

Pharmacist adjustment of preoperative antibiotic orders to the preferred preoperative antibiotic cefazolin for patients with penicillin allergy labeling

Sarah Lessard, PharmD, BCPS, BCIDP, Department of Pharmacy, Mayo Clinic Health System, La Crosse, WI, USA

Chris Huiras, MD, Department of General Surgery, Mayo Clinic Health System, La Crosse, WI, USA

Ala Dababneh, MD, Department of Infectious Disease, Mayo Clinic, Rochester, MN, USA

Raj Palraj, MBBS, MD, Department of Infectious Disease, Mayo Clinic, Rochester, MN, USA

Renee Thies, CRNA, APNP, Department of Anesthesia, Mayo Clinic Health System, La Crosse, WI, USA

Nate Woolever, PharmD, Department of Pharmacy, Mayo Clinic Health System, La Crosse, WI, USA

Kandi Holt, RN, Department of Surgery, Mayo Clinic Health System, La Crosse, WI, USA

Brenda Schwan, RN, Infection Prevention & Control, Mayo Clinic Health System, La Crosse, WI, USA

Jennifer Poelma, RN, Department of Nursing, Mayo Clinic Health System, La Crosse, WI, USA

Jennifer Tempelis, PharmD, Department of Pharmacy, Mayo Clinic Health System, La Crosse, WI, USA

Mark Sawyer, MD, Department of Surgery Specialties, Mayo Clinic Health System, La Crosse, WI, USA

Purpose: Emerging literature has detailed the safe use of cefazolin in patients with immunoglobulin E-mediated penicillin allergy labeling (PAL) such as hives and anaphylaxis. The purpose of this article is to detail efforts led by an antimicrobial stewardship pharmacist working with an interdisciplinary team to optimize preoperative antimicrobials in patients with PAL.

Methods: A pharmacist-led, interdisciplinary collaborative practice agreement (CPA) was activated in January 2020 to permit pharmacists to independently optimize preoperative antibiotics to the preferred cefazolin in patients with PAL if nonsevere or severe reactions had been reported. A patient registry was established covering the timeframe between January 8, 2020, and January 6, 2022. Reaction during surgery was assessed via 2-provider documentation, which included surgeon and anesthesiology staff documentation of any complications during the procedure related to a suspected allergic safety event. Utilization of cefazolin, clindamycin, and vancomycin for preoperative prophylaxis was monitored before and after implementation of the CPA.

Results: During the stated timeframe, 10,182 procedures and/or surgeries were completed on 1,572 (15.4%) patients with PAL and 659 (41.9%) patients previously reporting at least one reaction categorized as a severe reaction, which was hives for 71.2% of these patients. Of the 659 patients with PAL reporting a severe reaction, 356 received a preoperative cephalosporin (cefazolin, 98.8%; ceftriaxone, 1.2%) and tolerated it without a reported safety event, including 52 patients with PAL previously reporting anaphylaxis. An increase in preferred preoperative antimicrobial prophylaxis utilization was noted (cefazolin: 86% to 96.3%, $P < 0.001$; 2019 to 2021) with reductions noted in the use of nonpreferred preoperative antibiotics (clindamycin: 2.1% to 0.2%, $P < 0.001$; vancomycin: 3.2% to 0.4%, $P < 0.001$; 2019 to 2021).

Conclusion: A pharmacist-led, interdisciplinary CPA increased preferred preoperative antimicrobial use in patients with PAL reporting severe allergic reactions, including hives and anaphylaxis, without reported safety events.

