

# Beta-Lactam Antibiotic Use in Penicillin-Allergic Patients

by Jeffrey Fish, PharmD

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**H**ealth care professionals frequently deal with patients who report antibiotic allergies. The reported penicillin allergy rate for inpatients and outpatients is 10%.<sup>1</sup> Of these patients, 80 to 90% will not have had positive penicillin skin testing for IgE-mediated reactions.<sup>2,3</sup> Switching from the prescribed antibiotic to another due to a reported allergy may adversely affect patient care if that different antibiotic is less effective, has more adverse effects, has a broader spectrum of activity (potentially leading to increased antimicrobial resistance), or is more expensive.<sup>2</sup> The University of Wisconsin Hospital and Clinics has developed a clinical practice guideline to assist pharmacists in the care of penicillin-allergic patients who are prescribed cephalosporins.

## BACKGROUND

The different types of allergic drug reactions are classified by the Gell and Coombs classification (see Table 1).<sup>2-6</sup> There are a few reasons for the negative skin tests. First, the patient may state he or she is allergic to a medication, but the reaction could actually be an adverse drug reaction (e.g., gastrointestinal intolerance) or attributed to the disease being treated (e.g., rash caused by viral infection while on amoxicillin). It is very important to discuss with the patient or family the history of the allergic reaction to determine the likelihood of a true penicillin allergy. The UWHC guideline includes a variety of patient assessment questions that should be asked. Second, the positive penicillin skin test decreases 10% annually after a penicillin allergic reaction and 78% of penicillin allergic patients have negative skin tests after 10 years of avoidance.<sup>7</sup>

Penicillins and cephalosporins share a common beta-lactam ring, but have different alpha ring structures. Penicillins have a thiazolidine ring and cephalosporins have a dihydrothiazine ring (see Figure 1). Some penicillins and cephalosporins also share common side chains. Specific examples of common side chains include: penicillin G and cefamandole, cephalothin and cephaloridine, ampicillin and cephalexin, and amoxicillin and cefadroxil.<sup>3</sup> Due to these facts, there is a risk of cross-reactivity between the two classes of antibiotics. The degree of cross-reactivity appears to be greater between different cephalosporins than between cephalosporins and penicillins.<sup>8</sup> Prior to 1980, the cross-reactivity between penicillins and cephalosporins was reported to be 10 to 20%. This was probably due to the fact that the cephalosporins used at the time, cephalothin and cephaloridine,

TABLE 1. GELL AND COOMBS CLASSIFICATION OF ALLERGIC REACTIONS<sup>2-6</sup>

### Type 1: IgE-mediated

- a. Immediate reactions (onset <1 hour after drug administration):
  - i. Systemic manifestations of anaphylaxis (urticaria, hives, pruritus, bronchospasm, laryngeal edema, hypotension, and/or cardiac arrhythmias)
  - ii. Life-threatening
  - iii. Tested by minor determinant of penicillin skin test
  - iv. Immediate reactions occurring greater than one hour after infusion, or during sustained therapy, even in the presence of urticaria, are rare.<sup>2,5</sup>
- b. Accelerated reactions (onset 1-72 hours after drug administration)
  - i. Urticaria, angioedema, laryngeal edema, wheezing
  - ii. Rarely life-threatening
  - iii. Tested by major determinant of penicillin skin test
- c. Usually associated with beta-lactam antibiotics

### Type 2: Cytotoxic/antibody-mediated (IgG-, complement-mediated)

- a. Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis
- b. Usually associated with quinidine, methyldopa and penicillins

### Type 3: Immune complex (IgG, IgM immune complexes)

- a. Serum sickness (fever, rash, urticaria, lymphadenopathy, and arthralgias)
- b. Usually associated with antisera, penicillin, sulfonamides and phenytoin

