

Perioperative Management of the Penicillin-Allergic Patient

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AN ESTIMATED 32 MILLION AMERICANS have a documented penicillin allergy in their medical record, which equates to approximately 10% of the population in the United States.¹ Yet more than 97% are not at risk for an acute allergic reaction to penicillin.² Many agents recommended as first-line therapy for surgical infection prophylaxis are among the β -lactam pharmaceutical class, such as penicillin, aminopenicillins, cephalosporins, monobactams, and carbapenems (Table 1).³ Studies indicate that 76% to 93% of patients who report a penicillin allergy receive second-line antibiotics for surgical infection prophylaxis.^{4,6}

Current antimicrobial guidelines recommend reserving alternative antibiotics for patients with a presumed or known type 1 immunoglobulin E (IgE)-mediated hypersensitivity reaction or severe hypersensitivity syndrome.³ Characteristics of an IgE-mediated reaction include hives, angioedema, wheezing, shortness of breath, and anaphylaxis. IgE-mediated reactions typically occur within minutes to hours of exposure. IgE-mediated cutaneous reactions are raised, pruritic lesions that last less than 24 hours. These characteristics differ from T-cell mediated cutaneous drug reactions, which have a delayed onset, are typically less pruritic than IgE-mediated reactions, last more than 24 hours, and are characterized as a fine desquamation that resolves over days to weeks. Severe delayed drug hypersensitivity reactions occur days to weeks into the treatment course and often involve blistering and skin desquamation of the mucosal and other organs that usually requires hospitalization. Patients with

β -lactam-related severe delayed drug hypersensitivity syndromes, such as Steven-Johnson's syndrome, toxic epidermal necrolysis, serum sickness, acute interstitial nephritis, hemolytic anemia, and drug rash with eosinophilia and systemic symptoms, have contraindications to all β -lactam therapy.^{1,3}

The clinical consequences of the penicillin allergy label are often unrealized by the patient and even many health care clinicians. In the perioperative space, alternative antibiotics for surgical prophylaxis may be less effective, more prone to adverse effects, more expensive, and a means of promoting antibiotic resistance by using agents with broad spectrums of activity. Cefazolin, a first-generation cephalosporin, is the preferred surgical prophylaxis agent for many surgical procedures because of its spectrum of activity (ie, activity against select gram-negative organisms, including *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella* species and common skin flora, including methicillin-susceptible *Staphylococcus aureus* and *Streptococcus*), bactericidal nature, and ability to rapidly distribute into the tissue.^{3,7} Cefazolin is a recommended first-line agent, with or without metronidazole, in 97% of procedure types in the clinical practice guidelines for surgical prophylaxis.³ Deviating from first-line recommended agent use for surgical prophylaxis may in fact place patients at risk for surgical delays, treatment failure, resistance development, adverse effects, surgical site infections, and increased mortality.^{5,8,9}

Several studies have evaluated the incidence of surgical site infections in patients labeled as penicillin allergic. In a retrospective cohort study of 8,385 patients undergoing a variety of surgical procedures, 11% reported a history of penicillin allergy. Those labeled with a penicillin allergy had a 50% increased odds of surgical site infection (adjusted odds ratio [OR], 1.51; 95% confidence interval [CI], 1.02 to 2.22).⁵ The authors attributed this finding to the receipt of second-line perioperative antibiotics. Patients who reported a penicillin

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Table 1. β -Lactam Antimicrobials in the Surgical Prophylaxis Guidelines³

Penicillin Derivatives	Cephalosporins	Monobactam	Carbapenem
Ampicillin	Cefazolin	Aztreonam	Ertapenem
Ampicillin-sulbactam	Cefotetan		
Piperacillin-tazobactam	Cefoxitin		
	Cefotaxime		
	Ceftriaxone		
	Cefepime		

allergy were administered less cefazolin (12% vs 92%; $P < .001$) and more clindamycin (49% vs 3%; $P < .001$), vancomycin (35% vs 3%; $P < .001$), and gentamicin (24% vs 3%; $P < .001$) compared with those without a reported penicillin allergy.⁵ A similar observation was made in 250 patients undergoing free tissue transfer in head and neck surgery. Patients labeled with a history of penicillin allergy were provided clindamycin as an alternative therapy to first- or second-generation cephalosporin plus metronidazole. This substitution was associated with a four-fold increase in surgical site infections (OR, 3.78; 95% CI: 1.37 to 10.47; $P = .010$).¹⁰ Clindamycin's escalating resistance to methicillin-susceptible *Staphylococcus aureus* across much of the country and its inferior gram-negative coverage in comparison to first- and second-generation cephalosporins are key contributors to surgical site infections when this agent is used.

