

Allergic Cross-reactivity Among Beta-lactam Antibiotics

—Continue to the section on “Treatment Recommendations” for
a list of questions to ask prior to treating a penicillin-allergic patient—

Background

Beta-lactam antibiotics are first-line therapies for many types of infections. Historically, some patients allergic to penicillins were also considered to be allergic to cephalosporins. Historical data suggested that 8% to 10% of patients allergic to penicillins were also allergic to cephalosporins.^{1,2} Unfortunately, many of these patients were and still are prescribed a second-line therapy that can be less effective, more expensive, or more toxic and also have a broader-spectrum of activity. Recent data suggest that the true incidence of allergic cross-reactivity between the penicillins and cephalosporins is much lower than that originally reported and is believed to be less than 1%.³

Types of Penicillin Allergies

Approximately 10% of the population will report having a penicillin allergy. Several types of penicillin allergic reactions are described in the medical literature.^{4,5} One method of classifying penicillin allergic reactions is as immediate/accelerated or type I reactions; late or type II, III, and IV reactions; and other or idiopathic reactions. Immediate/accelerated reactions typically occur within one hour (immediate) or one to 72 hours (accelerated) of penicillin administration and are mediated by penicillin-specific IgE antibodies. Clinical signs of an immediate reaction include anaphylaxis, decreased blood pressure, swelling of the larynx, wheezing, angioedema, and hives or an itchy rash. Late reactions tend to occur more than 72 hours after penicillin exposure and, as mentioned previously, are sometimes referred to as type II, III, and IV reactions. Type II reactions are mediated by IgG antibodies and complement; clinical signs include increased red blood cell and

platelet clearance by the lymphoreticular system. Type III reactions are mediated by IgG and IgM immune complexes; clinical signs include serum sickness and tissue injury. Type IV reactions are mediated through an unknown mechanism; a clinical sign is contact dermatitis. Finally, idiopathic reactions also tend to occur after 72 hours of penicillin exposure. Idiopathic reactions are also mediated through unknown mechanisms; clinical signs include a maculopapular or morbilliform rash which can progress to Stevens-Johnson syndrome.

An example of an idiopathic reaction is the rash that often occurs following antibiotic administration with drugs such as ampicillin and amoxicillin in patients with an Epstein-Barr virus (EBV) infection. Infectious mononucleosis is caused by EBV. The risk appears to be highest in patients who receive ampicillin.⁶ This rash typically occurs seven to ten days after beginning antibiotic therapy and is described as a red, itchy maculopapular rash, involving primarily the upper extremities and trunk, although the palms, soles, and oral mucosa may also be involved. The rash can be accompanied by fever, swelling of the lips and eyelids, diarrhea, and joint pain. Patients who develop this rash can be safely administered penicillins in the future.⁶

Diagnosis of a Penicillin Allergy

Only immediate or accelerated penicillin allergies can be diagnosed using penicillin skin testing. Results from studies suggest that 10% to 20% of patients who report a penicillin allergy will have a positive penicillin skin test.⁵ However, patients with a negative skin test can still be allergic to penicillin; in most cases, the allergy is not mediated by IgE antibodies and

More . . .

therefore, is a late or idiopathic type reaction. What this means is that patients with a negative penicillin skin test will rarely have an anaphylactic reaction or IgE-mediated reaction to penicillin. However, these patients could still have a late or idiosyncratic reaction.

Skin testing, usually performed by an allergist, typically involves an epidermal or intracutaneous prick test. Anaphylaxis can occur with skin testing. Therefore, physicians performing penicillin skin testing must be prepared to quickly treat patients who have an anaphylactic reaction. If the penicillin skin test is negative, an intradermal skin test is done. In some cases, the epidermal or intracutaneous prick test may be omitted. Current recommendations for penicillin skin testing are to administer both the major determinant of penicillin allergy, benzylpenicilloyl-polylysine (*PrePen*) and the minor determinant.⁴ Unfortunately, minor determinant skin testing is not standardized and can vary from place to place. Recommendations are for the minor determinant mixture to contain penicillate, penilloic acid, and penicillin G. However in most cases, diluted aqueous penicillin G is administered as the minor determinant. The risk of a false-negative penicillin skin test is increased if only penicillin G and not a minor determinant mixture is administered.

Unfortunately, there is currently no major determinant or standardized minor determinant mixture commercially available in the United States. The last batch of *PrePen* expired in August of 2004 and a minor determinant mixture was never approved by the Food and Drug Administration (FDA). The American Academy of Allergy, Asthma, and Immunology (AAAA&I) is working with the FDA to get both the major and minor determinants available in the United States. The plan is to sell both the major and minor determinants together as a single, penicillin allergy skin test.⁷

Other diagnostic tests that can be used to determine immediate type penicillin allergies include measuring penicillin-specific IgE levels by radioallergosorbent testing (RAST) or fluorescent enzyme-linked immunosorbent assay (ELISA). However, both of these methods only determine the presence of antibodies to the major determinant and not the minor determinant. Patch testing can also be used; this is not commonly done in the United States.

