

Tolerability of Cefazolin in Nafcillin-Intolerant Patients for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections

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Summary: Cefazolin was safe among individuals with a suspected non-IgE-mediated hypersensitivity reaction (HSR) to nafcillin. Few did not tolerate cefazolin due to an unrelated reaction or persistent effects of the same HSR within 7 days of switching.

Abstract

Background: Non-IgE-mediated hypersensitivity reactions (HSRs) to nafcillin are commonly reported, but scarce data are available to guide appropriate antibiotic change following these reactions. While cefazolin is an attractive therapeutic alternative in methicillin-susceptible *Staphylococcus aureus* (MSSA) infections when patients experience an HSR to nafcillin, more data are needed to evaluate the tolerability of cefazolin after switching from nafcillin. The purpose of this study was to describe the tolerability of cefazolin in patients who develop a suspected non-IgE-mediated HSR to nafcillin.

Methods: This was a retrospective, descriptive case series of patients who received nafcillin for an MSSA infection, experienced a suspected non-IgE-mediated HSR, and were switched to cefazolin between October 2015 and November 2019 at a single academic medical center. The primary objective was to identify the percentage of patients who completed cefazolin after experiencing a suspected non-IgE-mediated HSR to nafcillin.

Results: There were 80 patients with 87 pre-specified non-IgE-mediated HSRs during the study period. Seventy-one (89%) patients completed cefazolin, with 53 (75%) of these patients completing at least 2 weeks of therapy. One patient was ultimately switched from cefazolin to daptomycin due to concern for treatment failure. Eight patients (10%) did not tolerate cefazolin after switching from nafcillin. Of these, 3 patients experienced an unrelated HSR, while 5 patients experienced the same non-IgE-mediated HSR that was attributed to nafcillin and discontinued cefazolin within 7 days. The most common HSR cited was immune-mediated nephritis; however, the majority were clinically presumed but did not meet objective diagnostic criteria.

Conclusions: Treatment with cefazolin after experiencing a suspected non-IgE-mediated HSR to nafcillin appears to be safe, even for patients requiring a prolonged duration of cefazolin.

Keywords: cefazolin, nafcillin, hypersensitivity reaction, MSSA

Introduction

Penicillins are the most common reported cause of drug allergies with a worldwide prevalence estimated at approximately 10% [1, 2]. True IgE-mediated drug allergy, which can result in life-threatening anaphylaxis, is one of four types of hypersensitivity reactions (HSRs) first classified by Gell and Coombs in 1963 [3]. The remaining categories, types II-IV, describe non-IgE-mediated reactions including hemolytic anemia, thrombocytopenia, serum sickness, maculopapular rash, and organ-specific tissue injury caused by activated T-cells [1].

Anti-staphylococcal penicillins (e.g., nafcillin) are considered first-line therapy for invasive methicillin-susceptible *Staphylococcus aureus* (MSSA) infections [4]. However, they have been associated with a variety of type II through IV non-IgE-mediated HSRs including rash, immune-mediated nephritis, and immune-mediated hepatitis [5-7]. While vancomycin may be considered in these situations, treatment outcomes are inferior when compared to β -lactams for management of MSSA infections, particularly in patients with bacteremia [8-10]. Cefazolin is an effective alternative agent for MSSA infections that is generally well tolerated, which makes it an attractive option for patients who develop an HSR to nafcillin [8].

While the rate of IgE-mediated cross-reactivity between penicillins and cephalosporins is well known, much less is known about non-IgE-mediated cross-reactivity between nafcillin and cefazolin [11-13]. Published literature supporting tolerance of cefazolin after a non-IgE-mediated HSR to a penicillin is sparse, with only two prior studies addressing this issue. These studies are limited by small sample sizes, short duration of cefazolin, and stringent diagnostic criteria that were resource intensive [13, 14]. We describe our real-world institutional experience with cefazolin in patients intolerant of nafcillin due to suspected non-IgE-mediated HSRs.