### Type 4: Cellular immune-mediated/delayed hypersensitivity reaction (contact dermatitis)

**Unknown mechanism:** erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug reaction, pulmonary infiltrates (nitrofurantoin), autoimmune disease (vasculitis, lupus), drug fever, drug-induced hypersensitivity syndrome (antiepileptics)



share a similar side chain with benzyl penicillin.<sup>3</sup> Also during this time, some cephalosporins were contaminated with trace amounts of penicillin.<sup>3</sup> Since 1980, reaction rates in penicillin history-positive and skin test-positive patients who received cephalosporins decreased to between 2 and 4.4%.<sup>3,8</sup> A review of cross-reactivity and post-marketing studies of second- and third-generation cephalosporins revealed no increase in allergic reactions in those patients with a history of penicillin allergy.<sup>7</sup> If a patient is penicillin history-positive, but skin test-negative, there is no increased risk of cephalosporin cross-reactivity.<sup>8</sup> If patients with a history of penicillin allergies aren't skin tested, the risk of a reaction when given a second or third generation cephalosporin is about 1%. Unfortunately, most of these reactions are anaphylaxis.<sup>3</sup> Penicillin skin testing has a high negative predictive value for type 1 reactions since 97-99% of patients with a negative skin test to both the major and minor determinants will not have an immediate type 1 reaction.<sup>3</sup> In general, patients with a history of penicillin allergy are three times more likely to have an adverse reaction to any additional antibiotics given (including cephalosporins).<sup>7,9</sup>

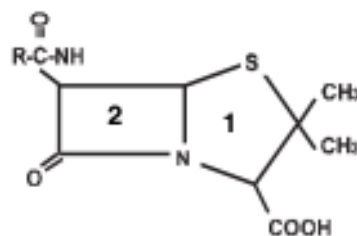
Cross-reactivity with other beta-lactams varies by class. The carbapenem's alpha ring is a modified version of the thiazolidine ring of penicillins and the risk of cross-reactivity is greater than in a patient without a penicillin allergy (may be as high as 11%).<sup>6,10</sup> Monobactams (aztreonam) do not have a true beta-lactam antibiotic structure since they are missing the alpha ring.<sup>11</sup> Cross-reactivity between monobactams and other beta-lactams is rare.<sup>6</sup> Aztreonam shares a common side chain with ceftazidime, so there is a risk of cross-reactivity between these agents.<sup>6</sup> ●

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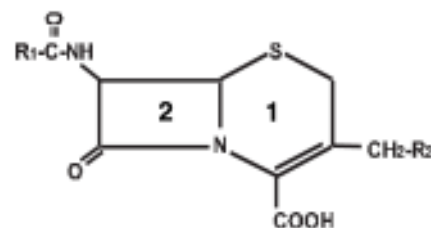
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FIG 1. STRUCTURE OF BETA-LACTAM ANTIBIOTICS<sup>6,11,12</sup>



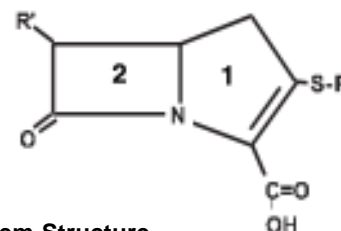
#### Penicillin Structure

- 1-thiazolidine ring
- 2-beta-lactam ring
- R<sub>1</sub>- side chain



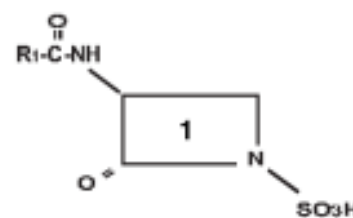
#### Cephalosporin Structure

- 1-dihydrothiazine ring
- 2-beta-lactam ring
- R<sub>1</sub>, R<sub>2</sub>- side chains



#### Carbapenem Structure

- 1- modified thiazolidine ring
- 2-beta-lactam ring
- R, R<sub>1</sub>- side chains



#### Monobactam Structure

- 1-beta-lactam ring
- R<sub>1</sub>- side chain

**UNIVERSITY OF WISCONSIN HOSPITAL AND CLINICS GUIDELINES  
FOR THE USE OF CEPHALOSPORIN ANTIBIOTICS IN PATIENTS WITH REPORTED ALLERGIES TO PENICILLIN**

Please address questions, comments, and suggestions regarding this guideline to  
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**A. Introduction**

This guideline outlines the safe and appropriate use of cephalosporins in penicillin-allergic patients.

