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Original Article

A comparison of safety and outcomes with cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* bloodstream infections

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Abstract *Background:* Methicillin-susceptible *Staphylococcus aureus* (MSSA) is a frequent cause of bloodstream infections (BSI). Treatment with nafcillin (NAF) has been preferred to cefazolin (CFZ). However, comparable outcomes have been found with CFZ with possibly lower risk for side-effects. This study compared safety and effectiveness of NAF versus CFZ for MSSA BSI.
Methods: This single center retrospective study evaluated adults admitted with MSSA BSI who received NAF or CFZ. Patients receiving ≥24 h of antibiotics were included for safety analyses. Patients receiving NAF or CFZ for ≥75% of a 14 day minimum treatment course were assessed for clinical effectiveness. The primary safety outcome was incidence of renal toxicity with multiple secondary safety endpoints. Clinical success was defined as symptom resolution, repeat negative cultures, lack of additional therapy for presumed failure, and lack of recurrence within 30 days.
Results: A total of 130 patients receiving NAF (n = 79) or CFZ (n = 51) were included for safety analysis. Of those, 90 met criteria for effectiveness assessment (NAF n = 40, CFZ n = 50).

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Baseline characteristics were well matched. NAF was associated with a higher incidence of nephrotoxicity compared to CFZ (25% vs. 2%, RR 1.31, 95% CI 1.15—1.5, $p < 0.001$), allergic reactions ($p = 0.01$) and a trend for hepatotoxicity ($p = 0.08$). Clinical success was achieved in 82% NAF and 94% CFZ treated patients ($p = 0.1$).
Conclusion: CFZ was associated with less nephrotoxicity and no difference in clinical success compared to NAF for MSSA BSI. A prospective study comparing NAF to CFZ for MSSA BSI should be conducted to elucidate differences in therapies.

Introduction

Staphylococcus aureus is a frequent cause of both hospital-acquired and community-onset bloodstream infections (BSI), with methicillin-susceptible isolates (MSSA) representing nearly half the cases.[1] Important risk factors for the acquisition of staphylococcal BSI includes intravenous drug use, diabetes mellitus, presence of central-venous catheters, and receipt of renal replacement therapies.[2] Associated morbidity and mortality for MSSA BSI remain high. Additionally, patients with community-onset MSSA BSI are more likely to have complications of endocarditis, vertebral osteomyelitis, and death within 30 days compared to hospital-acquired cases.[3] Administration of anti-staphylococcal penicillins such as nafcillin (NAF) remains the standard of care for MSSA infections, with first-generation cephalosporins such as cefazolin (CFZ) providing an alternative treatment option.[4]

NAF use is limited by frequent administration requirements and lower rates of patient tolerability.[5–8] CFZ is a narrow-spectrum first-generation cephalosporin which has shown comparable activity for MSSA infections and an improved safety profile.[4] However, concerns for pronounced inoculum effects with CFZ use have been raised owing to increased concentrations of β-lactamase, particularly type A BlaZ.[9–11] Despite this, studies describe comparable clinical success between CFZ and NAF for MSSA infections, with improved patient tolerability favoring CFZ use.[4–8,12,13] These studies included few patients with complicated BSI in the CFZ group.[5,6,12,13] Evaluation of clinical outcomes between NAF- and CFZ-treated cases of MSSA BSI with an analysis to detect any differences based on the presence of high inoculum infections would be beneficial. The aim of this study was to 1) compare the safety/tolerability of NAF and CFZ for the treatment of MSSA BSI, 2) to determine any differences in effectiveness, 3) identify factors which may influence effectiveness and safety outcomes from the prescribed therapy.

Materials and methods

Study design and setting

This single center, retrospective study was conducted at a 467 bed tertiary academic medical center. The study was approved by the local institutional review board.

Data collection and definitions

Unique patients were identified from microbiology laboratory records of positive blood cultures for *S. aureus* from October 2011 through December 2013. Patient charts were retrospectively reviewed for baseline demographics, comorbidities, susceptibility data, site and/or type of infection, antimicrobials administered with doses and durations of therapy, physical findings, clinical laboratory data, and hospital encounter data using electronic medical records. Patients were included on the basis of positive blood culture for MSSA, age of 18—89 years, and treatment with NAF or CFZ for a minimum of 24 h. Patients with methicillin-resistant *S. aureus* or polymicrobial culture results were excluded.