Keywords: cefazolin, cross-reaction, dual allergy, penicillin allergy labeling, preoperative antibiotic

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Address correspondence to Dr. Lessard (lessard.sarah@mayo.edu).
Twitter: @LessardSarah1

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Cefazolin is the preferred preoperative antibiotic for clean surgeries, including in patients with nonsevere penicillin allergies that are not mediated by immunoglobulin E (IgE; eg, rash and general intolerances).¹ Emerging

literature has also detailed the safe use of cefazolin in patients with IgE-mediated penicillin allergies (eg, hives and anaphylaxis).²⁻⁸ Previous publications have highlighted the low likelihood of cross-reaction in patients with penicillin

allergy labeling (PAL) receiving cephalosporins with unrelated side chains, including cefazolin.⁹⁻¹⁷ Several recent reports on optimization of perioperative antibiotic selection for patients with PAL have highlighted the critical and integral contributions of pharmacists to antimicrobial stewardship.^{2,3,5,6}

At our institution, we commonly provided patients with nonsevere PAL preoperative cefazolin without reported safety events. Cefazolin is the guideline-recommended preoperative antimicrobial therapy for prophylaxis in multiple clean and clean-contaminated procedures, is easily delivered within the surgical suite to facilitate complete administration of preoperative antibiotics before surgical incision, has a low cost and is well tolerated. Cefazolin is unique in that it does not share a side chain with any other cephalosporin or penicillin.¹⁸⁻²⁰ Switching to another class of antibiotics due to reported PAL may adversely affect patients. For example, an alternative antimicrobial may be less effective, have more adverse effects, have prolonged infusion times leading to surgical delays, have more broad-spectrum activity leading to increased risk of resistance, and/or be more expensive.^{2-4,18-24} Because of variability and the often unconfirmed nature of patient-reported penicillin allergies together with literature detailing the low likelihood of cross-reaction in patients with PAL receiving cefazolin and suggesting worse outcomes for patients receiving alternative preoperative antibiotics, our team aimed to expand optimization of preoperative antibiotics to include patients with PAL reporting severe penicillin allergies. Herein we detail antimicrobial stewardship efforts led by an antimicrobial stewardship pharmacist working with an interdisciplinary team to optimize preoperative antimicrobials in patients with PAL.

Methods

A pharmacist-led, interdisciplinary collaborative practice agreement (CPA) was activated in January 2020 at our community-based teaching institution

KEY POINTS

- Cefazolin is the preferred preoperative prophylaxis for clean surgical procedures, but patients with penicillin allergy labeling (PAL) are at risk for receiving suboptimal preoperative prophylaxis.
- In our cohort, preoperative cefazolin was safely used in patients with nonsevere and severe PAL, including in those with reported hives and anaphylaxis.
- The benefit of preoperative cefazolin outweighs the risk in patients with PAL, even in those with a confirmed penicillin allergy.

to permit pharmacists to independently optimize preoperative antibiotics to preferred preoperative cefazolin in patients with PAL if nonsevere or severe reactions or intolerance was reported.

Before CPA activation, stakeholders, including antimicrobial stewardship team members, surgical and procedural providers, infection prevention and control team members, surgical nurse team members, and anesthesia team members, were engaged. Education was provided on the rationale and logistics for the procedure, with intermittent reinforcement. Following agreement by relevant stakeholders, the CPA was activated for all surgeries and procedures performed in the main surgical operating rooms for both pediatric and adult patients. Included disciplines were otolaryngology, general surgery, gynecology, neurosurgery, obstetrics (eg, C-sections), ophthalmology, orthopedics, podiatry, and urology. Gastroenterology and radiology were excluded from assessment due to reporting limitations. The CPA permitted pharmacists to independently adjust alternative preoperative antibiotics (eg, clindamycin and vancomycin) to

a preferred preoperative antibiotic (eg, cefazolin) in patients with PAL.

