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

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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-
bacteriologic mechanism is not clear. Examples include the

a. Erythema multiforme minor, Stevens Johnson
syndrome, and toxic epidermal necrolysis.

b. Fixed drug eruption. This can present as ery-
thematosus or violaceous plaques, localized blisters,
bruises [6], or a generalized bullous rash. After re-
exposure to the drug, the rash recurs in the same loc-
tion (often on the genitals or face).

c. Pulmonary infiltrates. Nitrofurantoin can cause
pulmonary hypersensitivity that resolves when the drug
is withdrawn [7].

d. Autoimmune disease. Antibiotics have been im-
plicated in vasculitis [8] and lupus [9], but it is not
clear that immune mechanisms are involved.

e. 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 character-
ized 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.

f. Drug-induced hypersensitivity syndrome. Severe
multiple-organ involvement with fever, rash, lymphad-
enopathy, and hematologic abnormalities occurs most
frequently in patients receiving antiepileptic drugs, but
this syndrome has also been attributed to use of anti-

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 al-
lergic 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 oth-
ewise 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 van-
comycin, 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 re-
currence 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 anti-
biotic, which could manifest as urticaria, pruritus, angio-
edema, 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 anti-
biotic allergies in children whose parents had a history of an-
tibiotic 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 hy-
persensitivity [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-polysine) 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 thiadizidine 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 piperaclincillin, 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...
(cephalothin, cephaloridine, and cefamandole) have a side chain similar to that of penicillin and were often contaminated with penicillin. These 2 facts may account for some of the early reports of cross-reactivity between penicillins and cephalosporins. There is evidence that, among patients with a history of penicillin allergy, the rate of allergic reaction to any other antibiotic is 3 times the rate among control subjects [28]. In the general population, the risk of serious allergic reactions to cephalosporins appears to be <0.02% [26]; the risk is lowest for third-generation cephalosporins (possibly because free drug competes with bound drug for antibodies to the side chain) [20]. Therefore, even if patients with a history of penicillin allergy have twice as great a risk of having a serious reaction to cephalosporins that do control subjects, this risk may be lower than the risk that they will have a serious reaction to any alternative antibiotic. In 4 studies, a total of 101 patients with positive penicillin skin test results were given cephalosporins, and only 1 patient had an immediate reaction [29]. Furthermore, the results of penicillin skin testing do not predict cephalosporin allergy—which again suggests that there is limited cross-reactivity [29].

One study showed that patients who had a history of probable IgE-mediated reactions to cephalosporins (mainly third-generation cephalosporins) had a 13% chance of having a skin test or RAST for penicillin with a positive result [30]. However, the patients were not challenged with penicillin, so it is not clear how many of them would have tolerated it. A previous study by the same investigators found a 50% incidence of possible sensitivity to penicillin among patients who had a reaction to first-generation cephalosporins [31], a finding that suggests that there is cross-reactivity with penicillin is less common with newer cephalosporins.

On the basis of the structure of the drugs, cross-reactivity between penicillin and carbapenems was expected. A retrospective study of 63 febrile neutropenic bone marrow transplant recipients who had a history of penicillin allergy and received imipenem–cilastatin revealed 1 definite, 3 probable, and 2 possible allergic reactions [32]. To our knowledge, there are no published data on allergy to meropenem in patients who are allergic to imipenem or to penicillins. The cross-reactivity rate between cephalosporins and carbapenems is unknown but is probably quite low, because most reactions to cephalosporins involve side chains rather than the β-lactam ring.

Allergic reactions to the monobactam aztreonam are thought to involve the side chain, so cross-reactivity with other β-lactams should be rare; the exception is ceftazidime, which shares the same side chain. However, there is one report of a patient with an allergy to aztreonam who tolerated ceftazidime [33].

**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 an orally administered formulation first, if possible [26].

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 150% 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.

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.
NONDUGR 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 to a penicillin extremely unlikely. The majority of patients with proven penicillin allergy will tolerate newer cephalosporins. For the small percentage of patients with a genuine serious allergy to a penicillin, extremely unlikely. The majority of patients with proven penicillin allergy will tolerate newer cephalosporins. For the small percentage of patients with a genuine serious allergy reaction, desensitization is usually a successful strategy.

References