The identified population meeting all inclusion and no exclusion criteria were further stratified into two groups for the purpose of data analysis. The intent-to-treat (ITT) population included all patients receiving at least 24 h of NAF or CFZ, and was used to assess safety outcomes. The second group constituted a modified-intent-to-treat (mITT), defined as receiving NAF or CFZ for ≥ 75% of a minimum 14-day initial intravenous (IV) antibiotic treatment course. The mITT population was used to assess treatment effectiveness.[6,12] Therefore, if patients had an adverse event to one therapy (NAF or CFZ) but successfully finished a minimum 14-day IV course of therapy with the alternative therapy (NAF or CFZ) which was ≥75% of the total treatment, they were counted as having an adverse event requiring a change in therapy for one therapy but clinical success was accredited to the other definitive therapy. If the change in therapy did not account for ≥75% of the duration of therapy, only the adverse event was counted. Healthcare associated infections were defined according to previously published definitions.[14] High inoculum infections were defined as presence of endocarditis, deep-seated abscess, osteomyelitis, or presence of irremovable foreign materials involved in the infection.[5,10]

Outcomes

Outcome and safety measures were defined prior to data retrieval. The primary safety outcome was incidence of renal toxicity according to previously published criteria (increase in serum creatinine ≥ 1.5 times or 0.5 mg/dL from baseline).[15] Secondary safety outcomes included thrombocytopenia (platelet count decreased to ≤ 50 × 10^3/μL

without other identifiable cause), hepatic impairment (increased transaminases and/or bilirubin $\geq$3 times the upper limit of normal without other identifiable cause), allergic reactions (including rash) not attributable to other medications, and change from or interruption in prescribed initial therapy for documented reasons of intolerance or adverse event. The primary effectiveness outcome was rate of clinical success defined as resolution or improvement in infectious signs and symptoms, continued negative growth from repeated blood cultures, no need for alternative antibiotic therapy for presumed treatment failure, and no readmission for recurrent *S. aureus* infection within 30 days of initial positive culture. Infectious signs and symptoms evaluated for improvement were fever resolution, WBC normalization, and hemodynamic stability. Secondary effectiveness outcomes included 30-day hospital readmission or ED visit after treatment conclusion, the rate of clinical improvement and microbiological success as assessed by measuring time to first negative blood culture, time to being afebrile for 24 h, and time to WBC normalization after initiation of NAF or CFZ therapy.

Data analysis

Categorical variables were compared using either Chi square or Fisher's exact test. Continuous variables were compared between groups using the Student's T-test or Mann—Whitney. Normality was determined through Goodness of Fit testing. Forward step multiple variable analyses were carried out to identify factors that may predict outcomes. Variables associated with treatment outcome at a p value < 0.2 by univariate analysis were eligible to be added to forward step multivariate regression. Previously identified potential confounding variables (e.g. gentamicin or rifampin use in the case of renal or hepatic injury, respectively) were controlled for even in the absence of univariate association. All statistical tests were two-sided, using a 95% confidence interval. Due to the retrospective nature of the study, we conducted a power analysis only for feasibility of showing a meaningful difference given our limited cohort. On the basis of previously published data and the anticipation of insufficient patient numbers to reach a non-inferiority margin of clinical effectiveness, we chose a primary safety endpoint. We estimated that a sample size of 50 patients per group would be needed to detect a 20% absolute difference in nephrotoxicity in CFZ recipients assuming a 25% incidence in NAF, an α of 0.05 and power of 0.8. All statistical analyses were conducted using JMP® Pro software and verified in version 13.1.0 (SAS Institute Inc., Cary, NC, 2016).

Results

Sample and baseline demographics

A total of 331 patients were identified as having *S. aureus* BSI of which 194 had MSSA and 130 met inclusion criteria. In the ITT population, 79/130 (61%) received NAF and 51/130 (39%) received CFZ. Further, 90/130 (69%) met criteria for inclusion in the mITT population: 40/90 (44%) treated with NAF and 50/90 (56%) treated with CFZ. Within the mITT population, six patients were initiated on NAF but required a switch for definitive therapy with CFZ following an adverse event attributable to NAF. Hence, six patients crossed over from the ITT population with a NAF adverse event to CFZ in the mITT analysis.

