



HealthPartners

Institute for Medical Education

Vice President and Executive Director: Carl Patow, M.D., M.P.H.

The
INSTITUTE FOR MEDICAL EDUCATION
BULLETIN

Penicillin Allergy and the Cephalosporins

By
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And
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Developed: July 2006 **Approved:** August 2006 **Expiration Date for CME Credit:** August 31, 2007
Estimated Time to Complete: 15 Minutes **Target Audience:** Family Practice, Internal Medicine and Other Primary Care Physicians; Nurse Practitioners and Physician Assistants; Pharmacists; Nurses; Other Health Care professionals

Description

This learning activity addresses the risk of cephalosporin cross-reactivity in patients with a history of penicillin allergy.

Objectives

Following this learning activity, the learner will be able to:

- State three reasons why the risk of allergic cross-reactivity between the penicillins and cephalosporins is much lower than the commonly cited 10% rate.
- Name two cephalosporins on the HealthPartners Formulary that should be prescribed cautiously for patients with a history of IgE-mediated penicillin allergy.
- Name three cephalosporins on the HealthPartners Formulary that may be prescribed safely for patients with a history of IgE-mediated penicillin allergy.

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Gary Freeman, M.D. and Peter Marshall, PharmD have indicated no financial interests, affiliations, or intent to discuss unapproved or investigative use of commercial products or devices.

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Penicillin Allergy and the Cephalosporins

Risk of Cross-Reactions to Second- and Third-Generation Cephalosporins Is Believed to Be Low

By

Gary Freeman, M.D.

And

Peter Marshall, PharmD.

Penicillin allergy is reported by 5-20% of patients and often complicates the choice of an alternative antibiotic when these individuals require antibiotic therapy. Many infections treated with a penicillin could also be treated effectively with a cephalosporin and clinicians are often tempted to prescribe a cephalosporin when confronted with a penicillin-allergic patient. Because both classes of antibiotics share a common β -lactam ring, it is often believed that moderate allergic cross-reactivity between the two groups of antibiotics is likely and a 10% cross-reactivity rate is often cited. **As discussed below, the true risk of allergic cross-reactivity between these two drug classes is probably much lower.**

Many people (perhaps 80%) labeled as penicillin-allergic have had non-IgE-mediated reactions⁽¹⁾ and are not truly allergic to penicillin. These non-allergic reactions may include toxic effects such as vomiting or diarrhea; a non-allergic rash due to the antibiotic, a virus, or an interaction between the two⁽²⁾; or a contemporaneous adverse event unrelated to the antibiotic therapy. **These patients can be prescribed a cephalosporin without concern about allergic cross-reactions⁽³⁾.** Unfortunately, many people with a history of penicillin allergy have only a vague recollection or description of the type of reaction that they had when exposed to a penicillin.

Although there are structural similarities between the penicillins and cephalosporins, the metabolism of these drug classes produces different degradation products that reduce the likelihood of immunogenic cross-reactions. The β -lactam ring of penicillin has an attached thiazolidine ring. In the

cephalosporins, the thiazolidine ring is replaced by a dihydrothiazine ring. Following degradation, the β -lactam ring of penicillin forms a stable penicilloate ring with preservation of the thiazolidine ring. Cephalosporin metabolism results in rapid fragmentation of both the β -lactam and dihydrothiazine rings. **Based on these differences in degradation products, the likelihood of cross-reactivity between the β -lactam rings of these drug classes is believed to be minimal.**

Cross-reactions between the penicillins and cephalosporins are believed to be more dependent on similarities in their molecular side chain structures than on the β -lactam and thiazolidine or dihydrothiazine rings⁽⁴⁾. The risk of cross-reactions between the cephalosporins on the HealthPartners Formulary and penicillins based on side chain similarities is summarized below. **In general, first generation cephalosporins should be used cautiously in patients with a history of an IgE-mediated reaction to a penicillin while second- and third-generation cephalosporins may be used without significant risk of an allergic cross-reaction.**