Penicillin allergy was defined as an allergy to any penicillin, including a natural penicillin, aminopenicillin, or antistaphylococcal penicillin, with or without a β -lactamase inhibitor. Severe penicillin allergy was defined as any IgE-mediated (type 1) allergy, including immediate hypersensitivity reactions such as anaphylaxis (tightening of the airways and throat, difficulty breathing, loss of consciousness, drop in blood pressure) and hives. Allergies were defined as nonsevere if they did not meet the previously described criteria for severe allergy; reactions reported for nonsevere allergies included rash, itching, gastrointestinal intolerance, various central nervous system reactions (hallucinations, nightmares, aggressive behavior), and unknown reactions. Patients with unknown reactions listed in their medical record were assumed to have nonsevere allergies, and further intervention to assess unknown reactions was not completed as part of this project given that allergy review and assessment is performed as part of the standard workflow for each patient-provider encounter within our healthcare system. Patients with PAL were excluded from the CPA if the reactions were labeled as serum sickness, drug-induced anemia, a drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, or nephritis.

Implementation of the CPA was led by pharmacists reviewing preoperative orders, in most cases 24 hours in advance of the procedure. The pharmacist would independently adjust preoperative orders for nonpreferred preoperative antimicrobials, such as clindamycin and vancomycin, to preoperative cefazolin, according to the CPA criteria, by submitting the order as "per protocol" and notifying the surgeon of the change using the messaging system in the electronic health record intended for nonurgent communications.

A patient registry was established to monitor implementation of the CPA

Table 1. Patients With Penicillin Allergy Labeling Reporting a Severe Reaction

Reaction	No. (%)
PAL with nonsevere or severe reaction	1,572
PAL with severe reaction ^a	663
Anaphylaxis	102 (15.4)
Hives	469 (70.7)
Angioedema, shortness of breath, difficulty breathing, or throat swelling	42 (6.3)
Swelling, edema, or flushing (undefined location, not specifically listed as throat)	31 (4.7)
Other	15 (2.3)
Serum sickness, drug-induced anemia, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, or nephritis ^b	4 (0.6)

Abbreviation: PAL, penicillin allergy labeling.

^aSevere penicillin allergy was defined as any immunoglobulin E-mediated (type 1) allergy, including immediate hypersensitivity reactions such as anaphylaxis (tightening of the airways and throat, difficulty breathing, loss of consciousness, drop in blood pressure) and hives.

^bPatients with penicillin allergy labeling were excluded from the collaborative practice agreement if the reactions were labeled as serum sickness, drug-induced anemia, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, or nephritis.

for the timeframe of January 8, 2020, through January 6, 2022, including Monday through Friday of each week. Registry data collected included the date of the procedure, the patient's medical record number, the patient's age, the severity of the reported penicillin allergy, the preoperative antibiotic received, whether a corticosteroid was received for postoperative nausea and vomiting prevention, and the status of cephalosporin tolerance before and after the procedure. Cephalosporin tolerance before the procedure was defined as use of any cephalosporin in the timeframe after a patient reported a penicillin allergy. For example, chart review would be performed for a patient with a penicillin allergy label with a date of onset in 2006 to determine whether any cephalosporin was used after 2006 and before the planned surgical procedure. Pharmacists were not asked to interpret reported allergies to determine whether they qualified as anaphylaxis. For example, patients reporting shortness of breath or throat swelling were captured as reported and these reactions were not interpreted to be anaphylaxis. Reaction during surgery was assessed by 2-provider documentation, which included surgeon and anesthesiology staff documentation of any complications

during the procedure related to a suspected allergic event. Delayed reactions, occurring after discharge following the surgical procedure, were not assessed. Antimicrobial utilization (days of therapy per 1,000 patient days, or DOT/1,000 PD) of cefazolin, clindamycin, and vancomycin for preoperative prophylaxis was monitored before and after CPA implementation. This project was reviewed and deemed exempt by our institutional review board. Descriptive statistics were used to present the data. A χ^2 test was used for comparisons.

Results

During the stated timeframe, 10,182 procedures and/or surgeries were performed for 1,572 (15.4%) patients with PAL and 663 (42.2%) patients previously reporting at least one reaction categorized as severe, which was hives for 71.2% of these patients (Table 1). Among the patients with PAL, the label was listed as "unknown" for 168 patients.

