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Safety of cefazolin for perioperative prophylaxis in patients with penicillin allergy labels



Cefazolin is a first-line antibiotic for perioperative prophylaxis of surgical site infections.¹ Between 8% and 15% of the US population have penicillin allergy labels (PAL).² Patients with PAL receive perioperative cefazolin less frequently and are more likely to receive alternative antibiotics, increasing their risk of surgical site infection.¹ This practice is likely from overestimating the risk of cross-reactivity between penicillin and cephalosporins. Cross-reactivity among these antibiotics is thought to be from a common R1 side chain, absent in cefazolin. Recent studies have found that cross-reactions rarely occur.³ In a meta-analysis, the rate of cross-reactivity of penicillin with cefazolin was 0.7%.⁴ Furthermore, PALs often include intolerances, adverse effects, or reported childhood allergies, which often resolve by adulthood.³ We hypothesize that cefazolin is safe to use in most patients with PAL. In this study, we aim to learn on the use of cefazolin in patients with PALs, a population typically encountered by clinicians in the perioperative setting who may not have confirmed immunoglobulin E-mediated penicillin allergies.

Patients with PAL at the University of Washington Medical Center (UWMC) who underwent surgical procedures from January 1, 2020 to December 31, 2020 were studied through direct query of the electronic medical record. Data recorded included dates, times, locations, and perioperative antibiotics. Demographics, including age, sex, race, ethnicity, penicillin allergy (PA), and cephalosporin allergy status, were extracted. Procedures in patients with PAL who received cefazolin perioperatively were identified for further review. The PA index reaction and type of penicillin the patient reacted to were identified by manual chart review. When patients had multiple index reactions, all were recorded. Anesthesia and operative notes were reviewed for any documented perioperative reactions. For procedures in which an apparent allergic reaction occurred, an additional review of reaction type, timing of cefazolin administration, concurrent medications given, postoperative clinical notes, and subsequent allergy evaluation (when applicable) was completed. The final determination of whether a reaction was attributable to cefazolin was made by an allergy attending physician. This project was approved by the UWMC institutional review board. All data were recorded in a standardized data collection form in Research Electronic Data Capture.⁵

Of the 16,628 procedures performed at UWMC facilities in 2020, 1741 (10.4%) were for patients with PAL, and 549 (31.5%) of these cases used perioperative cefazolin. Patient demographics and outcomes are described in Table 1. The 549 procedures identified for manual chart review occurred in predominantly white (424, 77.2%) and female (340, 61.9%) patients, similar to procedures in patients with PAL who did not receive cefazolin (1398, 80.3% white; 1113, 63.9% women). Among these procedures, patients with PAL most typically reported a reaction to all penicillins (287, 52.3%), amoxicillin (157, 28.6%), or amoxicillin-clavulanate (76, 13.8%). Some patients reported allergies to multiple penicillin types, and all were recorded (583). Of these procedures in which patients with PAL had index reactions documented (427, 77.8%), the most common were rash (171, 40.0%), gastrointestinal upset (108, 25.3%), or hives (88, 20.6%). A small percentage of patients reported more severe index reactions such as respiratory distress (8, 1.9%), anaphylaxis (5, 1.2%), or angioedema (3, 0.7%). Through manual chart review, 544 (99.1%) of patients with PAL who received cefazolin were found to have no documented allergic-type reaction postoperatively.

Of the 549 cases, 5 involved patients with PAL experienced allergic-type symptoms, none of which seemed related to cefazolin administration. Cases 1 and 2 had index reactions of rash and developed postoperative pruritus 4 hours after cefazolin was given. These reactions were thought most likely related to opioid medication given near the end of the cases. Case 3 had an index reaction of rash and hives and had intraoperative anaphylaxis. Cefazolin had been given 3 hours earlier. Case 4 had an index reaction of rash and developed postoperative pruritus and rash. The cause of this reaction is unknown; however, cefazolin was given 2.5 hours beforehand and did not cause an immediate reaction. Case 5 had an index reaction of rash and developed intraoperative anaphylaxis 15 minutes after cefazolin administration. On outpatient evaluation, this patient had skin testing negative to cefazolin and penicillin, and positive to rocuronium which had been given immediately before the reaction. Therefore, in each of these 5 cases, reactions were thought to be unrelated to cefazolin.