The most frequent sites of infection identified were musculoskeletal (26%), endocarditis (17%), central line-related (14%), and vascular graft (14%). In the mITT group, high inoculum infections were identified in 25/40 (63%) and 32/50 (64%) of NAF and CFZ treated patients, respectively. Adult dosing was 12 g/day continuous IV infusion for NAF and 6 g/day by divided intermittent or continuous IV administration for CFZ, or the dose adjusted equivalent in patients with renal impairment. A majority of patients (122/130 [94%]) received initial empiric therapy with vancomycin before switching to definitive NAF or CFZ. Overall median duration of empiric therapy prior to switching to NAF or CFZ was 63 (IQR, 43—82) hours. Baseline characteristics (Table 1) were comparable between ITT groups with the exception of a higher Charlson comorbidity index, and more frequent diabetes mellitus, end stage renal disease (ESRD), and classification as a health care associated infection in the CFZ group. Concomitant gentamicin was used more frequently in the NAF group for both ITT and mITT. For the mITT group, Charlson comorbidity index was higher, as was diabetes and ESRD more frequent in the CFZ group. The median duration of IV antibiotic use was not statistically different among the two groups and was between 31 and 38 days.

Safety

Therapy change for reasons other than treatment failure was higher in NAF recipients compared to CFZ (41/79 [51.9%] vs. 16/51 [31.4%], respectively, $p < 0.03$). Reasons for change included: toxicity, ease of administration, and broadened therapy for suspected secondary infections during admission. NAF was interrupted more frequently for toxicity compared to CFZ (25/79 [31.6%] vs. 1/51 [2%], respectively, $p < 0.001$). NAF use was associated with higher rates of nephrotoxicity (25.3% vs. 2%, $p = <0.001$), hepatotoxicity (11.4% vs 0%, $p = 0.01$), and allergic reactions (11.4% vs 0%, $p = 0.01$), not all resulting in treatment interruption (Table 2). Nephrotoxicity remained significantly higher in the NAF group versus CFZ after removing patients with baseline ESRD (20/73 [27.4%] vs. 1/34 [3%], $p = 0.003$) and comparing NAF to CFZ in the subset of ESRD-free and gentamicin-free patients (18/64 [28.8%] vs. 1/33 [3%], $p = 0.0025$). In patients without baseline ESRD, NAF ($p = 0.019$) and age ($p = 0.035$) were significantly associated with nephrotoxicity whereas baseline cirrhosis ($p = 0.068$) trended towards significance by multiple variable logistic regression (Table 3). Three NAF recipients required renal replacement modalities; two patients recovered baseline function and one continued to require intermittent hemodialysis throughout duration of hospital admission. The median time to nephrotoxicity in the NAF group was following the third full day of NAF initiation (IQR, 2—7 days). All nine cases of hepatotoxicity were associated with NAF, three of which included the addition of rifampin. Hepatotoxicity was no longer

Table 1 Summary of patient baseline characteristics.