Patients labeled as penicillin allergic experience more adverse events and drug reactions. Alternative antibiotics for surgical prophylaxis, used alone or in combination, include agents, such as aztreonam, vancomycin, clindamycin, gentamicin, and fluoroquinolones (eg, ciprofloxacin). Patients who receive alternative therapy for surgical prophylaxis are less likely to receive prophylaxis in the recommended time frame, increasing the incidence of surgical delays or inadequate tissue concentrations at the time of surgical incision. Perioperative administration of non- β -lactam antibiotics has been associated with increased risk of *Clostridium difficile* from clindamycin and fluoroquinolones, nephrotoxicity from gentamicin and vancomycin, and red man syndrome from vancomycin.¹¹⁻¹³ In a prospective cohort study of 507 inpatients, 19% had a reported penicillin allergy.¹⁴ Those who received second-line therapy were at a greater risk of adverse effects (adjusted

OR, 3.1; 95% CI, 1.28 to 7.89) compared with those without reported allergy. The composite primary outcome included readmission, acute kidney injury, *Clostridium difficile* infection, and drug reaction requiring discontinuation of therapy.¹⁴ Deviating from first-line β -lactam therapy in patients with a history of penicillin allergy increases the risk of adverse events and may lead to worse clinical outcomes.

Health care clinicians often choose to administer second-line antibiotics for surgical prophylaxis out of concern for cross-reactivity. The penicillin-cephalosporin cross-reactivity rate of a patient with a history of penicillin allergy was originally postulated to be 10%.¹⁵ This rate dates back to data from the 1960s and 1970s when the manufacturing process of cephalosporins started with the production of penicillin derived from *Penicillium* mold. Early cephalosporins, therefore, were often contaminated with trace amounts of penicillin. Additional limitations of these early studies include cross-reactivity testing with primarily first-generation cephalosporins, nonstructured documentation and definitions of allergic reaction types, and inclusion of patients with self-reported allergies. These limitations, among others, likely contributed to the overestimation of cross-reactivity, which is now a widespread misconception.^{16,17} Further propagating this misconception are the Food and Drug Administration-mandated cross-reactivity warnings in the package insert of all cephalosporins, the incorporation of misleading cross-reactivity alerts in the electronic health record, and outdated references in drug resources.

Mounting evidence indicates that the risk of penicillin-cephalosporin cross-reactivity is vastly overestimated. Structural similarities in the R₁ side chain appear to be the predominant driver

Table 2. Generations of FDA-Approved Intravenous Cephalosporins²⁰

First Generation	Second Generation	Third Generation	Fourth Generation	Fifth Generation
Cefazolin	Cefoxitin* Cefotetan Cefuroxime*	Ceftriaxone* Cefotaxime*	Cefepime*	Ceftaroline*

FDA, Food and Drug Administration.

*Have structural similarities to the R₁ or R₂ side chains of other FDA-approved cephalosporins.

of IgE-mediated cross-reactivity between these two pharmacologic classes.¹⁷ Cephalosporins with an identical R₁ side chain to penicillin (or penicillin derivatives) are primarily found in the first- and second-generation classes and include oral cephalexin, cefaclor, cefadroxil, and cefprozil. Observed reaction rates of cross-reactivity among agents with identical side chains have been demonstrated to exceed 10% in previous clinical studies.^{18,19} According to a literature review conducted by Campagna et al,¹⁵ penicillins exhibited cross-reactivity with first-generation cephalosporins (OR, 4.8; 95% CI, 3.7 to 6.2) but a negligible cross-reactivity with second-generation cephalosporins (OR, 1.1; 95% CI, 0.6 to 2.1) and third-generation cephalosporins (OR, 0.5; 95% CI, 0.2 to 1.1). These results support that the cross-reactivity between penicillins and cephalosporins primarily stems from whether the R₁ side chain of the molecule is structurally similar and cannot be solely related to the β -lactam ring. Contrary to the previously postulated 10% cross-reactivity rate, in this study, the overall cross-reactivity rate was 1% when using first-generation cephalosporins or cephalosporins with similar R₁ side chains.¹⁵

Cefazolin, the most common surgical prophylaxis agent, has a unique R₁ side chain that is dissimilar to the R₁ side chains of penicillin or its derivatives. Additionally, it is dissimilar to the R₁ and R₂ side chains of other available cephalosporins.¹⁷ Other cephalosporins commonly used for surgical prophylaxis also have dissimilar side chains to penicillin and its derivatives, but some have similarities to the R₁ or R₂ side chains of other cephalosporins (Table 2). Overall, the cross-reactivity between penicillins and cephalosporins is rare, and documented reactions are strongly associated with the similarity in the R₁ side chain of the molecule. Likewise, cross-reactivity between cephalosporins is rare, and documented re-

actions are associated to the similarity in the R₁, R₂, or both side chains.²⁰ Patients with a confirmed allergy to a β -lactam antibiotic may experience an allergic reaction to a β -lactam antibiotic that does not share any side chain similarities. In this event, the reaction should be considered an independent hypersensitivity reaction that is not related to cross-reactivity.

