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Is Cefazolin Inferior to Nafcillin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bacteremia?▽

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About 20% of methicillin-susceptible *Staphylococcus aureus* (MSSA) isolates have a substantial inoculum effect with cefazolin, suggesting that cefazolin treatment may be associated with clinical failure for serious MSSA infections. There are no well-matched controlled studies comparing cefazolin with nafcillin for the treatment of MSSA bacteremia. A retrospective propensity-score-matched case-control study was performed from 2004 to 2009 in a tertiary care hospital where nafcillin was unavailable from August 2004 to August 2006. The cefazolin group ($n = 49$) included MSSA-bacteremic patients treated with cefazolin during the period of nafcillin unavailability, while the nafcillin group ($n = 84$) comprised those treated with nafcillin. Treatment failure was defined as a composite outcome of a change of antibiotics due to clinical failure, relapse, and mortality. Of 133 patients, 41 patients from each group were matched by propensity scores. There were no significant differences in baseline characteristics between the matched groups. The treatment failure rates were not significantly different at 4 or 12 weeks (10% [4/41] versus 10% [4/41] at 4 weeks [$P > 0.99$] and 15% [6/41] versus 15% [6/41] at 12 weeks [$P > 0.99$]). Cefazolin treatment was interrupted less frequently than nafcillin treatment due to drug adverse events (0% versus 17%; $P = 0.02$). Cefazolin had clinical efficacy similar to that of nafcillin and was more tolerable than nafcillin for the treatment of MSSA bacteremia.

Methicillin-susceptible *Staphylococcus aureus* (MSSA) is a major pathogen in community-acquired infections, although methicillin resistance is increasing (7). Cefazolin, a narrow-spectrum cephalosporin, has been used for the treatment of MSSA infections since the 1970s. Some case reports from the 1970s suggested that cefazolin use was associated with treatment failure because it is efficiently hydrolyzed by *S. aureus*-produced β-lactamase (Bla) (2, 12). Among 4 identified Blas, type A Bla most efficiently hydrolyzes cefazolin (14). Recently, a study demonstrated that about 20% of MSSA isolates showed a substantial inoculum effect and suggested that cefazolin treatment might be associated with clinical failure for serious MSSA infections (10).

Despite concerns about the risk of failure, cefazolin is widely used for MSSA infections and is recommended as an alternative agent, even for endocarditis, because of its convenient dosing and tolerability (1). This is despite the fact that no studies have directly compared the tolerability of cefazolin to those of other antistaphylococcal penicillins such as nafcillin or cloxacillin. To our knowledge, there have also been no prospective studies that have compared cefazolin with antistaphylococcal penicillin for the treatment of MSSA bacteremia. A recent retrospective study suggested that there was no significant difference between cefazolin and cloxacillin treatments of MSSA bacteremia (11). However, the data could be skewed because physicians tend to use antistaphylococcal penicillin for more serious infections and cefazolin for less serious infections. In order to minimize these confounding factors, we designed this propensity-score-matched case-control study.

The purpose of this study was to compare clinical outcomes and drug tolerabilities between cefazolin and nafcillin for the treatment of MSSA bacteremia.

MATERIALS AND METHODS

Study design. A retrospective, propensity-score-matched, case-control study was conducted from 2004 to 2009 in a tertiary care hospital in Seoul, South Korea. No penicillinase-resistant penicillin, including nafcillin, was available at this hospital from August 2004 to August 2006 due to problems with the supplier. During the period of nafcillin unavailability, the patients with MSSA bacteremia were treated mainly with cefazolin, but those with suspected infection of the central nervous system received vancomycin or a broad-spectrum cephalosporin.

All patients with MSSA-positive blood cultures who received cefazolin or nafcillin as definite antibiotics between January 2004 and June 2009 were identified from computerized records. The cefazolin-treated group included MSSA-bacteremic patients treated with cefazolin as the antibiotic of choice during the period of nafcillin unavailability, while the nafcillin-treated group comprised those treated with nafcillin. Blood cultures were repeated every 48 h until a negative conversion of the cultures occurred; only the first episode of *S. aureus* bacteremia was included in our analysis. The institutional review board at Seoul National University Hospital approved the study protocol.

