

G9: What is the optimal antibiotic prophylaxis for patients who have penicillin allergy?

Jason M. Jennings, Hitoshi Honda, Michael Yayac, Meeri Honkanen, Christopher E. Pelt, Piret Mitt, Nicholas J. Giori, Daniel Schweitzer, Kristen I. Barton

Response/Recommendation:

It is safe and appropriate to administer a first-generation cephalosporin (cefazolin) as first-line antibiotic prophylaxis in the operating room setting for patients who have a documented penicillin allergy.

Strength of Recommendation: Strong

Delegates Vote:

Rationale:

Selection of preoperative antibiotic prophylaxis can be challenging in patients who have a history of penicillin allergy [1]. For patients who have an IgE-mediated hypersensitivity reaction, previous guidelines recommend the use of alternative agents. However, those alternative agents are associated with worse outcomes, including an increased risk of surgical site infection (SSI) and higher cost [1]. Approximately 10% of the population will report a penicillin allergy [2], yet few have clinically relevant reactions [3]. Over-reporting of penicillin allergies and the safety of cephalosporins in patients who have reported penicillin allergies have been well established throughout the evidence [4]. The overall cross-reactivity rate between penicillins and cephalosporins is low at approximately 1 to 2% when using first-generation cephalosporins or cephalosporins with similar R1 side chains [4, 5]. Moreover, the use of third- or fourth-generation cephalosporins or cephalosporins with dissimilar side chains than the offending penicillin carries a negligible risk of cross-allergy in penicillin-allergic patients [4]. Evaluation of penicillin allergy before prophylactic antibiotics is crucial for antimicrobial stewardship [3]. A recent systematic review [6] demonstrated that penicillin allergy screening and testing markedly increase the use of first-line antibiotics. Porto et al. [6] showed low rates of true penicillin allergy (0.7 to 3%), and allergic reaction frequency for patients who have reported penicillin allergy receiving cephalosporins was between 0 and 2%.

Reported Penicillin Allergy and Adverse Reactions

From the systematic review (Figure 1), in the six studies [7-12] that reported the adverse reactions related to penicillin allergy, the majority were non-severe allergic reactions (rash, hives, pruritis, gastrointestinal upset, local swelling, intolerance, or remote history/unknown). All but one study [13] used cefazolin for prophylactic antibiotics in their non-penicillin allergy patients, and they used cefuroxime. In all the reviewed studies, alternatives to cefazolin for penicillin allergy included clindamycin or vancomycin (Tables 1-3).

Risk of Allergic Reaction

The risk of allergic reactions in patients who have a reported penicillin allergy and are given cephalosporin prophylaxis is that allergic reactions occurred in 0 to 1.5% of patients (Table 4). In all the patients that received cefazolin who previously had a severe penicillin allergy, no patients had severe adverse reactions, and cefazolin was well tolerated.

All symptoms resolved promptly with antibiotic discontinuation and administration of antihistamines and/or corticosteroids [7]. Bukowski et al. [7] demonstrated that perioperative prophylaxis with cefazolin resulted in a 0.1% incidence of allergic reactions that were clinically indolent. Jones et al. [9] reported that no patients had signs of an allergic reaction related to cefazolin, including eight patients who had severe penicillin allergies. Similarly, Michaud and Yen [10] reported that among those with non-IgE-mediated reactions to penicillin who received cefazolin there were no adverse reactions. Furthermore, Stone et al. [12] also reported that no patient who had a penicillin allergy and was given cefazolin prophylaxis experienced a reaction. Lastly, Goh et al. [8] reported there were no differences in total allergic reactions or severity between cephalosporin and non-cephalosporin antibiotics. Also, one study reported that the frequency of intraoperative hypersensitivity reactions was not different between groups (cefazolin = 0.2 versus clindamycin/vancomycin = 1.3%; $P = 0.06$) [11].

Postoperative Infections

The incidence of postoperative infections when using alternative antibiotic prophylaxis has been reported in six studies (Table 4) [7, 8, 11-14]. Bukowski et al. [7] observed no differences in the rates of superficial infections (0.1 versus 0.2%; $P = 0.58$), deep infections (0.3 versus 0.4%; $P = 0.68$), or *Clostridioides difficile* (*C. difficile*) infections (0.04 versus 0%; $P = 0.99$) within 90 days of surgery in reported penicillin allergy patients who received cefazolin versus alternative preoperative antibiotics. Similarly, Goh et al. [8] found there were no differences in the rates of superficial wound, periprosthetic joint infection (PJI), or *C. difficile* infections between the protocol and control groups. Stevoska et al. [13] demonstrated there was no difference in the presence of PJI (2.1 versus 2.9%; $P = 0.440$), presence of culture-positive PJI (2.0 versus 2.9%; $P = 0.309$), presence of polymicrobial infection (19.7 versus 16.7%; $P = 0.860$), or number of pathogens isolated between cefuroxime-administered cases and non-cefuroxime-administered cases. Also, Stone et al. [12] concluded that there was no difference in the incidence of postoperative infection by reported penicillin allergy (0.6 versus 0.4%; $P = 0.473$) or antibiotic prescribed (0.5 versus 0.6%; $P = 0.4817$). However, Norvell et al. [11] found that there were fewer surgical site infections in the cefazolin group compared with the clindamycin and/or vancomycin group (0.9 versus 3.8%; $P < 0.001$), including fewer PJIs (0.1 versus 1.9%). Wyles et al. [15] reported that after allergy-tested patients ($n = 2576$ of 22705), 97% ($n = 2,493$) were cleared to use cephalosporins. For the cohort ($n = 28,174$ total joint arthroplasties (TJA)), 94.9% went on to receive cefazolin and 5.1% received non-cefazolin antibiotics. The authors found that infection-free survival was significantly higher among patients receiving cefazolin compared with those with non-cefazolin antibiotics. Although the results were mixed, there may be a higher rate of SSI in penicillin allergy patients when non-cefazolin antibiotics are used for perioperative TJA prophylaxis.

Antibiotic Stewardship

The studies were all in agreement that evaluation of severe penicillin allergy before prophylactic antibiotics is crucial from an antimicrobial stewardship perspective. In a study by Jones et al. [9], a multifaceted antibiotic stewardship intervention increased the appropriateness of antibiotic prophylaxis in elective primary TJA. In this study, patients who have non-severe penicillin allergies, even those reporting hives or local swelling, tolerated cefazolin. In another study, a

simple screening protocol allowed two-thirds of patients who had a self-reported allergy to receive cefazolin without the need for additional consultations or testing. The authors concluded that this protocol could be safely implemented to increase the rate of cefazolin usage without a corresponding increase in the number of allergic reactions [8]. Furthermore, prophylaxis protocols should promote appropriate indications for the use of cephalosporins and alternative prophylactic antibiotics to mitigate infectious risks after TJA [14]. Antibiotic stewardship interventions and protocols [12, 14] can be utilized in patients who have a reported penicillin allergy.

Conclusion

Based on the current systematic review, we found that there are very low rates of cross-reactivity between penicillins and cephalosporins. The reviewed studies concluded that it is appropriate to administer a first-generation cephalosporin (cefazolin) as the first choice for antibiotic prophylaxis for patients who have a documented penicillin allergy (Table 5). When cefazolin is not available, a second-generation cephalosporin (cefuroxime) can be used. The majority of patients who have a penicillin allergy can safely receive first-line antibiotic therapy [12] without experiencing adverse reactions. Allergy to first or second-generation cephalosporins is exceedingly rare, and if it does occur, it is most often mild and can be easily treated.

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