Materials and Methods

Study design and population

This was a retrospective, descriptive case series that was approved by the institutional review board at University of Virginia (UVA) Health. Patients admitted to UVA Health between October 2015 and November 2019 who received nafcillin for an MSSA infection, experienced a suspected, pre-specified non-IgE-mediated HSR, and were switched to cefazolin were included in the study. Those switched from nafcillin to cefazolin for all other reasons, including other non-IgE-mediated HSRs, were excluded. An electronic medical record (EMR) report identified patients who received nafcillin with a subsequent cefazolin prescription within 84 days. Patients were reviewed in reverse chronological order to target a convenience sample of 100 patients, and were included only once during the study timeframe. Clinical data collected from the EMR included patient demographics, infection diagnosis, HSR classification with associated laboratory values, time to development of an HSR (defined as the day of nafcillin initiation to the day of the HSR), time to cefazolin switch (defined as the day of nafcillin initiation to the day of cefazolin initiation), and duration of therapy.

Objectives and definitions

The primary objective was to identify the percentage of patients who completed cefazolin after experiencing a suspected non-IgE-mediated HSR to nafcillin. Suspected HSRs evaluated included eosinophilia, immune-mediated hepatitis, immune-mediated nephritis, leukopenia or neutropenia, and maculopapular rash. Patients who did not complete cefazolin were further analyzed to identify whether the discontinuation was related to a primary or a secondary HSR. Primary HSR was defined as recurrence or persistence of the original HSR that led to the switch from nafcillin to cefazolin. Secondary HSR was

defined as development of a new HSR that differed from the original HSR attributed to nafcillin. Two investigators determined the rationale for cefazolin discontinuation, and in the event of a discrepancy between the two investigators, a third investigator reconciled the assessment.

Secondary objectives included the proportion of HSRs that met pre-established objective diagnostic criteria for each suspected HSR and the proportion of HSRs in each category of the Naranjo Scale. Objective diagnostic criteria utilized for HSR classification were derived from literature definitions and previously reported cases (Table 1) [13, 15-16]. Baseline value was defined as the minimum value in the last 3 months prior to the hospital encounter. If a value within the last 3 months was unavailable, the last value available prior to the hospital encounter was used. Suspected HSRs also underwent a subjective assessment using the Naranjo Scale to determine the likelihood that the HSR was due to the antibiotic [17]. These were primarily reviewed by one investigator and cases with any uncertainty were discussed with another investigator.

Statistical analysis

A descriptive analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, NY). Descriptive data were displayed as numbers and frequencies or medians with interquartile ranges, where applicable.

Results

Clinical characteristics

Among 183 patients with MSSA infections who were switched from nafcillin to cefazolin within the study timeframe, 103 patients were excluded for experiencing a non-IgE-mediated HSR that was not pre-specified or for reasons other than a reaction to nafcillin, such as dosing inconvenience, fluid overload, and cost (Figure 1). Therefore, there were 80 patients included in the study. Baseline patient characteristics are shown in Table 2. Median age was 60 years and the majority were Caucasian males. Overall, 62 patients (78%) had bacteremia and the most common identified foci of infection were bone and joint and endovascular (Table 2). The median total duration of therapy was 43 days (24 – 48), while the median duration of cefazolin alone was 25 days (14 – 37).

Among the 80 patients, there were 87 total suspected non-IgE-mediated HSRs, with 7 patients experiencing more than one HSR. The most common pre-specified HSRs were immune-mediated nephritis (54%), leukopenia or neutropenia (21%), and maculopapular rash (15%) (Table 3). The median time to development of an HSR was 6 days (2 – 14).

Outcomes

Of the 80 patients who were switched from nafcillin to cefazolin due to a suspected HSR, 71 patients (89%) tolerated and completed cefazolin therapy. The duration of cefazolin varied among these 71 patients. Eighteen patients (25%) received cefazolin for less than 2 weeks, 18 (25%) received cefazolin between 2 and 4 weeks, and 35 (50%) received cefazolin for more than 4 weeks.

Cefazolin was discontinued in 8 patients (10%) due to rash or immune-mediated nephritis, with three instances of emergence of a secondary HSR (Figure 2). All 5 patients with persistence of a primary HSR discontinued cefazolin within 7 days of initiation. Among these patients, the median time to nafcillin HSR was 8 days (5 – 10.5), which was the same as the median time to cefazolin switch. The median duration of cefazolin was 5.5 days (3 – 15). Therapy was ultimately changed to daptomycin (n=2), vancomycin (n=3), ceftriaxone (n=1), and doxycycline suppression (n=1). One patient who was thought to have immune-mediated nephritis from nafcillin was re-trialed with nafcillin after experiencing an HSR to cefazolin as the renal biopsy showed infection-associated proliferative glomerulonephritis. One patient was switched from cefazolin to daptomycin due to concern for treatment failure. In all patients who did not tolerate cefazolin, the HSR resolved without lasting abnormalities.