Beta-lactam Cross-reactivity

Studies performed in the 1960's and 1970's suggested that the rate of cross-reactivity between penicillins and cephalosporins was as high as 50%.⁸ However, early cephalosporins may have been contaminated with trace amounts of penicillins. In addition, patients with, compared with those without, a penicillin allergy are three-times more likely to have an adverse effect to an unrelated drug.³ Current data suggests that the rate of cross-reactivity between penicillins and cephalosporins is probably less than 1% and determined by similarity in side chains and not the beta-lactam structure.³ In general, the rate of allergic cross-reactivity is highest between penicillins and first-generation cephalosporins. Beta-lactams with similar side chains at the 7-position of the beta-lactam ring include the following:

- Penicillin G (*Wycillin*, *Pen-Tids*), cefoxitin (*Mefoxin*)
- Amoxicillin (*Amoxil*), ampicillin (*Omnipen*), cefaclor (*Ceclor*), cephalixin (*Keflex*), cephadrine (*Velosef*), cefprozil (*Cefzil*), cefadroxil (*Duricef*)
- Cefotaxime (*Claforan*), ceftizoxime (*Cefizox*), ceftriaxone (*Rocephin*), cefpodoxime (*Vantin*), cefepime (*Maxipime*)

Beta-lactams with similar side chains at the 3-position of the beta-lactam ring include the following:

- Cefdinir (*Omnicef*), cefixime (*Suprax*)
- Cephadrine, cefadroxil, cephalixin
- Cefoperazone (*Cefobid*), cefotetan (*Cefotan*)
- Cephapirin, cefotaxime
- Cefuroxime (*Zinacef*, *Kefurox*), cefoxitin
- Ceftibuten (*Cedax*), ceftizoxime (*Cefizox*)

Cross-reactivity between penicillins and carbapenems (e.g., imipenem [*Primaxin*], meropenem [*Merrem*], ertapenem [*Invanz*]) has been reported. In most cases, these should not be administered to patients with a type I penicillin allergy.^{9,10,11} In contrast, cross-reactivity between penicillins and aztreonam (*Azactam*), a monobactam, is believed to be rare. However, aztreonam and ceftazidime (*Fortaz*) have the same side chain and therefore the potential for cross-reactivity exists.⁹

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Treatment Recommendations

Prior to treating a patient who reports a penicillin allergy, a thorough history of the patient's allergy should be obtained. Examples of questions the patient should be asked include the following:⁵

- How old were you when the reaction occurred?
- Can you describe the reaction?
- When did the reaction occur? After the first dose? After the tenth dose?
- How was the penicillin administered? Orally? Intravenously?
- Were you taking any other medications at the same time?
- When the penicillin was stopped, what happened?
- Have you since taken a penicillin or cephalosporin?

In general, patients who report symptoms consistent with an immediate or accelerated reaction (Type I) to penicillin should not receive any penicillin, unless they undergo desensitization. An example of a penicillin desensitization protocol is available in the May 10, 2002 *Morbidity and Mortality Weekly Report* found at

<http://www.cdc.gov/mmwr/PDF/rr/rr5106.pdf>. Historically, data suggested that patients who reported an immediate or accelerated reaction to a penicillin should not receive a cephalosporin. However, some experts suggest that cephalosporins, specifically some second, third, and fourth generation cephalosporins, may be able to be administered to patients with an immediate or accelerated reaction to a penicillin.³ More research is needed but it appears that side chain similarity may be important in allergic cross-reactivity between the penicillins and cephalosporins. For example, patients with an immediate or accelerated reaction to penicillin G should not receive cefoxitin because it has a similar side chain. Likewise, patients with an immediate or accelerated reaction to amoxicillin or ampicillin should not receive cephalixin, cephadrine, cefadroxil, cefaclor, or cefprozil because these agents have similar side chains. Imipenem, meropenem, and ertapenem should also be avoided in patients who report an immediate or accelerated type reaction with penicillin administration.

The decision to administer a cephalosporin to a patient who reports an immediate or accelerated penicillin allergy should be done cautiously until additional data are available. In some cases, it may be preferable to use an antibiotic from a different drug class.

Treatment recommendations for patients reporting a cephalosporin allergy may also be able to be based on side-chain similarities. Patients with an immediate or accelerated allergy to a cephalosporin should not receive a cephalosporin with a similar side chain. However, some experts suggest that a cephalosporin with different side chains may be able to be used safely.³ Additionally, patients who report an immediate or accelerated allergy to ceftazidime should not receive aztreonam.

Conclusions

The incidence of allergic cross-reactivity among beta-lactam antibiotics is controversial but probably less than historically thought. Although guidelines published in the year 2000 suggest performing penicillin skin testing on all patients reporting a penicillin allergy prior to administering a cephalosporin,⁴ more recent pediatric guidelines suggest that this is not necessary [Evidence Level B; Lower-quality RCT].³ The patient's allergic history should be carefully obtained and a decision on which antibiotic class to administer be based on this information. Preliminary data suggest that patients with an immediate or accelerated penicillin allergy may be able to safely receive a cephalosporin, particularly second, third, and fourth generation cephalosporins. However, additional research is needed before this can be routinely recommended.

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A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.



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