Four of the 663 (0.6%) patients with severe PAL had reported a reaction labeled as serum sickness, nephritis, or erythema multiforme and were excluded from the CPA and subsequent analysis. Of the 1,572 patients with undifferentiated PAL, 881 (56%) received a corticosteroid

intraoperatively for postoperative nausea and vomiting prevention. An intraoperative corticosteroid was administered at similar rates for patients reporting a nonsevere allergic reaction (385 of 649, 58.4%) and those reporting a severe allergic reaction (495 of 908, 54.5%) ($P < 0.12$). The average patient age was 56 years (range, 1 to 95 years), with 73 patients (4.6%) aged 1 to 17 years.

Of the 1,572 patients with PAL, 971 (61.8%) received a preoperative antimicrobial while 601 (38.2%) did not because this was not indicated for the procedure; among the patients who received a preoperative antimicrobial, 867 (89.3%) were administered a β -lactam and 104 (10.7%) were administered a non- β -lactam antimicrobial. Of the 867 patients receiving a β -lactam antimicrobial, 854 (98.5%) received preoperative cefazolin. Of the 104 patients receiving non- β -lactam preoperative prophylaxis, 54 (51.9%) received a sulfa-based antimicrobial based on the local protocol for the given procedure (eg, a urological procedure).

Of the 659 patients with PAL reporting a severe reaction, 356 received a preoperative cephalosporin (cefazolin, 98.8%; ceftriaxone, 1.2%) and tolerated it without a reported safety event. In

our cohort, there were 52 patients with PAL reporting anaphylaxis as a reaction, and these patients tolerated preoperative cefazolin. Of all 1,572 patients with PAL, 691 (44 %) with listed penicillin allergies, regardless of their severity, tolerated a cephalosporin before a surgical procedure. Among the 659 patients for whom a severe reaction was reported, 298 (45%) had known tolerance to cephalosporins before their surgical procedure, including 28 of 52 (53.8%) patients with PAL who had reported anaphylaxis reactions. Twenty-five (3.8%) patients had documentation of negative penicillin skin testing or known tolerance to penicillin or amoxicillin within their PAL.

An increase in preferred preoperative antimicrobial prophylaxis utilization was noted (cefazolin: 86% to 96.3%, $P < 0.001$; 2019 to 2021) with reductions noted in use of nonpreferred preoperative antibiotics (clindamycin: 2.1% to 0.2%, $P < 0.001$; vancomycin: 3.2% to 0.4%, $P < 0.001$; 2019 to 2021; Table 2).

Discussion

Activation of the pharmacist-led, interdisciplinary CPA resulted in increased use of preferred preoperative antimicrobials in patients with PAL while use of nonpreferred preoperative antimicrobials, such as clindamycin and vancomycin, was reduced without affecting patient safety. All patients reporting a severe allergic reaction ($n = 356$) tolerated preoperative cefazolin without an allergic reaction or reported safety event, including 52 patients with PAL reporting anaphylaxis

in response to penicillin. Our findings are similar to those in Bhathal et al,² Grant et al,³ and Kuruvilla et al⁷ where safe use of preoperative cefazolin was demonstrated in patients with PAL reporting anaphylaxis.

Historically, application of similar protocols has been limited due to concerns for cross-reaction between penicillin and cephalosporin antibiotics. Avoidance of preoperative cefazolin in patients with PAL may carry higher risk than benefit, the opposite intent of historical practice. Use of alternative antibiotics in the setting of PAL does not reduce the prevalence of hypersensitivity reactions but does increase the rates of surgical site infection, adverse reactions, and resistance and leads to logistical complications for delivery of preoperative antibiotics in a timely manner.^{2-4,6,18-24} Blumenthal et al²² conducted a retrospective cohort study to assess the impact of a reported penicillin allergy on risk of surgical site infection and found that patients with a reported allergic reaction to penicillin had 50% increased odds of surgical site infection, which the authors attributed to receipt of nonpreferred preoperative antibiotics. Fosnot et al⁶ reported similar rates of hypersensitivity reactions for cefazolin, clindamycin, and vancomycin in patients with PAL. Recent efforts to promote preoperative cefazolin use and optimize preoperative antimicrobial selection and delivery in patients with PAL have demonstrated successful and safe use.²⁻⁷