Of the 87 evaluable HSRs, full objective diagnostic criteria were available in 64 (74%), with 31 of these HSRs (48%) meeting criteria for classification (Table 3). Immune-mediated nephritis or hepatitis were least likely to meet criteria [3/24 (13%) and 0/5 (0%), respectively]. This was primarily due to missing data related to the absolute eosinophil count at the initiation of nafcillin or at the time when therapy was switched to cefazolin or not meeting the pre-specified definitions outlined in Table 1. In patients suspected of immune-mediated nephritis who had data available, the median increase in absolute eosinophil count from the day of nafcillin initiation to the day of cefazolin initiation was 115 cells/ μ l and the median increase in serum creatinine was 1 mg/dL. Of the HSRs that met criteria, 28/31 (90%) completed cefazolin therapy while 3/31 (10%) were unable to tolerate the switch to cefazolin because of a rash. All 3 were discontinued within 7 days of initiation due to a primary HSR.

When using the Naranjo Scale to determine the likelihood that the suspected HSR was due to nafcillin, none were categorized as definite, 55 (63%) were probable, 31 (36%) were possible, and 1 (1%)

was doubtful. In the 8 patients who did not tolerate the switch to cefazolin, the Naranjo Scale to determine the likelihood that the suspected HSR was due to cefazolin showed that 2 (25%) were possible and 6 (75%) were doubtful.

Discussion

Our findings suggest that cefazolin may be safe in patients who develop a suspected non-IgE-mediated HSR to nafcillin, as 89% of patients tolerated the switch to cefazolin. Notably, most patients who tolerated cefazolin completed at least 2 weeks of therapy. Even among those who did not tolerate the change and showed persistent HSRs, they were able to discontinue cefazolin without lasting medical problems.

Anti-staphylococcal penicillins and cefazolin are preferred therapy for the treatment of MSSA infections and are associated with improved outcomes when compared to treatment with vancomycin [4, 8, 22]. While it is unknown how daptomycin compares to β -lactams for MSSA infections, some may favor it over cephalosporins in cases of severe or suspected non-IgE-mediated HSRs due to concerns of cross-reactivity. However, daptomycin requires additional monitoring of creatine phosphokinase and may pose financial challenges that can impact patient disposition. Cefazolin is generally well-tolerated and only requires routine monitoring, thereby making it a more attractive option as compared to vancomycin or daptomycin in patients who develop HSRs to nafcillin [5-10]. Among the 8 patients who did not tolerate the switch to cefazolin, 3 patients developed a different HSR to cefazolin that likely could not have been predicted by the HSR that developed with nafcillin and may possibly have occurred without receiving nafcillin initially. There were 5 patients who had the same HSR that developed with nafcillin. Interestingly, all 5 of these patients discontinued cefazolin within 7 days of initiation. With delayed HSRs, the HSR may temporarily worsen despite discontinuing the offending agent [1]. It is worth

noting that in our study, most of these patients were immediately switched to cefazolin without a washout period, as evidenced by the equivalent median time to nafcillin HSR and time to cefazolin switch. While cefazolin was discontinued in those 5 patients due to concern for persistent or worsening HSR, this could potentially be attributed to lingering effects of nafcillin rather than a true HSR to cefazolin.

A small subset of patients in this study actually met predetermined objective diagnostic criteria for non-IgE-mediated HSR classification. Overall, 64% of HSRs did not meet criteria, and this was even higher in the immune-mediated nephritis (94%) and immune-mediated hepatitis (100%) subsets. As noted previously, 23 (26%) HSRs did not have all necessary information available in the EMR for analysis and were classified as not meeting criteria. Although these data call into question if a closer evaluation of the need to switch is warranted, they also give a realistic view of what occurs inside healthcare facilities when resources cannot be allocated to confirming HSRs via invasive procedures such as biopsies.