Definitions. The sites of infection were defined as follows. Catheter-related infection was considered to be the source of bacteremia if the catheter had been in place for ≥72 h, if the culture of a specimen of purulent drainage from the insertion site showed *S. aureus*, or if clinical signs improved after the catheter was removed and there was no other source of bacteremia. Pneumonia was considered to be the source of *S. aureus* bacteremia if the patient had clinical symptoms and signs of a lower respiratory tract infection and if there was radiological evidence of pulmonary infiltrates not attributable to other causes. Soft tissue infection was considered to be the source of *S. aureus* bacteremia when patients had an *S. aureus* culture from a tissue or a drainage specimen from the affected site as well as signs of infection. Surgical wound infection was defined according to the definition of the Centers for Disease Control and Prevention (4). McCabe classification, which was performed by a clinician (S.L.), was used to determine the severity of the underlying illness. High-burden disease was defined as MSSA bacteremia that accompanied endocarditis, unremovable vascular graft infection, osteomyelitis, pneumonia, deep-seated abscess, or metastatic infection (10).

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Treatment failure was defined as (i) switching of antibiotics due to the clinician's opinion that treatment had failed (i.e., a lack of improvement of the clinical symptoms and signs, persistence of bacteremia, or development of metastatic infections during treatment), (ii) recurrence of MSSA infection (i.e., resolution of clinical signs of infection during therapy but recurrent MSSA infection during the follow-up period), or (iii) MSSA bacteremia-associated mortality.

Statistical analysis. SPSS software, version 15.0 (SPSS, Chicago, IL), was used for all statistical analyses. Multivariate logistic regression analysis was used to evaluate the effect of cefazolin on treatment failure after adjustment by potential confounders. Cefazolin treatment and variables with P values of less than 0.2 in univariate analyses were included in the multivariate analyses.

Logistic regression was used to model the probability of treatment with nafcillin based on risk factors reported by previous studies: age, McCabe classification, high-burden disease, site of infection, and focus eradication (6). The predicted probability of the model was used as the propensity score for each patient. For the propensity-score-matched case-control study, patients in the cefazolin treatment group were matched with patients in the nafcillin treatment group who had the closest propensity scores. We excluded 8 cases in which the propensity score difference was more than 0.01. The treatment failure rates were compared between the propensity-score-matched groups 4 and 12 weeks after the start of cefazolin or nafcillin treatment.

For unmatched analyses, Fisher's exact test or a Pearson χ^2 test was used as appropriate to compare categorical variables, and continuous variables were compared by using the Student t test. For propensity-score-matched analyses, we used McNemar's test to compare categorical variables and the paired t test for continuous variables. All tests of significance were 2 tailed; a P value of <0.05 was considered to be significant.

RESULTS

Clinical characteristics. Of the 174 patients with MSSA bacteremia, 84 were treated with nafcillin (nafcillin treatment group), and 90 were treated with cefazolin. Of 90 patients treated with cefazolin, 49 were treated during the period of nafcillin unavailability (cefazolin treatment group), and 41 patients treated during the period when nafcillin was available were excluded from further analyses. During the period when nafcillin was available, skin and soft tissue infections were more common in patients receiving cefazolin than in those receiving nafcillin (43.9% [18/41] versus 7.1% [6/84] [$P < 0.01$]), and endocarditis and metastatic infections were less common in patients receiving cefazolin (2.4% [1/41] versus 15.5% [13/84] [$P = 0.03$] and 2.4% [1/41] versus 27.4% [23/84] [$P < 0.01$], respectively).

Of the 133 patients in the cefazolin or nafcillin treatment group, there were 62 (46.6%) community-acquired cases and 71 (53.4%) hospital-acquired cases. Thirty-one patients (23.3%) had metastatic infections. Most patients with endocarditis (13/14) were in the nafcillin treatment group (Table 1).

Effect of cefazolin treatment on treatment failure. The treatment failure rates for MSSA bacteremia were 12.8% (17 of 133 patients) at 4 weeks and 15.8% (21 of 133) at 12 weeks. In a univariate analysis, underlying cardiovascular disease, metastatic infection, and endocarditis and pneumonia as the site of infection were significantly associated with treatment failure at 4 weeks (Table 2). In multivariate analyses, endocarditis (adjusted odds ratio [aOR], 8.6; 95% confidence interval [CI], 2.0 to 36.8; $P < 0.01$) and pneumonia (aOR, 6.0; 95% CI, 1.5 to 23.7; $P = 0.02$) were significantly associated with treatment failure. After adjustment for these variables, cefazolin treatment was not associated with treatment failure at 4 weeks (aOR, 1.2; 95% CI, 0.3 to 4.5; $P = 0.76$). The results at 12 weeks were similar to those at 4 weeks (Table 2).

