Practical Aspects of Choosing an Antibiotic for Patients with a Reported Allergy to an Antibiotic

Joan L. Robinson, Tahir Hameed, and Stuart Carr
Department of Pediatrics, University of Alberta, Edmonton, Canada

Physicians often must select antibiotics for patients who are reported to have an antibiotic allergy. For penicillins, the sensitivity of penicillin skin testing for predicting serious allergic reactions is excellent. For other β-lactam antibiotics, penicillin skin testing is useful for excluding the possibility of sensitivity to the β-lactam ring. For other antibiotics, the patient history remains the most useful tool for determining whether a serious reaction is likely to occur with further drug exposure. The cross-reactivity between penicillins and second- or third-generation cephalosporins (excluding cefamandole) is probably no higher than is the cross-reactivity between penicillins and other classes of antibiotics. When a patient has a suspected immunoglobulin E–mediated antibiotic allergy, desensitization therapy should be considered, if the efficacy of alternate antibiotics is in doubt. For the treatment of serious infections, it is usually possible to safely administer the antibiotic of choice despite a history of possible antibiotic allergy.

A common problem in clinical practice is determining which antibiotics to use to treat infection in a patient who has been labeled as being allergic to an antibiotic. In many cases, such patients are prescribed antibiotics that are less effective or more toxic, have a broader spectrum, or are more expensive than the drug of choice for their condition.

CLASSIFICATION OF ANTIBIOTIC ALLERGY

A reaction to a drug is considered an allergic reaction if it involves an immunologic reaction to a drug. Mechanisms of antibiotic allergy are as follows:

1. IgE mediation. This can cause any combination of diffuse erythema, pruritus, urticaria, angioedema, hyperperistalsis, bronchospasm, hypotension, and/or arrhythmias [1]. Symptoms usually start ≤15 min after drug administration; however, in a study of penicillin allergy, 5% of fatal reactions started >1 h after drug administration [2].

2. Antibody mediation. Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis can result, but only neutropenia is commonly attributed to antibiotics. Neutropenia has been stated to occur in 5%–15% of patients who receive high-dose cephalosporin therapy for >10 days [3].

3. Immune complex mediation. Serum sickness is a rare manifestation of antibiotic allergy. The “serum sickness–like reaction” that can be caused by cefaclor is thought to be the result of a direct cytotoxic effect of the drug that is related to an inherited aberrancy in drug metabolism, rather than an allergic reaction [4].

4. Delayed hypersensitivity reaction. There is increasing evidence that many delayed nonurticarial rashes (especially those caused by aminopenicillins) are the result of delayed hypersensitivity reactions [5].

5. Unknown mechanism. Many reactions to an-
Antibiotics meet the criteria for drug allergy, but their immunopathologic mechanism is not clear. Examples include the following:

- Erythema multiforme minor, Stevens Johnson syndrome, and toxic epidermal necrolysis.
- Fixed drug eruption. This can present as erythematous or violaceous plaques, localized blisters, bruises [6], or a generalized bullous rash. After re-exposure to the drug, the rash recurs in the same location (often on the genitals or face).
- Pulmonary infiltrates. Nitrofurantoin can cause pulmonary hypersensitivity that resolves when the drug is withdrawn [7].
- Autoimmune disease. Antibiotics have been implicated in vasculitis [8] and lupus [9], but it is not clear that immune mechanisms are involved.
- Drug fever. Although fever due to antibiotics can occur because of pyrogens induced by the drug (such as by amphotericin B) or dying organisms (such as those associated with the Jarisch-Herxheimer reaction), the most common cause of drug fever is thought to be immunologic. This entity has not been well characterized in the literature, but one study that assessed patients who had a discharge diagnosis of “drug fever” found that only 22% of patients had eosinophilia and 18% had a rash [10]. The only way to prove this diagnosis is to rechallenge the patient with the drug in question.
- Drug-induced hypersensitivity syndrome. Severe multiple-organ involvement with fever, rash, lymphadenopathy, and hematologic abnormalities occurs most frequently in patients receiving antiepileptic drugs, but this syndrome has also been attributed to use of antibiotics [11].

**DIFFERENTIAL DIAGNOSIS OF ALLERGIC REACTIONS TO ANTIBIOTICS**

Multiple studies of children and adult patients with a history of allergy to a variety of antibiotics have found that a minority of patients had convincing evidence of allergy, as indicated by the results of skin testing and oral challenge [12–14]. Some of these patients may have lost their sensitivity to a drug over time [15]. Many patients have experienced predictable adverse reactions (i.e., drug-related side effects) rather than a true allergic reaction. Often, the suspected allergy event was due to an infectious agent rather than a drug. One complicating factor is that some infections seem to create an inflammatory milieu that increases the chance that a drug will activate T cells and initiate an immunologic reaction in a patient who would otherwise not react to that drug. An example of this is the rash that commonly occurs when amoxicillin is given to patients with Epstein-Barr virus infection [16].