There are limited published data evaluating cefazolin tolerance in patients who experienced a non-IgE-mediated HSR to nafcillin. One study evaluated 54 patients presenting for total hip and knee arthroplasty who previously reported a non-IgE-mediated HSR to penicillin [14]. All patients who received cefazolin reported no adverse reactions. However, the study did not specify which penicillin was reported to have caused an allergy and cefazolin was only used for perioperative prophylaxis. Another study evaluated the tolerability of cefazolin after non-IgE-mediated HSRs to nafcillin in an outpatient setting [13]. Although limited by a small sample size, the authors concluded that cefazolin was safe to use, as 16 out of 17 patients who switched from nafcillin to cefazolin completed therapy. Their small sample size was likely due to stringent diagnostic criteria that were required for inclusion after review from two independent specialists from the Division of Rheumatology, Allergy and

Immunology to assess HSR types and likely mechanisms. Since these resources were not routinely utilized by or immediately available for primary providers for patients in our study, we included any patient who had switched from nafcillin to cefazolin due to clinical concern for a non-IgE-mediated HSR based on chart review. In the subgroup of patients who met objective criteria in our study, 28 of 31 patients completed cefazolin. Three patients did not complete cefazolin due to a primary HSR of rash, all of whom discontinued cefazolin within 7 days of initiation, which could potentially point to residual effects of nafcillin contributing to cefazolin intolerance.

The incidence of acute kidney injury with nafcillin can be as high as 33% [19-21]. Our study found that over half of the suspected non-IgE-mediated HSRs were immune-mediated nephritis, which is notably greater than what was observed by Blumenthal and colleagues (3/17, 18%), likely due to strict adherence to diagnostic criteria. In our study, there were 47 HSRs due to immune-mediated nephritis; however, only 3 met objective criteria and almost half of the HSRs did not have all available criteria to evaluate the HSR. These data demonstrate that immune-mediated nephritis is likely attributed to nafcillin more often than necessary and calls into question if a closer evaluation of laboratory values is warranted prior to change in therapy.

This study has several limitations. Given its retrospective nature, this study was subject to selection bias. This study does not include a subset of patients who many have experienced more severe HSRs to nafcillin and were not prescribed cefazolin. Additionally, there were limitations on data availability in the EMR, which led to the inability to completely assess objective criteria and some of the questions in the Naranjo Scale, such as if the reaction reappeared after a re-challenge or placebo. Few HSRs met objective diagnostic criteria in our study, especially for immune-mediated nephritis and hepatitis. Additional objective data are required to make a definitive diagnosis of an HSR, such as skin biopsy for maculopapular rash, renal biopsy and urinalysis (e.g., urine eosinophils and urine sediment)

for immune-mediated nephritis, or liver biopsy for immune-mediated hepatitis. While these data were unavailable in our study, this provides a more realistic perspective of resource allocation for confirming HSRs.

In conclusion, this study adds to the current body of literature as the largest study to date showing cefazolin tolerability in patients with suspected non-IgE-mediated HSRs to nafcillin. It provides a better understanding of non-IgE-mediated HSRs to nafcillin and cross-reactivity between nafcillin and cephalosporins. Not only could this impact the decision making of providers who are concerned about switching patients from nafcillin to cefazolin when a suspected non-IgE-mediated HSR is encountered and might choose suboptimal therapy with vancomycin or daptomycin, but this also further supports those who did switch to cefazolin previously in the setting of limited data. Future research is needed to analyze the tolerability of nafcillin in patients with select comorbidities, such as cirrhosis or chronic kidney disease, to evaluate whether these patients are more prone to HSRs, and to explore the tolerability of cefazolin in patients who experience more severe non-IgE-mediated HSRs to nafcillin.

Notes

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Table 1. Objective Criteria for Classification of Non-IgE-Mediated HSRs

Hypersensitivity Reaction	Diagnostic Criteria
Eosinophilia	AEC > 1000/mL without other symptoms
Immune-mediated hepatitis	- AEC > 500/μl - Rise in LFTs by 3x upper limit of patient's baseline
Immune-mediated nephritis	- AEC > 500/μl - Rise in SCr by 1.5x baseline or by > 0.3 mg/dL
Leukopenia or neutropenia	- WBC < 4000 cells/μl or 50% decrease in WBC if baseline < 4000 cells/μl OR - ANC < 1500/mm³ or 50% decrease in ANC if baseline is < 1500/mm³
Maculopapular rash	Described as "maculopapular rash" in the EMR

AEC: Absolute Eosinophil Count; ANC: Absolute Neutrophil Count; EMR: Electronic Medical Record; LFTs: Liver Function Tests; SCr: Serum Creatinine; WBC: White Blood Cell.