Overall, of all procedures performed in patients with PAL who were given perioperative cefazolin (549, 31.5%) at our institution, none resulted in allergic symptoms related to cefazolin administration. This suggests that cefazolin is safe to give as perioperative prophylaxis in patients with PAL, as seen in similar studies.^{6,7} The percentage of cases in which cefazolin was given to patients with PAL was higher than other recently published studies, which reported

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Table 1
Patient Demographics and Outcomes of Cefazolin Administration in PAL

Demographics	No PAL (n = 14,338)	PAL (n = 1741)	PAL, received cefazolin (n = 549)	Total (n = 16,628)
Age (y)				
18–49	5661 (39.5)	557 (32.0)	215 (39.2)	6433 (38.7)
50–69	5828 (40.6)	771 (44.3)	216 (39.3)	6815 (41.0)
70+	2849 (19.9)	413 (23.7)	118 (21.5)	3380 (20.3)
Sex				
Female	7481 (52.2)	1113 (63.9)	340 (61.9)	8934 (53.7)
Male	6857 (47.8)	628 (36.1)	209 (38.1)	7694 (46.3)
Race or ethnicity				
-Asian	1146 (8.0)	86 (4.9)	31 (5.6)	1263 (7.6)
-Latinx	1055 (7.4)	85 (4.9)	30 (5.5)	1170 (7.0)
-Multiple races	161 (1.1)	20 (1.1)	7 (1.3)	188 (1.1)
-Native Alaskan, Native Hawaiian, Native American	317 (2.2)	39 (2.2)	12 (2.2)	368 (2.2)
-Non-Latinx Black	829 (5.8)	82 (4.7)	29 (5.3)	940 (5.7)
-Non-Latinx White	10,413 (72.6)	1398 (80.3)	424 (77.2)	12,235 (73.6)
-Unknown	417 (2.9)	31 (1.8)	16 (2.9)	464 (2.8)
Penicillin allergen				
-Penicillin (G, V)			40 (7.3)	
-Amoxicillin			157 (28.6)	
-Amoxicillin-clavulanate			76 (13.8)	
-Ampicillin			6 (1.1)	
-Piperacillin-tazobactam			15 (2.7)	
-Penicillins			287 (52.3)	
-Other			2 (0.4)	
Penicillin index reaction				
-no description			122 (22.2)	
-rash			171 (31.1)	
-hives			88 (16.0)	
-GI upset			108 (19.7)	
-itching			32 (5.8)	
-swelling			25 (4.6)	
-flushing			3 (0.5)	
-headache			6 (1.1)	
-fever			6 (1.1)	
-angioedema			3 (0.5)	
-respiratory distress			8 (1.5)	
-anaphylaxis			5 (0.9)	
-childhood reaction			41 (7.5)	
-other			55 (10.0)	
Outcomes				
-no reaction			544 (99.1)	
-rash			2 (0.4)	
-hives			0	
-GI upset			0	
-itching			3 (0.5)	
-swelling			0	
-flushing			0	
-angioedema			0	
-respiratory distress			0	
-anaphylaxis			2 (0.4)	

Abbreviations: GI, gastrointestinal; PAL, penicillin allergy label.

22.3% (received cephalosporins⁶) and 28.4% (received cefazolin⁸) perioperatively. The future directions of this project are to create educational and clinical decision-making tools to encourage the use of cefazolin in patients with PAL.