Pseudoallergic or anaphylactoid reactions have the same symptoms as anaphylactic reactions, but they seem to result from direct release of mediators from mast cells and basophils; there is no evidence of production of IgE. An example would be the “red man syndrome” caused by rapid infusion of vancomycin, which, in one report, occurred in 35% of patients when vancomycin was infused over 6 min [17]. The resulting symptoms mimic a true allergic reaction, but the risk of recurrence is low, provided that the drug is infused more slowly the next time it is used.

The current purification techniques make it less likely than in the past that contaminants in antibiotics will be the source of an allergy. When studied on their own, dyes have not been shown to trigger allergic reactions in individuals reported to be sensitive to them [18].

**DIAGNOSIS OF ANTIBIOTIC ALLERGY**

The patient history is often the only tool available for making the diagnosis of antibiotic allergy. The main goal is to establish whether the patient had an IgE-mediated reaction to an antibiotic, which could manifest as urticaria, pruritus, angioedema, hyperperistalsis, bronchospasm, hypotension, and/or arrhythmia.

Patients generally develop allergic reactions when reexposed to an antibiotic or during the second week of a course of treatment with an antibiotic they have never received in the past. It is unusual for a patient to have an allergic reaction to an antibiotic they have been receiving continuously for months. Atopic individuals do not have a higher incidence of penicillin allergy, but they possibly have a higher risk of experiencing severe penicillin allergy [14].

Parents are often concerned that antibiotic allergy will be inherited. A study showed a high incidence of reported antibiotic allergies in children whose parents had a history of antibiotic allergy [19], but no attempt was made to verify these allergies. Often children appear to be allergic to different drugs than are their parents [19].

The presence of eosinophilia may support a diagnosis of drug allergy if there are compatible signs and symptoms, but the positive predictive value of eosinophilia is unknown. Treatment with an antibiotic does not need to be withdrawn if it is causing eosinophilia but the patient shows no other evidence of hypersensitivity [3].

Diagnostic tests for antibiotic allergy are limited and are only standardized for penicillin allergy. The literature on antibiotic allergy is dominated by information on penicillin allergy, which is probably because 5%–20% of patients consider themselves to be allergic to penicillin [20]. Penicillin skin testing usually
involves performance of an epidermal or intracutaneous prick test (this step of the test is often omitted if the patient’s history is not suggestive of anaphylaxis, because the chance of having a positive test result is quite low, but the official recommendation is to include this step for all patients). This will be followed by an intradermal skin test if the prick test result is negative. Skin testing will only be sensitive if antigens corresponding to all immunogenic metabolites of the antibiotic are used. For β-lactams other than penicillin and for non-β-lactams, the immunogenic metabolites have not been well studied, so the false-negative rate for skin testing has not been determined. Despite this fact, it is common for allergists to use skin testing for cephalosporins [21]. Traditional skin testing is only predictive of IgE-mediated drug reactions, so a negative result does not decrease the pretest probability that the drug will cause allergic drug reactions that are not mediated by IgE.

In performing skin testing for penicillin allergy, the goal is to inject all metabolites that could possibly result in an allergic reaction. The major determinant of allergy (benzyl-penicilloyl-polylysine) is the penicilloyl derivative that forms when the β-lactam ring is opened; this metabolite is available commercially (Pre-Pen; Schwarz-Pharma). To detect the ~16% of people with IgE-mediated penicillin allergy who react to other penicillin metabolites, skin testing must also be performed with minor determinants [22]. The problem is that there are no commercially available minor determinant mixtures available in North America (although they are available in Europe). This is because of the high cost of manufacturing minor determinant mixtures for a limited market. Therefore, the mixtures that are used for skin testing in different health care centers are not uniform. On the basis of experience, rather than studies, it is recommended that skin testing should not be performed immediately after anaphylaxis occurs, because there may be a period of anergy after mast cell degranulation [23].

For patients who have a history of penicillin allergy but who have a negative skin test result when major and minor determinants are used, studies show that the chance of having any reaction to a subsequent dose of penicillin ranges up to 9.1%, with an average incidence of ~3% [14]. However, only ~1% of such patients develop a reaction that appears to be IgE mediated, and the only serious reaction ever described was in an anesthetized patient who had also received other drugs [22].