Table 2. Baseline Characteristics of Patients

Characteristic	Overall (N = 80)
Age, years	60 (48 - 72)
Male sex	57 (71)
Race	
Caucasian	70 (88)
African-American	9 (11)
Other	1 (1)
Infection type	
Bloodstream	62 (78)
Bone/joint	27 (34)
Central nervous system	1 (1)
Endovascular	20 (25)
Pulmonary	4 (5)
Skin/skin structure	6 (8)
Time to nafcillin HSR, days	6 (2 – 14)
Time to cefazolin switch, days	8 (3 – 15)
Total duration of therapy, days	43 (24 – 48)

Data are represented as number (%) or median (IQR) unless otherwise stated

Table 3. Summary of Objective Criteria Met for Non-IgE-Mediated HSRs

Objective Classification Criteria	Number of HSRs (n)	HSRs with All Criteria Available in EMR (n)	Criteria Met (n)	Criteria Not Met* (n)
Eosinophilia	4 (4)	4	4	0
Immune-mediated hepatitis	5 (6)	5	0	5
Immune-mediated nephritis	47 (54)	24	3	44
Leukopenia or neutropenia	18 (21)	18	18	0
Maculopapular rash	13 (15)	13	6	7
Total	87 (100)	64/87 (74)	31/87 (36)	56/87 (64)

Data are represented as number (%)

*Criteria were not met if they did not concur with the definitions outlined in Table 1 or if data were not available in the EMR

Figure Legends:

Figure 1. Patient population

*Other included drug-drug interactions (n=13) and inconclusive data (n=24)

EMR: electronic medical record; HSR: hypersensitivity reaction; MSSA: methicillin-susceptible

Staphylococcus aureus

Figure 2. Description of patients who did not tolerate cefazolin after being switched from nafcillin due to a non-IgE-mediated reaction

HSR: hypersensitivity reaction

Figure 1

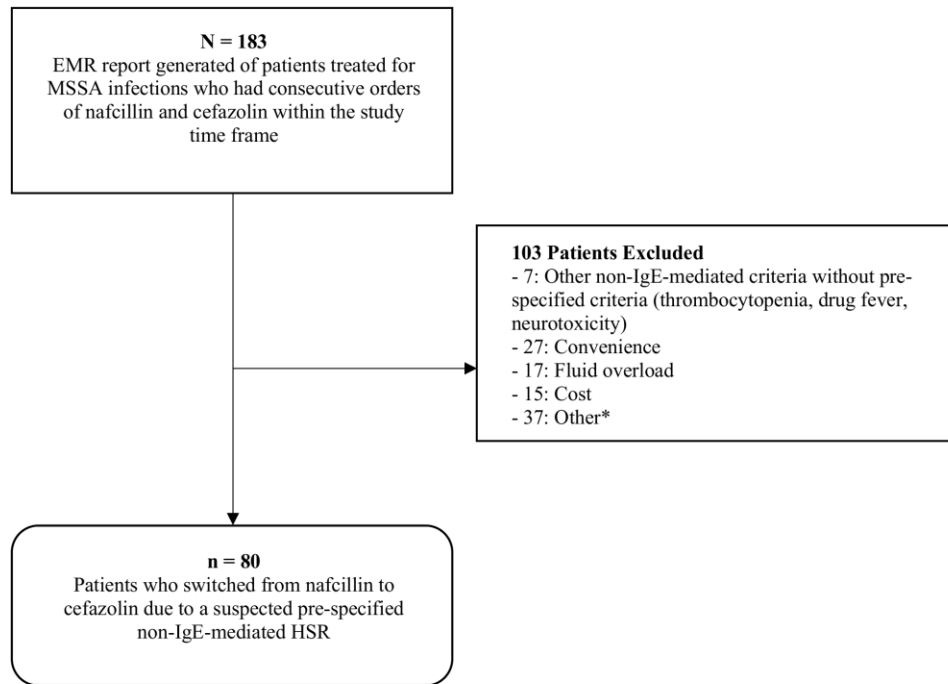


Figure 2