Index reactions of rash, gastrointestinal upset, and hives were overrepresented in our sample compared with the general population, as reported in previously published frequencies.⁹ This suggests a potential bias of provider comfort in prescribing cefazolin to patients with mild PA index reactions. Limitations of the study include the small sample size of severe PA index reactions, limiting generalizability to these patients; however, none had allergic symptoms attributable to cefazolin. Taken with a recent study that found no differences in anaphylaxis frequency when cephalosporin warnings were removed in patients with PAL,¹⁰ our results suggest that even those with severe index reactions can safely receive cefazolin. The study was limited to patients with PAL as we were unable to assess and compare the frequency of perioperative

reactions in patients without PAL with data accessible from the electronic medical record or chart review. In addition, our study included patients with PAL who may not have had confirmatory testing of their allergy. Given that most patients with PAL have not had formal allergy testing, the frequency of allergic reactions to cefazolin in this group has practical value for surgeons and anesthesiologists who make clinical decisions on the basis of PAL.

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Twenty-year comparison of delabeling pediatric patients with penicillin allergy with and without prior skin testing



Approximately 10% of the US population, including at least 5 million children, report a penicillin allergy though more than 90% of those individuals are found to have no allergy after evaluation.^{1,2} Less than 1% of patients with penicillin allergy have immunoglobulin (Ig)E-mediated reactions and approximately 80% of those patients will lose their sensitivity after 10 years.³ Inferior clinical outcomes, such as 50% increase in surgical site infections, prolonged hospitalization, use of less efficacious, more broad-spectrum antibiotics, and increased mortality, are associated with penicillin avoidance in adults with penicillin allergy.^{3,4} Newer data in children have revealed that antibiotic allergy has been associated with prolonged hospitalization and increased use of broad-spectrum antibiotics as well.^{5,6}

Penicillin allergy can be evaluated through a comprehensive history followed by skin testing and drug challenges. Ultimately, drug challenges are the standard to assess drug tolerance.^{3,4} There is growing evidence in the literature that supports direct oral challenge (DOC) without antecedent skin prick test (SPT) in children with a low-risk reaction history (cutaneous only).⁷ More studies are needed to reveal the safety and outcomes of children who undergo DOC or SPT followed by oral challenge regardless of reaction.

Our study seeks to evaluate the safety of DOC to penicillin without prior skin testing compared with negative SPT result followed by oral challenge in pediatric patients regardless of initial reaction. A retrospective chart review between January 1998 and December 2018 was completed as part of an institutional review board-approved study. A total of 166 patients between ages 0 and 19 years at the time of evaluation of any sex with history of penicillin or amoxicillin allergy, penicillin skin test, or penicillin or amoxicillin oral challenges were included in the study. Those who had negative SPT result were

offered 1- or 2-step oral challenges based on history using either oral amoxicillin or amoxicillin-clavulanate depending on initial reaction.

Table 1 outlines the difference in characteristic between the DOC only group and those with negative SPT result followed by oral challenge group. Although subjective symptoms occur during challenges, objective symptoms (ie, tachypnea, tachycardia) were used to evaluate whether patients passed or failed oral challenges. Both groups exhibited similar distributions in age of reaction, age of evaluation, culprit drug, and onset of symptoms. There were more patients who presented with milder symptoms, such as cutaneous symptoms, in the DOC group, whereas there was a higher percentage of anaphylaxis reported in those with negative SPT result followed by oral challenge group. The most common age of reaction was in patients less than 1 year old ($n = 80$). Patients were typically evaluated after 6 years old ($n = 84$). The most reported adverse reaction was rash ($n = 105$). The most reported culprit drug was amoxicillin ($n = 123$) with onset of symptoms after days of being on the medication ($n = 98$).

A total of 78 patients (47%) participated in DOC. The remaining 88 patients underwent SPT and then oral challenge. All but 1 patient passed between both groups. The proportion of patients who passed the oral challenge were similar between the DOC (100%) and those who had negative SPT result and then oral challenge (99%; $P = .99$). The 1 patient who did not pass had an equivocal response in those with the negative SPT result followed by oral challenge group. This patient developed a rash several hours after her oral challenge and was treated with oral antihistamine with no additional treatment required suggesting a T cell-mediated reaction.

Our study reveals that those patients who underwent DOC compared with those who had negative SPT result followed by oral challenge had similar pass rates regardless of initial reaction. The most common symptom our patients presented with was cutaneous. Caubet et al⁸ report that skin rashes are a most often reported reaction in

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