TABLE 1. Clinical characteristics of 133 patients in the cefazolin and nafcillin treatment groups

Characteristic	Value for group		
	Cefazolin treatment ($n = 49$)	Nafcillin treatment ($n = 84$)	Total ($n = 133$)
Mean age (yr) ± SD	55 ± 20	52 ± 17	53 ± 18
No. (%) of patients			
Male	29 (59)	49 (58)	78 (59)
Community-acquired infection	19 (39)	43 (51)	62 (47)
Length of hospital stay before SAB of:			
<72 h	19 (39)	47 (56)	66 (50)
3–7 days	8 (16)	12 (14)	20 (15)
8–28 days	16 (33)	20 (24)	36 (27)
>28 days	6 (12)	5 (6)	11 (8)
McCabe classification of:			
Nonfatal	19 (39)	24 (29)	43 (32)
Ultimately fatal	21 (43)	40 (48)	61 (46)
Rapidly fatal	9 (18)	20 (24)	29 (22)
Underlying disease			
Hematologic malignancy	12 (25)	22 (26)	34 (26)
Solid tumor	15 (31)	12 (14)	27 (20)
Cardiovascular disease	3 (6)	17 (20)	20 (15)
Liver cirrhosis	7 (14)	9 (11)	16 (12)
End-stage renal disease	2 (4)	10 (12)	12 (9)
Neutropenia	9 (18)	18 (21)	27 (20)
Site of infection			
Catheter related	11 (22)	17 (20)	28 (21)
Osteomyelitis	10 (20)	11 (13)	21 (16)
Soft tissue	10 (20)	10 (12)	20 (15)
Pneumonia	4 (8)	11 (13)	15 (11)
Endocarditis	1 (2)	13 (16)	14 (11)
Surgical site	4 (8)	8 (10)	12 (9)
Arthritis	1 (2)	10 (12)	11 (8)
Primary bacteremia	13 (27)	19 (23)	32 (24)
Eradicated foci of infection	14 (29)	22 (26)	36 (27)
Metastatic infection	8 (16)	23 (27)	31 (23)
High-burden disease	20 (41)	44 (52)	64 (48)

Propensity-score-matched case-control study. Forty-one patients in the cefazolin treatment group were matched with the 41 patients in the nafcillin treatment group with the closest propensity scores. The clinical characteristics and demographic data of the patients were comparable in the matched groups (Table 3). Nineteen patients (46%) in the matched cefazolin group and 18 patients (44%) in the matched nafcillin group had high-burden disease. The median durations of cefazolin and nafcillin treatment were 17 days (interquartile range [IQR], 10 to 28 days) and 15 days (IQR, 10 to 25 days). Times to defervescence were 4.4 ± 4.9 days in the matched cefazolin group and 5.4 ± 9.3 days in the matched nafcillin group ($P = 0.63$).

The treatment failure rates at 12 weeks were 15% (6/41) in the cefazolin treatment group and 15% (6/41) in the nafcillin treatment group ($P > 0.99$). The rates of *S. aureus* bacteremia (SAB)-related mortality were 2% (1/41) in the cefazolin treatment group and 12% (5/41) in the nafcillin treatment group ($P = 0.22$). There was no significant difference between the matched groups in terms of 4-week mortality (4% versus 4%; $P > 0.99$). For four patients in the cefazolin treatment group, the antibiotic agent was changed due to clinical failure; vancomycin replaced cefazolin in three cases, and nafcillin, which

TABLE 2. Multivariable logistic regression analysis for treatment failure and effect of cefazolin on treatment failure at 4 and 12 weeks

