Cephalosporins can be prescribed safely for penicillin-allergic patients

Practice recommendations

- The widely quoted cross-allergy risk of 10% between penicillin and cephalosporins is a myth (A).
- Cephalothin, cephalexin, cefadroxil, and cefazolin confer an increased risk of allergic reaction among patients with penicillin allergy (B).
- Cefprozil, cefuroxime, cefpodoxime, ceftazidime, and ceftriaxone do not increase risk of an allergic reaction (B).

Undoubtedly you have patients who say they are allergic to penicillin but have difficulty recalling details of the reactions they experienced. To be safe, we often label these patients as penicillin-allergic without further questioning and withhold not only penicillins but cephalosporins due to concerns about potential cross-reactivity and resultant IgE-mediated, type I reactions. But even for patients truly allergic to penicillin, is the concern over cephalosporins justified? It depends on the specific agent. What is certain is that a blanket dismissal of all cephalosporins is unfounded.

The truth about the myth

Despite myriad studies spanning decades and involving varied patient populations, results have not conclusively established that penicillin allergy increases the risk of an allergic reaction to cephalosporins, compared with the incidence of a primary (and unrelated) cephalosporin allergy. Most people produce IgG and IgM antibodies in response to exposure to penicillin that may cross-react with cephalosporin antigens. The presence of these antibodies does not predict allergic, IgE cross-sensitivity to a cephalosporin. Even penicillin skin testing is generally not predictive of cephalosporin allergy.

Reliably predicting cross-reactivity

A comprehensive review of the evidence shows that the attributable risk of a cross-reactive allergic reaction varies and is strongest when the chemical side chain of the specific cephalosporin is similar to that of penicillin or amoxicillin.

Administration of cephalothin, cephalexin, cefadroxil, and cefazolin in penicillin-allergic patients is associated with a significant increase in the rate of allergic reactions; whereas administration of cefprozil, cefuroxime, cefpodoxime, ceftazidime, and ceftriaxone is not.

Penicillin skin testing can accurately predict a penicillin-allergic reaction, but is not predictive for cephalosporin allergy unless the side chain of the penicillin or amoxicillin testing reagent is similar to the cephalosporin side chain being evaluated. Patients who have a reaction to a penicillin or a cephalosporin that is not
IgE mediated and not serious may receive repeated courses of that antibiotic and related antibiotics.

This article provides a comprehensive review of the frequency of allergic cross-reactivity between penicillin/amoxicillin and cephalosporin antibiotics, supporting the recent American Academy of Family Physicians evidence-based clinical practice guideline on treatment of acute otitis media recommending the use of cefuroxime, cefpodoxime, cefdinir, and ceftriaxone cephalosporins for patients allergic to penicillin.

■ Methods
We searched Medline and EMBASE databases for English-language articles using the keywords cephalosporin, penicillin, allergy, and cross-sensitivity for the years 1960 to 2005. Among 219 articles identified, 101 were included as source material for this review. Articles we excluded were reviews, republication of results, or ones irrelevant to our purpose.

Five articles described the rate of rashes following use of penicillin and cephalosporins, and 4 articles described rates of anaphylaxis. We included 26 articles for the evidence base evaluating penicillin/amoxicillin cross-allergy. Eleven articles relied on patient history of penicillin/amoxicillin allergy to categorize results and establish reaction rates and relative risks for the penicillin/amoxicillin allergic vs nonallergic when receiving cephalosporins. Fourteen articles relied on patient history of penicillin/amoxicillin allergy plus skin testing results to penicillin/amoxicillin to categorize patients.

■ Results
True incidence of reactions to cephalosporins
The most frequent reactions to cephalosporins are non-pruritic, non-urticarial rashes, which occur in 1.0% to 2.8% of patients; for most, the mechanism is idioopathic and not a contraindication for future use. Retrospective studies suggest a 1% to 3% incidence of immune or allergic reactions to cephalosporins independent of any history of penicillin/amoxicillin allergy. Anaphylactic reactions from cephalosporins are extremely rare, with the risk estimated at 0.0001% to 0.1%. A seminal study suggested approximately 0.004% to 0.015% of treatment courses with penicillin results in anaphylaxis.

Determining cross-reactivity
Penicillins and cephalosporins both possess a beta-lactam ring for antimicrobial activity. They differ in that the 5-membered thiazolidine ring of penicillin is replaced in the cephalosporins with a 6-membered dihydrothiazine ring. After degradation, penicillin forms a stable ring, whereas cephalosporins undergo rapid fragmentation of their rings. Immunologic cross-reactivity between the penicillin and cephalosporin beta-lactam rings is, therefore, very unlikely—an observation confirmed by monoclonal antibody analysis.