**B. Guideline**

- 1.0 When an order for a cephalosporin is received it should be determined if the patient has any medication allergies.
  - 1.1 The order may be processed if the patient does not have an allergy to cephalosporins or penicillins.
  - 1.2 In the case of a reported allergy to cephalosporins or penicillins:
    - 1.2.1 The pharmacist should investigate and determine the type and severity of the reaction (see Section D).
    - 1.2.2 If a rash is described, the pharmacist should ascertain the characteristics of the rash. Types of rashes include:
      - 1.2.2.1 Urticaria (IgE-mediated) rashes are an intensely pruritic, circumscribed, raised and erythematous eruption with central pallor.
      - 1.2.2.2 Maculopapular or morbilliform rashes (non-IgE-mediated) begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.
    - 1.2.3. The cephalosporin order may be processed if:
      - 1.2.3.1. The patient has received a cephalosporin in the past without a reaction.
      - 1.2.3.2. The patient or family does not recall the reaction.
      - 1.2.3.3. A nonsevere, non-IgE-mediated reaction is described.
      - 1.2.3.4. The pharmacist can ascertain that the rash is non-urticarial.
    - 1.2.4. The pharmacist should contact the prescriber for a change in antibiotic if:
      - 1.2.4.1. The type of rash cannot be ascertained (it should be assumed to be urticarial, IgE-mediated)<sup>6</sup>
      - 1.2.4.2. The patient's history is positive for another IgE-mediated (type 1) reaction
      - 1.2.4.3. The reaction is a severe, non-IgE-mediated reaction
    - 1.2.5. The prescriber and pharmacist should then determine if an agent in another antibiotic class could be used; or, if no alternative agent is available, whether the patient should be penicillin skin tested

**C. Choice of Antibiotic**

- 1.0 If the order is for a cephalosporin that has the same side chain as a penicillin the patient is allergic to, the prescriber should be contacted for another antibiotic choice.<sup>8</sup> Specific examples include:
  - 1.1 Penicillin G and cefamandole, cephalothin and cephaloridine
  - 1.2 Ampicillin and cephalexin
  - 1.3 Amoxicillin and cefadroxil
- 2.0 Carbapenems share a common beta-lactam ring with penicillins and the risk of cross-reactivity is greater than in a patient without a penicillin allergy (may be as high as 11%).<sup>6,10</sup> Due to this risk of cross-reactivity, the same guideline should be applied in this situation.
- 3.0 Monobactams (aztreonam) do not have a true beta-lactam structure since they are missing the alpha ring (thiazolidine ring in penicillins or dihydrothiazine ring in cephalosporins).<sup>11</sup>
  - 3.1 The risk of cross-reactivity between monobactams and penicillins is low.<sup>6</sup>
  - 3.2 If an order for a monobactam (aztreonam) is written for a patient with an IgE-mediated allergy to penicillins, the order may be processed.
  - 3.3 If the patient has an allergy to ceftazidime, aztreonam should not be used due to similar side chains for the two agents.
- 4.0 If a patient has a cephalosporin allergy and an order for a penicillin is received, the same guideline should be applied.

#### D. Patient Interview

Potential questions to ask a patient/family member when investigating a medication allergy include:<sup>2</sup>

1. Patient's age at the time of the reaction
2. Patient's recall of the reaction or who informed them of it
3. Time of onset of the reaction after beginning the penicillin (e.g., after 1 dose or several days)
4. Signs/symptoms of the reaction
5. Was an antidote given
6. Did it require a visit to emergency room
7. Was there a loss of consciousness
8. Route of administration (oral or IV)
9. Indication for penicillin (or cephalosporin)
10. Concurrent medications
11. Did the reaction abate after the penicillin (or cephalosporin) was discontinued
12. Had the patient taken other penicillins (or cephalosporins) before or after the reaction, and if yes, what was the outcome

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