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Nafcillin versus cefazolin for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia

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ABSTRACT

Background: Anti-staphylococcal penicillins have long been the first-line treatment option for methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. Recent retrospective data comparing nafcillin and cefazolin report similar clinical efficacy despite concerns about high inoculum MSSA infections.
Methods: This was a retrospective, non-inferiority, cohort study comparing treatment failure rates between nafcillin and cefazolin in patients with MSSA bacteremia from any source, other than meningitis. Multiple logistic regression was used to adjust for confounding variables.
Results: A total of 142 patients were included in the study. The overall treatment failure rate among patients receiving cefazolin was non-inferior to nafcillin (11.3% versus 8.5%; 90% confidence interval −5.2% to 10.8%). Rates of adverse drug events were significantly higher in the nafcillin arm (19.7% versus 7%; $p = 0.046$). After adjustment for confounding variables, no difference between treatment groups was found in treatment failure (adjusted odds ratio (OR) = 1.2; 95% CI, 0.3–4.5), but nafcillin was associated with significantly higher nephrotoxicity (adjusted odds ratio (OR) = 5.4; 95% CI, 1.1–26.8).
Conclusion: Cefazolin was associated with lower nephrotoxicity and similar treatment failure rates compared to nafcillin suggesting that cefazolin is an appealing first line agent for most MSSA bloodstream infections.

Introduction

Staphylococcus aureus is a Gram-positive bacterium that commonly colonizes human skin. However, under the right conditions it can transform into a significant human pathogen [1,2]. The production of virulence factors facilitating its pathogenesis have allowed *S. aureus* to become a leading cause of community- and hospital-acquired infections including bacteremia, endocarditis, skin and soft tissue infections, bone and joint infections, and device-related infections [3–5]. Fear of methicillin-resistant *S. aureus* (MRSA) often overshadows the concern for methicillin-susceptible *S. aureus* (MSSA) infections due to higher rates of mortality and limited treatment options. Nonetheless, MSSA infections have been associated with mortality rates ranging from 15 to 30%, making the selection of an appropriate treatment option vital to maximizing patient outcomes [6].

Beta-lactam therapy has been shown to be more effective than vancomycin in treating MSSA bacteremia, in terms of both preventing recurrence/relapse and reducing mortality [7–9]. Nafcillin is often recommended as first-line therapy for MSSA infections [10]. Unfortunately, the cost and frequent dosing schedule of this agent make it less than ideal for certain patients and healthcare systems compared to alternate options such as cefazolin.

In vitro data suggest that MSSA infections treated with cefazolin may result in higher rates of antibiotic failure due to the inoculum effect [11,12]. Roughly 20% of *S. aureus* isolates express β-lactamase(s) which preferentially hydrolyze cefazolin, leading to a higher cefazolin minimum inhibitory concentration (MIC) observed with higher bacterial inoculum levels [12,13]. However, the exact

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impact of the inoculum effect on clinical outcomes remains unclear. The previous studies compared anti-staphylococcal penicillin versus cefazolin but did not adjust for confounding variables, particularly for efficacy outcomes. Therefore, the purpose of this study was to compare clinical outcomes between patients receiving nafcillin and cefazolin for treatment of MSSA bacteremia.

Materials and methods

Study design and participants

This was a retrospective, non-inferiority, cohort study designed to compare the treatment failure rates of nafcillin and cefazolin in patients with MSSA bacteremia admitted to Parkland Health & Hospital System between August 1, 2011 and August 1, 2014. The study protocol was approved by the institutional review board at the University of Texas Southwestern (IRB# STU 092014-040). Patient data was collected using the electronic medical record and outpatient prescription database. Patients with ≥1 positive blood culture for MSSA were identified through computerized records provided by the microbiology laboratory and screened for inclusion. Patients were included if they had a blood culture positive for MSSA during the study period and they received treatment with nafcillin or cefazolin for at least 72 h. Patients were excluded if diagnosed with meningitis, were <18 years of age, or were pregnant.

Primary sources of infection were identified by concurrent microbiologic specimens positive for MSSA from the suspected site of infection or clinical signs and symptoms consistent with the suspected source of infection as identified via chart review. Data collected included patient demographics, length of stay, serum creatinine, comorbidities, Pitt bacteremia score [14], date of first positive MSSA blood culture, antibiotic treatment regimens, microbiological and clinical cure, adverse drug event (ADE) data, and concomitant nephrotoxins.

Outcomes

The primary objective of this study was to determine the treatment failure rates of patients receiving nafcillin or cefazolin for MSSA bacteremia. Treatment failure was defined as switching of antibiotics secondary to lack of clinical improvement (progression of infection) as documented in progress notes by a physician, recurrent bacteremia, persistent bacteremia, or MSSA bacteremia-associated mortality within 30 days. Treatment failure due to the switching of antibiotic secondary to lack of clinical improvement was determined via chart documentation by the physician. Recurrence was defined as return of *S. aureus* bacteremia within 90 days of documentation of negative blood cultures and/or clinical improvement after completing the prescribed course of antistaphylococcal antibiotic therapy [8]. Persistent bacteremia was defined as bacteremia > 72 h after initiation of appropriate therapy [7,8].