Cephalosporins have been safely used in individuals with both confirmed and unconfirmed penicillin allergies. The safety of cephalosporins in the perioperative space was evaluated in a retrospective review of 513 penicillin-allergic surgical patients undergoing 624 surgical procedures.⁶ A cephalosporin was administered in 24.5% of cases. Eighty-three percent received cefazolin, and 17% received cefoxitin. Only one patient (0.6%) had a documented nonanaphylactic reaction consisting of hives and erythema. Clindamycin was the most commonly used alternative antibiotic. Two percent of patients who received clindamycin had a documented allergic reaction. Of the 19 patients who received ciprofloxacin, 15% experienced an adverse reaction, including either rash, hives, or systemic hypotension.

Penicillin cross-reactivity among other nonpenicillin and noncephalosporin β -lactams is negligible. Penicillin and carbapenems only share the β -lactam ring resulting in unlikely cross-reactivity. Similarly, because of molecular structural differences, there is no cross-reactivity between penicillin or its derivatives and the monobactam, aztreonam. Some clinical data, however, support potential cross-reactivity between aztreonam and ceftazidime as a result of having identical side chains.¹⁷

Implementation of penicillin allergy evaluation before elective surgical procedures can assist in risk stratification and selection of the best antibiotic(s) for prophylaxis.²¹ Perhaps, most

Table 3. Key Takeaways About Penicillin Allergies^{5,27}

- Approximately 10% of the US population report having a penicillin allergy
- Less than 1% are truly allergic to penicillins
- Approximately 80% of patients with an IgE-mediated penicillin allergy lose their sensitivity after 10 y
- Cefazolin, an agent commonly used for surgical infection prophylaxis, does not share structural R₁ side chain similarities with penicillin or its derivatives and therefore does not convey cross-reactivity
- Use of alternative antibiotics for surgical prophylaxis in patients with a penicillin allergy history have up to a 50% risk of developing a surgical site infection

IgE, immunoglobulin E.

importantly, it is an access point to medical care that can aid in delabeling patients with false penicillin allergies. In a study by Moussa et al,²² implementation of a preoperative β -lactam allergy delabeling program optimized choice of antibiotic prophylaxis and reduced intraoperative time by 22 minutes. Preoperative penicillin allergy evaluation has demonstrated success in orthopaedic,²³ general,²¹ and cardiac surgeries.²⁴ The largest cohort of preoperative testing come from the Mayo Clinic where they have performed more than 29,000 penicillin-allergy tests with only 1% being positive.²⁵ Identifying penicillin allergies and escalating further evaluation as needed is an antimicrobial stewardship responsibility that should be advocated by physicians, nurses, advanced practice providers, and pharmacists.

Much of what we know about cross-reactivity among penicillin or its derivatives and cephalosporins is limited by the quality of the data. It is clear, however, that avoidance of cephalosporins in patients with a history of penicillin allergy places them at risk for untoward outcomes, including adverse events and treatment failures such as surgical site infections. Health care costs are also impacted. β -Lactam antibiotics are typically less expensive than the alternative antibiotic and the potential consequences of their avoidance may drive up healthcare costs through increased readmission rates secondary to surgical site infections and adverse drug reactions (eg, *Clostridium difficile* colitis) or through the promotion of antimicrobial resistance (eg, vancomycin-resistant *Enterococcus*).²⁶

As the impact of the penicillin allergy label on surgical outcomes becomes more apparent, it is imperative that perioperative health care professionals aid in rectifying false labels and educating patients about the unintended consequences (Table 3).²⁷ A thorough penicillin allergy history should be conducted with the ultimate goal of improving antibiotic selection and optimizing the use of β -lactam agents in the perioperative setting. Cefazolin, the most common surgical prophylaxis agent, does not share similar R₁ side chains with penicillin or its derivatives and therefore does not convey cross-reactivity. Ample evidence supports the safe use of commonly recommended cephalosporins for surgical prophylaxis in non severe penicillin-allergic patients.

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