An alternative to skin testing for penicillin allergy is to measure penicillin-specific IgE levels (formerly done by means of radioallergosorbent testing [RAST], but now usually performed by means of fluorescent ELISA). This type of testing is less sensitive than skin testing, because only antibodies to the major determinant are detected [24], and the negative predictive value is only ~50%. This testing is available but not standardized for other antibiotics.

Patch testing (which is done by applying antibiotic topically on a pad under hypoallergenic occlusive tape and looking for a local reaction after 48–72 h) is not widely accepted by allergists in North America. However, there is some evidence that it can be predictive of non-IgE-mediated reactions to β-lactam antibiotics [5] and that combining it with intradermal testing (which is interpreted at 48 h) may be useful in predicting delayed nonurticarial reactions to aminopenicillins.

**CROSS-REACTIVITY OF β-LACTAM ANTIBIOTICS**

Penicillins have a β-lactam ring attached to a thiazolidine ring with 1 side chain, and cephalosporins have a β-lactam ring attached to a dihydrothiazine ring with 2 side chains. Carbapenems have a β-lactam ring attached to a modified thiazolidine ring with 2 side chains, and monobactams have a β-lactam ring with 1 side chain.

If a patient has an allergy to penicillin and it is IgE mediated, the patient is likely to have a similar reaction to ampicillin, amoxicillin, cloxacillin, and piperacillin, because these agents all share the same β-lactam ring and so can form the same penicilloyl derivative. However, sometimes the patient has had an IgE-mediated reaction to the side chain of penicillin and will tolerate the other penicillins [25]. We are not aware of any case reports of serious allergic reactions to other penicillins in patients with negative penicillin skin test results. However, 8% of patients with a history of allergy to amoxicillin and a negative penicillin skin test result had nonserious IgE-mediated reactions when challenged with amoxicillin [26].

It is suspected that non-IgE-mediated reactions to penicillins are often related to the side chain [5] and may be one source of delayed nonurticarial rashes, which occur in 5%–9.5% of patients who are given amoxicillin but in only 2.7% of patients given other β-lactams [14]. Drug polymers are often present in ampicillin and amoxicillin and may be another source of delayed rashes, which are more common among patients receiving these drugs than in patients receiving other penicillins [20].

Soon after cephalosporins were introduced, there were reports of cephalosporin anaphylaxis in patients who also had experienced penicillin anaphylaxis. During the initial clinical trials with first-generation cephalosporins and cefamandole, 8.1% of patients with a history of allergy to penicillin had a possible allergy to a cephalosporin, versus 4.5% of patients with no such history [27]. Therefore, the standard teaching is that patients who have had possible penicillin anaphylaxis should not be treated with cephalosporins. However, it is not clear which reactions qualify as anaphylaxis. This dogma has been questioned [28, 29]; there is increasing evidence that, in most allergic reactions to cephalosporins, it is the side chain rather than the β-lactam ring that is the antigen. Older cephalosporins
Figure 1. Approach for patients with a suspected allergic reaction to a penicillin. *It is often difficult to obtain an accurate history of a rash. If there is any doubt, assume it could have been urticarial.* AVOID USE OF FIRST-GENERATION CEPHALOSPORINS AND CEFAMANDOLE. IF THE SUSPECTED DRUG REACTION WAS STEVENS JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS, SKIN TESTING SHOULD NOT BE PERFORMED, AND USE OF PENICILLINS SHOULD BE AVOIDED. SKIN TESTS WITH AMOXICILLIN ARE SOMETIMES PERFORMED IF THE REACTION WAS TO AMOXICILLIN, BUT THE INCIDENCE OF FALSE-NEGATIVE SKIN TEST RESULTS IS NOT KNOWN. IF THE REACTION WAS SERIOUS, CHALLENGE IN A SUPERVISED SETTING, AND USE A GRADED CHALLENGE: START WITH A SMALL DOSE IN AN ORALLY ADMINISTERED FORMULATION, IF THAT IS PRACTICAL, THEN INCREASE THE DOSE, THEN TRY AN INTRAVENOUS FORMULATION, IF IT IS REQUIRED [26]. THIS IS MOST RELEVANT IF THE REACTION WAS TO A PENICILLIN OTHER THAN NATURAL PENICILLIN (SUCH AS CLOXACILLIN OR AMPICILLIN), IN CASE THE REACTION WAS TO A SIDE CHAIN AND CANNOT BE DETECTED BY A PENICILLIN SKIN TEST. AVOID USE OF FIRST-GENERATION CEPHALOSPORINS AND CEFAMANDOLE.