How the “10% cross-reactivity” myth took hold. When the first-generation cephalosporins cephaloridine and cephalothin were introduced in the 1960s, allergic and anaphylactic reactions were reported in patients with previous allergic reactions to penicillins. Subsequent reports, which attributed up to 10% cross-reactivity between the 2 drug classes, involved these same first-generation cephalosporins plus cephalaxin and cefadroxil and a second-generation drug, cefamandole. However, these studies were flawed because the
Many other studies have suggested that cross-reactive immune responses to cephalosporins depend on side chain structure; that is, cephalosporins with a 7-position side chain similar to benzylpenicillin are more likely to cross-react with penicillin (Table 2). Cephalosporins that share a similar 7-position or 3-position side chain are more likely to cross-react with each other.

Cephalosporin/penicillin cross-reactivity
Few studies have evaluated whether patients with primary hypersensitivity to cephalosporins will experience cross-reactivity with penicillin. Romano et al. conducted skin tests and RASTs in patients with immediate allergic reactions to cephalosporins to examine responses to other cephalosporins and to classic penicillin determinants. About 1 in 5 patients allergic to a cephalosporin reacted to penicillin determinants, while most had positive results to other cephalosporins with the same or similar side-chains.

Limitations of skin testing
Penicillin skin testing in patients with a history of penicillin allergy does not reliably predict allergy to a cephalosporin unless the side chain of the penicillin or ampicillin reagent is similar to the cephalosporin side chain being tested. The positive and negative predictive values of skin testing results for cephalosporins are not well established; if the haptens that cause cephalosporin allergy were known, cross-reactivity with penicillins could be assessed directly. Cephalosporin skin testing works only for the specific drug and drugs with the same side chains, and can be done only if the drug is available in an IV or IM formulation.

Even a positive result does not guarantee a clinical reaction. When penicillin and cephalosporin skin tests or radioallergosorbent tests (RASTs) are positive, a clinical reaction is observed in only 10% to 60% of patients, depending on the reagent and study. For example, among
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### TABLE 1

Summary of studies in which penicillin/amoxicillin-allergic patients received cephalosporins

<table>
<thead>
<tr>
<th>CEPHALOSPORINS THAT SIGNIFICANTLY INCREASE ALLERGIC REACTIONS IN PENICILLIN-ALLERGIC PATIENTS</th>
<th>Penicillin/Amoxicillin Allergy by History*</th>
<th>RR Difference (95% CI)</th>
<th>Penicillin/Amoxicillin Allergy by History and Skin Testing†</th>
<th>RR Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug (Generation)</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Cephalothin (1)</td>
<td>8/160 5.0%</td>
<td>27/1343 2.0%</td>
<td>+3% (+0.5–5.5%) P=.035</td>
<td>2/11 18%</td>
</tr>
<tr>
<td>Cephaloridine (1)</td>
<td>34/390 8.7%</td>
<td>178/14,438 1.2%</td>
<td>+7.5% (6.3–8.7%) P&lt;.0001</td>
<td>2/19 10.5%</td>
</tr>
<tr>
<td>Cephalexin (1)</td>
<td>25/365 6.8%</td>
<td>160/14,392 1.1%</td>
<td>+5.9% (+4.6–6.9%) P&lt;.0001</td>
<td>4/79 5.1%</td>
</tr>
<tr>
<td>Cefadroxil (1)</td>
<td>8/21 38%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin (1)</td>
<td>3/74 4.1%</td>
<td>8/1369 0.6%</td>
<td>+3.5% (+1.4–5.5%) P=.008</td>
<td>0/41 0.0%</td>
</tr>
<tr>
<td>Cephamandole (2)</td>
<td>13/89 14.6%</td>
<td>83/1303 6.4%</td>
<td>8.2% (2.7–13.7%) P=.006</td>
<td>2/40 5.0%</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>83/989 (8.39%)</td>
<td>456/32,845 (1.39%)</td>
<td>+7.0% (6.1–7.8%) P&lt;.0001</td>
<td>16/171 (9.36%)</td>
</tr>
<tr>
<td>CEPHALOSPORINS THAT DO NOT SIGNIFICANTLY INCREASE ALLERGIC REACTIONS IN PENICILLIN-ALLERGIC PATIENTS</td>
<td>Penicillin/Amoxicillin Allergy by History*</td>
<td>RR Difference (95% CI)</td>
<td>Penicillin/Amoxicillin Allergy by History and Skin Testing†</td>
<td>RR Difference (95% CI)</td>
</tr>
<tr>
<td><strong>Drug (Generation)</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Cefprozil (2)</td>
<td>3/157 1.9%</td>
<td>23/1340 1.7%</td>
<td>+0.3% (-1.9–2.4%) P=.887</td>
<td>1/47 2.1%</td>
</tr>
<tr>
<td>Cefuroxime (2)</td>
<td>8/428 1.9%</td>
<td>89/5410 1.7%</td>
<td>-0.3% (-0.7–1.5%) P=.784</td>
<td>2/283 1.6%</td>
</tr>
<tr>
<td>Ceftazidime (3)</td>
<td>3/538 0.6%</td>
<td>57/3427 1.7%</td>
<td>-1.1% (-2.2–0.02%) P=.083</td>
<td>0/30 0.0%</td>
</tr>
<tr>
<td>Cefpodoxime (3)</td>
<td>2/234 0.9%</td>
<td>20/2025 0.9%</td>
<td>0% (-1.3–1.3%) P=.715</td>
<td>2/188 1.1%</td>
</tr>
<tr>
<td>Ceftriaxone (3)</td>
<td>0/142 0.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unspecified cephalosporins‡</strong></td>
<td>1/100 (1.0%)</td>
<td>6/310 1.9%</td>
<td>-0.9% (-3.8–1.9%) P=.872</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>16/1446 (1.11%)</td>
<td>189/12202 (1.55%)</td>
<td>-0.44% (-1.1–0.2%) P=.236</td>
<td>6/790 (0.76%)</td>
</tr>
<tr>
<td><strong>Grand total</strong></td>
<td>99/2435 (4.07%)</td>
<td>645/34047 (1.89%)</td>
<td>+2.18% (1.6–2.8%) P&lt;.0001</td>
<td>22/961 (2.29%)</td>
</tr>
</tbody>
</table>