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Treatment failure at 4 wk				
Male	2.6 (0.8–8.3)	0.11	2.9 (0.8–10.8)	0.12
Cardiovascular disease	5.5 (1.8–17.1)	0.01		
Site of infection				
Catheter related	0.2 (0.0–1.6)	0.12		
Pneumonia	4.4 (1.3–15.2)	0.03	6.0 (1.5–23.7)	0.02
Endocarditis	7.4 (2.2–25.1)	<0.01	8.6 (2.0–36.8)	<0.01
Surgical site	2.5 (0.6–10.5)	0.18		
Primary bacteremia	0.2 (0.0–1.3)	0.07	0.2 (0.0–1.8)	0.15
Eradicated foci of infection	0.3 (0.1–1.5)	0.16		
Metastatic infection	3.6 (0.1–10.3)	0.03		
Cefazolin treatment	0.7 (0.2–2.1)	0.50	1.2 (0.3–4.5)	0.76
Treatment failure at 12 wk				
Old age (≥65 yr)	2.1 (0.8–5.4)	0.14		
Male	2.6 (0.9–7.5)	0.08	3.0 (0.9–10.4)	0.08
Hematologic malignancy	0.3 (0.1–1.2)	0.07	0.2 (0.0–1.2)	0.08
Cardiovascular disease	5.1 (1.8–14.9)	<0.01		
Site of infection				
Catheter related	0.2 (0.0–1.2)	0.08	0.2 (0.0–1.5)	0.11
Pneumonia	4.6 (1.4–14.7)	0.02	5.6 (1.4–21.7)	0.01
Endocarditis	7.5 (2.3–24.5)	<0.01	6.7 (1.6–27.9)	0.01
Primary bacteremia	0.1 (0.0–1.0)	0.02	0.1 (0.0–0.9)	0.04
Eradicated foci of infection	0.2 (0.1–1.1)	0.05		
Metastatic infection	3.1 (1.1–8.2)	0.05		
Cefazolin treatment	0.8 (0.3–2.2)	0.72	1.6 (0.5–5.4)	0.45

TABLE 3. Clinical characteristics of 82 patients with methicillin-susceptible *S. aureus* bacteremia who were included in the propensity-score-matched analysis

Characteristic	Value for group		*P* value
	Cefazolin treatment (*n* = 41)	Nafcillin treatment (*n* = 41)	
Mean age (yr) ± SD	53 ± 19	54 ± 15	0.63
No. (%) of patients			
Male	23 (56)	25 (61)	0.83
Community-acquired infection	17 (42)	24 (59)	0.17
With McCabe classification of ultimately or rapidly fatal	27 (66)	30 (73)	0.58
Underlying disease			
Solid tumor	13 (31)	9 (22)	0.42
Hematologic malignancy	11 (27)	10 (24)	>0.99
Liver cirrhosis	7 (17)	5 (12)	0.75
End-stage renal disease	2 (5)	6 (15)	0.22
Cardiovascular disease	2 (5)	4 (10)	0.69
Neutropenia	8 (20)	9 (22)	>0.99
Site of infection			
Soft tissue	9 (22)	8 (20)	>0.99
Osteomyelitis	10 (24)	7 (17)	>0.99
Catheter related	8 (20)	7 (17)	>0.99
Surgical site	4 (10)	6 (15)	0.75
Pneumonia	3 (7)	4 (10)	>0.99
Endocarditis	1 (2)	1 (2)	>0.99
Arthritis	1 (2)	3 (7)	>0.99
Primary bacteremia	9 (22)	9 (22)	0.75
Eradicated foci of infection	12 (29)	11 (27)	>0.99
Metastatic infection	7 (17)	6 (15)	>0.99
High-burden disease	19 (46)	18 (44)	>0.99

was imported through the Korea Orphan Drug Center, was used in one case. Of these patients, clinical failure was determined by a lack of an improvement of the clinical symptoms and signs ($n = 2$), the persistence of bacteremia ($n = 1$), and the development of metastatic infections during treatment ($n = 1$).

Cefazolin treatment was interrupted less frequently due to adverse drug events than was nafcillin (0 [0%] versus 7 [17%]; $P = 0.02$) (Table 4). Of 7 patients who discontinued nafcillin due to adverse events, the adverse events were drug-induced fever ($n = 4$), cytopenia ($n = 2$), and phlebitis ($n = 1$), and the median time to the discontinuation of nafcillin was 19 days (IQR, 7 to 24 days). Three patients experienced adverse events within 2 weeks of the start of nafcillin treatment.