Characteristic	ITT Population, n = 130			mITT Population, n = 90		
	NAF (n = 79)	CFZ (n = 51)	P	NAF (n = 40)	CFZ (n = 50)	P
Age, mean years ± SD	56 ± 18	53 ± 18.1	0.36	56.8 ± 19.3	55.9 ± 16.7	0.82
Gender, n = male (%)	51 (65)	28 (55)	0.28	23 (57.5)	27 (54)	0.83
Weight, mean kg ± SD	81.5 ± 23	78.1 ± 20	0.38	80.7 ± 21.9	83.6 ± 24.2	0.54
Charlson comorbidity index, median score (IQR)	4 (1–7)	5 (3–8)	0.04	3 (0–6)	6 (3–8)	0.03
Duration of IV antibiotics, median days (IQR)	38 (17–51)	31 (17–46)	0.19	37 (19–51)	36 (17–47)	0.42
Time to adequate antibiotics, median hours (IQR)	3 (2–11)	5 (1–11)	0.68	3 (2–11)	5 (2–15)	0.42
Time to NAF or CFZ antibiotic, median hours (IQR)	64 (43–85)	58 (44–79)	0.77	57 (41–80)	60 (44–80)	0.54
Infectious diseases consulted, n (%)	64 (81)	38 (74.5)	0.4	34 (85)	38 (76)	0.43
ICU residence, n (%)	44 (55.7)	22 (43)	0.21	20 (50)	18 (36)	0.2
Underlying Disease, n (%)						
Diabetes	24 (30.4)	27 (53)	0.016	13 (33)	27 (54)	0.055
Cirrhosis	6 (7.6)	3 (6)	0.99	2 (5)	5 (10)	0.46
End stage renal disease	6 (7.6)	17 (33)	<0.001	2 (5)	17 (34)	<0.001
Active malignancy	12 (15.2)	9 (17.6)	0.8	3 (8)	7 (14)	0.5
History of transplantation	4 (5)	5 (9.8)	0.31	1 (3)	4 (8)	0.38
HIV infection	2 (2.5)	0 (0)	0.52	1 (3)	0 (0)	0.44
Neutropenia	5 (6.3)	2 (3.9)	0.7	2 (5)	1 (2)	0.6
Infectious Source, n (%)						
Musculoskeletal	25 (31.6)	9 (17.6)	0.1	12 (30)	13 (26)	0.8
Endocarditis	15 (19)	7 (13.7)	0.48	8 (20)	8 (16)	0.78
Line associated	10 (12.7)	8 (15.7)	0.62	5 (13)	7 (14)	0.99
Vascular	7 (8.9)	11 (21.5)	0.066	5 (13)	10 (20)	0.4
Pneumonia	7 (8.9)	5 (9.8)	0.99	2 (5)	3 (6)	0.99
Skin and soft tissue	8 (10)	7 (13.7)	0.58	4 (10)	5 (10)	0.99
Gastrointestinal/genitourinary	2 (2.5)	2 (3.9)	0.64	0 (0)	2 (4)	0.5
Other	5 (6.3)	2 (3.9)	0.7	4 (10)	2 (4)	0.4
Healthcare associated infection, n (%)	41 (52)	36 (70.6)	0.044	24 (60)	34 (68)	0.5
High inoculum infection, n (%)	47 (59.5)	28 (55)	0.72	25 (63)	32 (64)	0.99
Source control, n (%)	42 (72)[a]	26 (72)[b]	0.99	22 (73)[c]	26 (68)[d]	0.79
Synergistic gentamicin coadministration, n (%)	10 (12.6)	1 (2)	0.049	8 (20)	0 (0)	0.001

[a] Percentage of 58 patients eligible for source control.
[b] Percentage of 36 patients eligible for source control.
[c] Percentage of 30 patients eligible for source control.
[d] Percentage of 38 patients eligible for source control.
ITT, intention to treat; mITT, modified intention to treat; NAF, Nafcillin; CFZ, Cefazolin; SD, standard deviation; NS, non-significant; IQR, inter-quartile range; IV, intravenous; MSSA, methicillin-susceptible *Staphylococcus aureus*; ICU, intensive care unit; HIV, human immunodeficiency virus.

Table 2 Safety outcomes: intention to treat patient population.

Characteristic	NAF (n = 79)	CFZ (n = 51)	P
Nephrotoxicity, n (%)	20 (25.3)	1 (2)	<0.001[a]
Hepatotoxicity, n (%)	9 (11.4)	0 (0)	0.01[b]
Allergic reaction, n (%)	9 (11.4)	0 (0)	0.01
Thrombocytopenia, n (%)	1 (1)	0 (0)	0.99

[a] p value = 0.003 after excluding baseline ESRD and 0.014 after adjusting for concomitant gentamicin use.
[b] p value = 0.08 after excluding hepatotoxicity with concomitant rifampin use.
NAF, Nafcillin; CFZ, Cefazolin.

significantly associated NAF when the three cases of hepatotoxicity associated with rifampin were removed from analysis (p = 0.08).

Clinical success and rate of improvement

Clinical success was identified in 89% of patients overall (Table 4). There were no significant differences identified between the NAF and CFZ treatment arms. Relative risk calculated for clinical success with CFZ compared to NAF was 1.14 (95% CI, 0.97–1.3). Multiple variable logistic regression identified ICU residence, diabetes, and age as independent risk factors for treatment failure (each, $p < 0.05$). Source of infection, high inoculum infection or retained prosthesis had no significant effect on clinical success nor did they significantly modify estimates of clinical success by treatment group NAF or CFZ.

Table 3 Multiple variable associations with nephrotoxicity: intention to treat population.