* The data in these 2 columns are a tabulation (from various articles) of patients who reported a positive or negative history of allergy to penicillin or amoxicillin (denominator) and then received the specified cephalosporin and had an allergic reaction to that cephalosporin (numerator).

† The data in these 2 columns are a tabulation (from various articles) of patients who reported a positive history of penicillin or amoxicillin allergy and were skin tested and positive by skin test to penicillin or amoxicillin (denominator) and then received the specified cephalosporin and had an allergic reaction (numerator) or were history negative and skin test negative (denominator) and had an allergic reaction to the specified cephalosporin (numerator).

19 well-characterized patients allergic to penicillin who were studied for their sensitivity to the cephalosporins, cephaloridine and cefamandole (which have identical or very similar side chains to penicillin and were therefore potentially cross-reactive) only 2 (10.5%) reacted to cefamandole, while the other 17 patients tolerated both agents. In another study of clinical cross-reactivity between...
amoxicillin and cefadroxil in patients allergic to amoxicillin, only 12% had an immediate allergic reaction to cefadroxil, despite the 2 drugs sharing an identical side chain.33 In a third study, allergenic cross-reactivity with cefadroxil and cefamandole was studied among 21 patients selectively allergic to amoxicillin; 8 (38%) had a positive response to cefadroxil (same side chain) and none to cefamandole (different side chain).32

■ Discussion
Sensible approach to penicillin-allergic patients
Question patients who report penicillin allergy. In many cases, penicillin may not actually have been taken, or patients may have had non-immunologic adverse events such as vomiting, diarrhea, or nonspecific rash; toxic effects; or contemporaneous side effects inappropriately attributed to the drug. These patients can receive penicillin, amoxicillin, or the cephalosporins.

Without the ability to detect patients with IgE antibody to penicillin prospectively or to distinguish true IgE immunologic reactions from idiopathic reactions in patients receiving cephalosporins, it is impossible to definitely claim that increased immune or IgE-mediated reactions to cephalosporins occur in true penicillin-allergic (IgE) patients.

When a cephalosporin is/is not safe for a penicillin-allergic patient. Only IgE-mediated reactions—such as anaphylaxis or hypotension, laryngeal edema, wheezing, angioedema, or urticaria—are likely to become more severe with time. Therefore, with a patient who has had a true IgE-mediated reaction to a penicillin, avoid using cephalosporins with a similar side chain. You may, however, give cephalosporins that have different side chains. Cephalosporins may also be used for patients who have had non-IgE-mediated adverse reactions (“non-type I allergy”) to a penicillin, such as a non-pruritic, non-urticarial morbilliform or maculopapular rash.

How prevalent is primary cephalosporin allergy? Even if the patient is not allergic to penicillin, cephalosporins can cause allergic or immune-mediated reactions in approximately 1% to 3% of patients. A patient who had an allergic reaction to a specific cephalosporin probably should not receive that cephalosporin again. The risk of a reaction with a different cephalosporin is very low to nonexistent if the side chains of the 2 drugs are dissimilar.

Bottom line. Penicillin-allergic patients have indeed shown an increased incidence of allergic reactions to cephalothin, cephaloridine, cephalaxin, cefadroxil, cefazolin, and cefamandole. However, the risk has been overestimated because most studies reporting this cross-reactivity were flawed (because penicillins were contaminated with cephalosporins) and then failed to account for the fact that penicillin-allergic patients have a 3-fold increased risk of allergic reactions even to nonrelated drugs.11

For patients truly allergic to penicillin, the risk of a reaction from a cephalosporin with side chains that differ from penicillin/amoxicillin (cefuroxime, cefpodoxime, cefdinir, and ceftriaxone, as endorsed by the AAFP) is so low that use is justified and medico-legally defensible by the currently available evidence.

REFERENCES
is quite low side chain with a different reaction from truly allergic. Even for patients who tolerated benzylpenicillin, aztreonam, and cephalosporin antibiotics to patients with a history of penicillin allergy: reliability of examination assessed by skin testing and oral challenge. Pediatrics 1999; 104:367.