- *Cephalexin/Keflex*® and *cephradine/Velosef*®, and *cefprozil/Cefzil*® share side-chain similarities with penicillin and/or amoxicillin and may have a 0.5% to 6.5% greater likelihood of producing allergic cross-reactions among penicillin- or amoxicillin-allergic patients. Note that although the risk of an allergic cross reaction is increased, the *population attributable risk* (the excess risk associated with a use of first-generation cephalosporin in a penicillin-allergic patient) is still quite low (0.4%).
- *Cefuroxime/Ceftin*®, *cefдинир/Omnicef*®, and *ceftriaxone/Rocephin*® have side-chains that are dissimilar from those of penicillin and amoxicillin. These drugs are believed to be unlikely to cause allergic cross-reactions in penicillin- or amoxicillin-allergic patients.

CONCLUSIONS

- **Patients with a history of penicillin allergy are less likely to experience an allergic cross-reaction to a cephalosporin than is commonly thought.**
- **Many people labeled as penicillin-allergic have had non-IgE-mediated reactions and are not truly allergic to penicillin.** They can be prescribed cephalosporins without concern about allergic cross-reactions.
- **The metabolism of the β -lactam and thiazolidine or dihydrothiazine rings in the penicillins and cephalosporins results in the production of different degradation products.** This reduces the likelihood of allergic cross-reactions.
- **Allergic cross-reactions between the penicillins and cephalosporins are believed to be more dependent on their molecular side chain structures than on the β -lactam and thiazolidine or dihydrothiazine rings.** First-generation cephalosporins such as cephalexin, cephradine, and cefprozil should be used cautiously in patients with a history of an IgE-mediated reaction to penicillin or amoxicillin. Second- and third-generation cephalosporins such as cefuroxime, cefдинир, and ceftriaxone may be used without increased risk of an allergic cross-reaction.

1) Symptoms of IgE-mediated hypersensitivity include urticaria, laryngeal edema, bronchospasm/wheezing, hypotension, hyperperistalsis, and dysphagia. Reactions that begin within the first hour after administration are IgE-mediated. Accelerated

reactions occurring 1-72 hours after administration are usually associated with prior drug sensitization and are also IgE-mediated.

- 2) Approximately 5%-9% of patients treated with amoxicillin develop a non-pruritic maculopapular rash after 7-10 days of treatment. This increases to 70%-100% if the patient has a concurrent infection with infectious mononucleosis. The incidence of rash is also increased if the patient has chronic lymphocytic anemia, has an elevated uric acid level, or is on allopurinol.
- 3) Primary allergic reactions to cephalosporins may occur unrelated to a patient's history of penicillin allergy. Anaphylactic reactions to cephalosporins are rare (0.0001% to 0.1%). Cephalosporin-induced rash occurs in 1% to 3% of patients. Patients with a history of drug allergy are felt to be at increased risk of developing allergic reactions to unrelated, non-cross reacting compounds. Penicillin-allergic patients are believed to have a threefold increased coincidental risk of adverse reactions to unrelated drugs. Penicillin skin testing does not predict cephalosporin allergy reliably.
- 4) Allergic cross-reactions between cephalosporins are also believed to be dependent on their side chains. Patients with a history of an allergic reaction to a specific cephalosporin may have a low risk of allergy to other cephalosporins with dissimilar side chains. Groups of cephalosporins with similar side chains at the 3-position of the beta-lactam ring are summarized below:
 - Cefdinir/Omnicef® and cefixime/Suprax®
 - Cephadrine, cefadroxil, and cephalixin
 - Cefoperazone/Cefobid® and cefotetan/Cefotan®
 - Cephapirin and cefotaxime
 - Cefuroxime/Zinacef®/Kefurox® and cefoxitin
 - Cefibuten/Cedax® and Ceftizoxime/Cefizox®

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