The secondary objective was to determine the rates of potential treatment induced ADEs observed in each treatment group. ADEs included nephrotoxicity defined as an increase in serum creatinine of 0.5 mg/dL or a ≥50% increase from the baseline for two consecutive measurements, neutropenia defined as a neutrophil count <1000 cells/μL, thrombocytopenia defined as a platelet count <100,000 cells/μL, drug-induced fever, and infusion site reaction determined via chart documentation [15,16].

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21 (Armonk, NY: IBM Corp). Descriptive statistics were used to summarize patient demographic data. Continuous data were analyzed using the Student's *t*-test or Mann–Whitney *U* test. Chi-square or Fisher's exact test was used to compare categorical data. For the primary outcome, inclusion of at least 71 patients in each group was required to establish a power of 80% to exclude a difference in favor of the nafcillin group of more than 15%. The non-inferiority margin of 15% was based on the past performance of the antibiotics, demonstrating success rates of 85% for both agents [17,18]. An a priori alpha level of less than or equal to 0.05 was used to determine statistical significance for all other findings. We adjusted for confounding variables and used a multivariable logistic regression analysis to assess both treatment failure and nephrotoxicity. If a variable was considered clinically relevant or its *p*-value was <0.2, that variable was considered for the regression analysis.

Table 1
Clinical characteristics of 142 patients treated with nafcillin or cefazolin for Methicillin-Susceptible *Staphylococcus aureus* bacteremia.

Variable	Value[a] for patients treated with: Nafcillin (*n* = 71)	Cefazolin (*n* = 71)	*p*-Value
Median age (year)	53 [44,60]	50 [39,61]	0.22
Male gender	53 (74.6)	47 (66.2)	0.27
Median weight (kg)	77 [61,90]	75 [65,92]	0.61
Median serum creatinine (mg/dL)	1 [0.7, 2.5]	1.14 [0.7, 5.5]	0.70
ICU admission	23 (32.4)	8 (11.4)	0.002
Mean Pitt bacteremia score ± SD	1.1 ± 1.7	0.76 ± 0.89	0.82
Comorbidities	58 (82)	60 (85)	–
Intravenous Drug Use	11 (15.5)	3 (4.2)	0.02
Diabetes	32 (45.1)	35 (49.3)	0.61
Cerebrovascular accident	2 (2.8)	1 (1.4)	1.00
Coronary artery disease	8 (11.3)	8 (11.3)	1.00
Cirrhosis	8 (11.3)	5 (7)	0.38
Cancer (current)	14 (19.7)	12 (16.9)	0.66
End stage renal disease	10 (14.1)	22 (31)	0.16
Leukopenia/neutropenia	3 (4.2)	3 (4.2)	1.00
Systemic corticosteroids	6 (8.5)	5 (7)	0.75
HIV/AIDS	3 (4.2)	4 (5.6)	1.00
Systemic lupus erythematosus	1 (1.4)	2 (2.8)	1.00

NS, not significant; kg, kilograms; SD, standard deviation; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ICU, intensive care unit.

[a] Values are numbers (with percentages in parentheses and interquartile range in brackets) unless otherwise indicated. Percentages are rounded to the nearest whole number.

Results

Clinical characteristics

A total of 142 patients with MSSA bacteremia were included in the study. Of these, 71 patients received nafcillin and 71 received cefazolin. Baseline clinical characteristics were similar between the two arms and are presented in Table 1. Fifty-eight patients in the nafcillin arm and 60 patients in the cefazolin arm had one or more comorbidities (81.7% versus 84.5%). The most common comorbidity in both arms was diabetes, making up 33.8% (67/198) of total comorbidities documented. Sources of infection for each arm are depicted in Table 2. The most common source of infection overall was intravenous (IV) catheter (23.9%), followed by skin and soft tissue (16.2%). Forty-eight (33.8%) patients were identified as having deep-seated infections, including 16 cases of osteomyelitis (10 nafcillin versus 6 cefazolin), 14 deep abscesses (8 versus 6), 8 cases of infective endocarditis (5 versus 3), 3 cases of septic arthritis (2 versus 1), and 7 cases of pneumonia (4 versus 3).

The majority of patients in the nafcillin arm received 12 g/day (97%). Two patients received off-label doses of 6 g/day for unknown reasons. Of the 49 patients receiving cefazolin who did not have end-stage renal disease (ESRD), 3 (6%) received 8 g/day, 39 (80%) received 6 g/day, and the remaining 7 patients (14%) received a reduced dose of 4 g/day or less due to reduced renal function.

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