Corticosteroids are used in many surgical patients for prevention of

postoperative nausea and vomiting.²³ When used, corticosteroids are typically administered at about the same time as preoperative cefazolin. In our assessment, we identified similar rates of corticosteroid use in patients reporting a nonsevere (54.5%) and severe (58.4%) PAL ($P < 0.12$), indicating no difference in the use of corticosteroids based on the severity of PAL. Given the anti-inflammatory effects of corticosteroids, in addition to their activity to prevent postoperative nausea and vomiting, their ability to minimize an allergic response may be of concern when assessing cephalosporin tolerance in patients with PAL. As corticosteroids have delayed onset of action and have limited evidence of effectiveness in the management of anaphylactic reactions, the ability of these agents to prevent immediate allergic reactions in surgical procedures where antimicrobials are received is unclear.^{24,25} In recent publications demonstrating safe use of cefazolin preoperatively in PAL, the role of corticosteroids has not been routinely assessed.³⁻⁷ However, Bhathal et al² demonstrated no difference in use of corticosteroids within 48 hours of the procedure when comparing patients receiving β -lactam preoperative prophylaxis to those receiving non- β -lactam preoperative prophylaxis.

A meta-analysis by Sousa-Pinto et al¹⁸ calculated a dual-allergy rate for penicillin and cefazolin of 0.6% for patients with unconfirmed PAL and 3.0% for those with confirmed PAL. Applying these figures to our patient population, of the 854 patients with unconfirmed

Table 2. Antimicrobial Utilization of Cefazolin, Clindamycin, and Vancomycin for Preoperative Prophylaxis Before and After CPA Implementation

	Cefazolin		Clindamycin		Vancomycin	
	DOT/1,000 PD	Rate, %	DOT/1,000 PD	Rate, %	DOT/1,000 PD	Rate, %
Before CPA (2019)	81.3	86	1.9	2.1	2.7	3.2
After CPA (2020)	82.5	94.2	0.5	0.4	1.1	1.1
After CPA (2021)	90.6	96.3 ^a	0.2	0.2 ^a	0.5	0.4 ^a

Abbreviations: CPA, collaborative practice agreement; DOT/1,000 PD, days on therapy per 1,000 patient days.

^aThe difference in rate between 2019 and 2021 was statistically significant ($P < 0.001$).

nonsevere and severe PAL who received preoperative cefazolin, 5 would be expected to experience a reaction to preoperative cefazolin. However, we did not observe this during our 2-year-long cohort study, as none of our patients had documented allergic reactions to preoperative cefazolin. We believe that the benefit from use of preoperative cefazolin outweighs the risk in patients with PAL.

National guidelines published in 2010²⁶ encourage the use of cephalosporins in patients with PAL who are confirmed to not be allergic after penicillin skin testing; however, in our experience, resources are limited for penicillin allergy testing. On the basis of emerging literature, including our experience, detailing safe use of preoperative cefazolin in patients with nonsevere and severe PAL, our team encourages national guidelines to permit preoperative cefazolin use in patients with PAL, including in those reporting hives and anaphylaxis.

Conclusion

A pharmacist-led, interdisciplinary CPA increased preferred preoperative antimicrobial use in patients with severe PAL, including in those with hives and anaphylaxis, without reported safety events. Our findings support the use of a CPA as a safe and effective practice.

Disclosures

The authors have declared no potential conflicts of interest.

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