DISCUSSION

This propensity-score-matched case-control study found that cefazolin and nafcillin show similar treatment outcomes for MSSA bacteremia. Although some investigators have suggested that cefazolin use might be associated with treatment failure in serious *S. aureus* infections due to the inoculum effect of type A Bla (9, 10), our results support the use of cefazolin for the treatment of MSSA bacteremia.

Although there have been retrospective studies that compared the outcomes of treatment with cefazolin with those of treatment with antistaphylococcal penicillins for MSSA bacteremia, those studies may have had selection bias because physicians tend to select nafcillin for the treatment of more serious infections, as our study demonstrated. Our study was designed to minimize this selection bias. First, the cefazolin

TABLE 4. Comparison of treatment outcomes with cefazolin and nafcillin for methicillin-susceptible *S. aureus* bacteremia[a]

Characteristic	Value for group		*P* value
	Cefazolin treatment ($n = 41$)	Nafcillin treatment ($n = 41$)	
Mean time to defervescence (days) ± SD	4.1 ± 3.8	5.4 ± 9.5	0.62
No. (%) of patients with:			
Treatment failure at 4 wk	4 (10)	4 (10)	>0.99
Antibiotic change due to clinical failure	4 (10)	0 (0)	0.13
Relapse	0	0	
SAB-related death	0 (0)	4 (10)	0.13
Treatment failure at 12 wk	6 (15)	6 (15)	>0.99
Antibiotic change due to clinical failure	4 (10)	0 (0)	0.13
Relapse	1 (2)	1 (2)	>0.99
SAB-related deaths	1 (2)	5 (12)	0.22
Overall mortality at 4 wk	4 (10)	4 (10)	>0.99
Treatment interruption due to adverse drug event	0 (0)	7 (17)	0.02

[a] The study included 1:1 propensity-score-matched patients.

treatment group included only patients who received cefazolin during a period when nafcillin was unavailable at our institute due to problems with the supplier. During this time, cefazolin was used for the treatment of serious MSSA infections except for infections of the central nervous system. Second, we used propensity scores to match the patients between the two groups in order to optimize the comparison.

Our study has several clinical implications. First, we could not find any difference in clinical efficacy between cefazolin and nafcillin for the treatment of MSSA bacteremia, although few endocarditis cases were included in the study. This finding is compatible with recently reported retrospective clinical study data (11, 13) and with an earlier experimental study that showed that cefazolin was as effective as nafcillin in reducing bacterial titers in vegetations using a rabbit endocarditis model (3). Second, treatment failure was significantly associated with the site of MSSA infection in our study, especially for endocarditis and pneumonia, rather than with cefazolin use. Previous studies showed that pneumonia and endocarditis are predictors of poor outcomes of MSSA bacteremia (5, 6, 8). After adjustment for these risk factors, cefazolin use was not a risk factor for treatment failure for MSSA bacteremia. This finding suggests that the site of infection is more important for MSSA bacteremia prognoses than is the selection of cefazolin or nafcillin. Third, our study suggests that cefazolin is significantly more tolerable than nafcillin. In our study, there were no significant adverse events that interrupted cefazolin use, while 17% of nafcillin-treated patients discontinued nafcillin due to adverse events.

This study had limitations in that some data should be interpreted with caution. First of all, the number of patients in each group was limited in order to have better matching between the groups; thus, the number of patients may have been too small to detect differences in treatment outcomes between cefazolin and nafcillin, especially considering that approximately 20% of isolates showed an inoculum effect on cefazolin (10). A sample size of 110 in each group was needed to detect a 10% difference in mortality with 80% power and a 5% alpha error. A study with a sample size of 41 in each group, as in this study, is adequately powered to detect a 25% difference.

Second, no meningitis cases and few cases of endocarditis were included in our study because cefazolin poorly penetrates the blood-brain barrier, and concerns regarding metastatic infection of the brain could hamper the use of cefazolin in the case of endocarditis. Therefore, these results cannot be generalized for MSSA bacteremia associated with meningitis or endocarditis. Finally, we did not measure the inoculum effect of the clinical isolates, nor did we analyze the Bla type. Therefore, we could not determine the possible association between cefazolin failure and an inoculum effect by type A Bla.

In conclusion, cefazolin showed clinical outcomes similar to those of nafcillin for the treatment of MSSA bacteremia and was more tolerable than nafcillin. Notably, this study included no cases of meningitis and only a few of cases of endocarditis.

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