Characteristics Associated with Nephrotoxicity Excluding ESRD	Univariate Association	Multiple Variable Logistic Regression	Forward Step Parsimonious Regression Estimates	
	p-value	p-value	Unit Odds (95% CI)	p-value
Nafcillin	0.0002	0.018	12.6 (1.5—103.8)	0.019
Cirrhosis	0.037	0.037	4.8 (0.89—26.2)	0.068
Age	0.092	0.12	1.04 (1—1.07)	0.035
Serum creatinine at 24 h	0.1	0.6	NA	NA
Intravenous drug abuse	0.13	0.99	NA	NA
ICU Residence	0.15	0.097	2.37 (0.78—7.24)	0.13
Gentamicin synergy used	0.99	0.66	NA	NA

ESRD, End Stage Renal Disease; ICU, Intensive Care Unit; NA, not applicable because the variable did not meet pre-planned forward step entry criteria for the logistic regression.

Table 4 Clinical outcomes: modified-intention to treat patient population.

Endpoints	NAF (n = 40)	CFZ (n = 50)	P
Clinical Success, n (%)	33 (83)	47 (94)	0.1
Microbiological cure, n (%)	40 (100)	49 (98)	0.99
Resolution of signs and symptoms, n (%)	35 (88)	48 (94)	0.46
Antibiotic changed for presumed failure, n (%)	2 (5)	1 (2)	0.58
Infection related mortality, n (%)	4 (10)	3 (6)	0.48
30-day hospital readmission after treatment conclusion, n (%)	9 (23)	7 (14)	0.29
30-day ED visit after treatment conclusion, n (%)	9 (23)	9 (18)	0.6
Time to fever resolution, median hours (IQR)	28 (18—59)	21 (12—38)	0.1
Time to WBC normalization, median days (IQR)	3 (2—7)	4 (2—8)	0.47
Time to repeat negative blood culture, median days (IQR)	3 (2—5)	3 (2—5)	0.98

NAF, Nafcillin; CFZ, Cefazolin; IQR, inter-quartile range; ED, emergency department; WBC, white blood cell.

No differences were identified for rates of microbiological cure or resolution of signs and symptoms (Table 4). Infection-related mortality was not different between groups (NAF 4/40 [10%] vs. CFZ 3/50 [6%], p = 0.48). Time to event analyses for fever resolution, white blood cell count normalization, and negative culture were not significantly different between groups.

Discussion

This retrospective study found comparable outcomes between NAF and CFZ in the treatment of MSSA BSI, including a majority characterized as complicated and high inoculum infections. Despite previous data raising concerns with CFZ use in high inoculum infections such as endocarditis owing to increased concentrations of type A BlaZ, we did not find differences in rates of clinical success, microbiological cure, symptomatic improvement, or time to improvement.[9—11] We are unable to provide any information on the presence of the specific serotypes of BlaZ expressed in our population, as this determination is not readily performed by the microbiology laboratory at our institution. In vitro assessment of MSSA inoculum effects against CFZ may be influenced by regional differences, and may account for some rationale as to why our group and others did not identify differences in failure or recurrence in patients receiving CFZ. Bai et al. found no significant difference in 90-day mortality when comparing CFZ to cloxacillin, suggesting non-inferiority of CFZ and a trend towards lower mortality in those who received CFZ. A non-significant greater risk of relapse with CFZ use compared to cloxacillin (6/105 [6%] vs. 5/249 [2%], respectively) was also found.[13] However, shorter median treatment durations (17 days, IQR 13—31 days) and lower median CFZ doses (3 g) may have contributed to a numerically higher risk when considering deep-seated foci. Rao et al. retrospectively compared CFZ to oxacillin for MSSA BSI, including deep-seated infections. They found no significant differences in treatment failure overall, including those subgroups with deep-seated infection or endocarditis. Oxacillin was identified as a non-significant variable associated with treatment failure (OR 3.76 [95% CI 0.98—14.4], p = 0.053).[16] Compared to earlier studies that included fewer patients with endocarditis,[5,6,12,13] we included 16 patients with endocarditis evaluated for effectiveness (n = 8 for CFZ) and our results concur with those of Rao et al.[16] In multiple variable analyses, CFZ use was not associated with inferior outcomes, including patients with complicated courses and high initial bacterial burden.

