration would have substantially reduced the sample size in this retrospective study. Treatment durations were accounted for in the analysis; however, there were no patients who received more than 7 days of cefazolin before being placed on OPAT with ceftriaxone.

In conclusion, our study results suggest that cefazolin may be preferred to ceftriaxone for MSSA bacteremia in a high-acuity Veteran population, based on higher rates of treatment failure in the ceftriaxone group. Further research, preferably prospective, randomized clinical trials, are needed to validate that ceftriaxone may not be a suitable alternative to cefazolin for MSSA bacteremia, as previous retrospective studies have found similar clinical outcomes between cefazolin and ceftriaxone when used for various MSSA infections.

Acknowledgments

The authors thank the VISN 10 Geriatric Research Education and Clinical Center's Statistical Resource Center for its support and assistance with biostatistical analysis for this project.

Financial support. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors and was conducted as a routine part of our work and the work of the organization.

Potential conflicts of interest. S.V.S. serves on the Speaker's Bureau for Allergan (formerly Actavis). R.A.B. is supported by funds from the National Institutes of Health and VA Merit Award. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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