**TREATMENT OF PATIENTS WITH A POSSIBLE OR PROBABLE ANTIBIOTIC ALLERGY**

Figures 1–3 outline steps that should be taken if a patient is thought to have had a reaction to an antibiotic. If a patient has weak evidence of an antibiotic allergy and is likely to require that antibiotic in the future, rechallenge may be appropriate. This rechallenge should be performed in a setting where anaphylaxis can be treated, if the physician thinks the previous reaction could have been 
IgE mediated or if the patient remains anxious about taking the drug. Rechallenge can be performed when the patient is assessed, or it can be delayed until the patient requires the antibiotic.

For patients with a possible IgE-mediated reaction to an antibiotic that they require, desensitization is a safer option.
Figure 2. Approach for patients with a suspected allergic reaction to a cephalosporin. It is often difficult to obtain an accurate history of a rash. If there is any doubt, assume it could have been urticarial. Use a cephalosporin of a different generation than the one associated with the reaction. If the suspected drug reaction was Stevens Johnson syndrome or toxic epidermal necrolysis, skin testing should not be performed and use of cephalosporins should be avoided. The negative penicillin skin test result means that, if the previous reaction was IgE mediated, the antigen was likely a cephalosporin side chain rather than the β-lactam ring. Therefore, use a cephalosporin of a different generation than the one that was associated with the reaction. If the reaction was serious, challenge in a supervised setting, and use orally administered formulation first, if possible [26].

than rechallenge, but desensitization needs to be repeated each time they require the antibiotic and after any missed doses. If an antibiotic is clearly the drug of choice and there is a convincing history of allergy to that antibiotic or a positive skin test result, desensitization should be considered. Desensitization involves administering tiny quantities of the drug (initially by mouth, if possible) and increasing the dose approximately every 15 min until the patient has received a therapeutic dose of the drug. Desensitization is thought to be effective either because IgE is neutralized by the increasing dose of antigen or because the mast cells are slowly degranulated [35]. Urticarial rashes occur in approximately one-third of patients, but anaphylaxis is rare [36]. The traditional teaching was that desensitization could not alter the incidence of reactions that are not IgE mediated. However, it seems to work sometimes for sulfonamide reactions that are not thought to be IgE mediated [37].

MULTIPLE ANTIBIOTIC SENSITIVITY SYNDROME

Patients are sometimes thought to be allergic to multiple antibiotics because they were given multiple antibiotics during the course of a single viral illness and developed various virus-induced rashes. However, one study found that 21% of patients with a history of a probable IgE-mediated reaction to penicillin also had a history of a probable IgE-mediated reaction to another class of antibiotics [38]. Another study prospectively looked at the incidence of suspected allergic reactions to antibiotics prescribed in the hospital and found the incidence to be 13% in patients who gave a history of allergy to other antibiotics, versus 1% in a control group [39]. However, these reactions to multiple antibiotics may not be IgE mediated (or even immunologic): one study found that the incidence of reactions to multiple antibiotics was no higher among patients with positive penicillin skin test results than among patients with negative penicillin skin test results or among patients with allergic rhinitis [34].

A patient with multiple antibiotic sensitivity syndrome often can be treated without antibiotics, because many common conditions for which antibiotics are prescribed are self-limiting. If the patient requires antibiotics, it is important to remember that it is rare to develop a serious allergic reaction to non-β-lactam antibiotics. Nonurticarial rashes can be treated with antihistamines. Desensitization should be considered if the patient is thought to have had an IgE-mediated reaction to an antibiotic that they absolutely require.

Figure 3. Approach for patients with a suspected allergic reaction to a non-β-lactam antibiotic. It is often difficult to obtain an accurate history of a rash. If there is any doubt, assume it could have been urticarial. Desensitization is successful for >50% of HIV-infected patients who have trimethoprim-sulfamethoxazole reactions [34]. If the reaction was serious, challenge in a supervised setting, and use orally administered formulations first, if possible. If the suspected drug reaction was Stevens Johnson syndrome or toxic epidermal necrolysis, the drug should be avoided.
NONDRUG SOURCES OF ANTIBIOTIC ALLERGY

Residual penicillin in meat products, milk, and the air of hospitals was suggested to be a cause of antibiotic allergy in the past [2]. Government regulations now prohibit the sale of meat with residual antibiotics, but producers may not always comply with the regulations.

SUMMARY

In most instances, a patient will tolerate the antibiotic of choice for treatment of their infection despite a history of antibiotic allergy. If the suspected allergy is to a penicillin, a negative penicillin skin test result makes a subsequent serious reaction unlikely. The majority of patients with proven penicillin allergy will tolerate newer cephalosporins. For the small percentage of patients with a genuine serious allergic reaction, desensitization is usually a successful strategy.

References