A large United States-based Veterans Affairs retrospective cohort study associated CFZ with lower 30- and 90-day mortality compared to NAF or oxacillin.[17] The adjusted odds of recurrence in this large database was not different between treatment groups. To date, this remains the largest comparison between CFZ and NAF for MSSA BSI and

suggests a therapeutic benefit of CFZ. Although retrospective, this analysis included 3167 patients with 1167 receiving CFZ as definitive therapy, 52 of whom had endocarditis. Outcomes in the endocarditis group were not significantly influenced by CFZ use.[17]

Tolerability of the prescribed therapy in our study favored CFZ with fewer therapy interruptions for reasons not associated with treatment failure. Both nephrotoxicity and allergic reactions were significantly less frequent among patients receiving CFZ, with a trend towards reduced hepatotoxicity. Although unable to definitively attribute all nephrotoxic events to the antibiotic used, timing of onset and consulting nephrology and/or infectious diseases services documented a strong possibility of interstitial nephritis resulting from the initial antibiotic selection. It should be noted that 14% of NAF patients received concomitant gentamicin compared to 2% of CFZ patients despite a lack of data supporting routine synergistic use of gentamicin in MSSA BSI. After excluding patients who received gentamicin and those with ESRD at baseline, nephrotoxicity remained significantly higher in the NAF group. Infective endocarditis itself is a significant contributor to pathologic kidney injury.[18] NAF recipients remained at higher risk of renal toxicity considering that an endocarditis diagnosis was not different between the groups (Table 1). Our safety findings are similar to other retrospective analyses. Flynt et al. associated NAF with a significant increase in kidney injury compared to CFZ (33% vs 13%, $p = 0.007$).[19] Furthermore, a large outpatient parenteral antimicrobial therapy (OPAT) clinic database showed significant reductions in both premature antimicrobial discontinuation and drug-emergent events with CFZ use.[7] These differences in adverse events were not found in all previous studies, although significantly less changes to an alternative therapy with CFZ were reported.[16]

Avoidance of treatment emergent adverse events, especially nephrotoxicity and renal replacement therapies, is likely to reduce indirect treatment costs. Minimizing treatment interruptions may correlate with improved overall clinical outcomes given low failure rates and fewer interruptions in therapy identified in the CFZ group. Although this study was not designed to evaluate economic outcomes, CFZ use is considerably less costly compared to NAF when taking into account only average wholesale price and the median treatment duration. A similar economic impact has been suggested by others.[19] Future studies to assess the cost-benefit of using primarily CFZ as opposed to NAF would be ideal to include both direct and indirect cost differences.

Based on the retrospective nature of this study, several limitations exist. First, this study was not powered to detect significant differences in effectiveness; however, given the trends towards improved outcomes in the CFZ group it is reasonable to infer that with more patients either no difference or a difference favoring CFZ therapy would be demonstrated.[4] Secondly, approximately 71% of all patients in the mITT group received some form of source control early in the course of therapy which may have led to improved outcomes despite antibiotic choice. Early source control in high inoculum infections may decrease the clinical impact of type A beta-lactamase on CFZ. Previous studies of MSSA BSI found retained hardware is significantly associated with mortality (adjusted OR, 7.8; 95% CI, 2.02–29.9) irrespective of CFZ treatment.[11] Early source control was achieved with similar frequency in both the CFZ and NAF groups in our study. Third, this was a single center experience, which may impact the external validity of the data, especially considering we were unable to test for BlaZ serotypes. Fourth, despite being able to include eight patients in each arm with endocarditis, this is still a relatively small number of subjects and does not eliminate the risk of CFZ inoculum effects noted in models of endocarditis and those with severe MSSA infections.[20] Next, we did not analyze patients with regards to central nervous system involvement. Finally, we chose to look at clinical success at 30 days, which does not account for late failures and relapses. However, definitive treatment durations without failure (total median of 36 days), and 30-day hospital and emergency department readmissions after treatment conclusion were not different between NAF and CFZ. Despite these limitations, and given the significant association of toxicity with NAF, the use of CFZ may be considered with close monitoring, aggressive source control and dose optimization.

In conclusion, CFZ was better tolerated and therapy was less frequently interrupted for treatment emergent adverse events compared to NAF. CFZ showed comparable effectiveness to NAF for treating MSSA BSI. Notably, this study included a comparatively large number of high inoculum infections and more endocarditis cases than in previous studies. Larger, prospective studies are necessary to fully evaluate differences in effectiveness and safety between these two agents for complicated MSSA BSI and endocarditis.

Conflicts of interest

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Authors report no relevant conflicts of interest and are alone responsible for the content and writing of the paper.

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