

Hypersensitivity Reactions to Beta-Lactam Antibiotics

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Abstract

Clinicians commonly encounter patients with a history of allergy to penicillin and other beta-lactam antibiotics, since about 10% of the population reports such an allergy. At the same time, it is known that about 90% of these patients are not truly allergic and could safely receive beta-lactam antibiotics. Instead, these patients are treated unnecessarily with alternate broad-spectrum antibiotics, which increases costs and contributes to the development and spread of multiple drug-resistant bacteria.

In the case of penicillin, relevant allergenic determinants that elicit immune responses are known. Hence, validated diagnostic skin testing to detect the presence of drug-specific IgE antibodies is available. For non-penicillin beta-lactams, the immunogenic determinants that are produced by degradation are unknown, and diagnostic skin testing is of more limited value. Ideally, patients with a history of penicillin allergy should be evaluated when they are well and not in immediate need of antibiotic therapy. Patients who are found to be penicillin skin test-negative may be safely treated with all beta-lactam antibiotics. Penicillin skin test-positive patients should only receive a penicillin-class antibiotic via rapid desensitization, and only in cases when an alternative agent cannot be substituted. Penicillin skin test-positive patients may be safely treated with monobactams. The extent of allergic cross-reactivity between penicillin and cephalosporins/carbapenems is uncertain; therefore penicillin skin test-positive patients should only receive these antibiotics via cautious graded challenge or desensitization.

Identification of patients who erroneously carry a label of beta-lactam allergy leads to improved utilization of antibiotics and slows the spread of multiple drug-resistant bacteria.

Index Entries:

Penicillin; cephalosporins; beta-lactams; hypersensitivity; skin testing.

Introduction

Beta-lactam antibiotics are known to cause various predictable and unpredictable adverse reactions. Hypersensitivity reactions are a subset of unpredictable reactions that are known (or presumed) to be mediated by an immunologic mechanism. The term “allergic reactions” is synonymous with hypersensitivity reactions, although it is often mistakenly applied to all adverse drug reactions. Beta-lactam antibiotics have been implicated in a wide variety of hypersensitivity reactions (Table 1). Although the immune system is believed to play a role in all of these disorders, in many cases the underlying mechanism does not fit into the traditional Gell and Coombs classification scheme, and has not yet been elucidated. This article focuses primarily on IgE-mediated reactions, since we have considerable insight into their pathogenesis, and because physicians are often faced with the evaluation and management of patients with possible immediate-type beta-lactam allergies.

Epidemiology

Allergies to beta-lactam antibiotics are the most commonly reported medication allergy. Penicillin allergy alone is reported by up to 10% of patients. At the same time, when patients with a history of penicillin allergy are evaluated, more than 90% of them are found to lack penicillin-specific IgE antibodies, and can tolerate the antibiotic safely (1,2). The discrepancy between “claimed” and “real” penicillin allergy probably results from several factors, including the fact that the previous reaction was caused by the underlying illness rather than the antibiotic, or that the reaction was predictable rather than allergic. Penicillin-allergic patients are known to lose drug-specific antibodies over time (3–6), which also contributes to the discrepancy.

No studies have prospectively evaluated the sensitization rate during treatment courses with penicillin or other beta-lactam antibiotics.

Table 1 Hypersensitivity Drug Disorders Associated with Beta-Lactam Antibiotics	
Multisystem	Anaphylaxis Serum sickness-like reaction Drug fever Vasculitis Generalized lymphadenopathy
Skin	Maculopapular/morbilliform eruption Urticaria/angioedema Stevens-Johnson syndrome Toxic epidermal necrolysis Contact dermatitis Fixed drug eruption
Bone Marrow	Hemolytic anemia Thrombocytopenia Neutropenia Aplastic anemia Eosinophilia
Lung	Pulmonary infiltrates with eosinophilia
Kidney	Interstitial nephritis Nephrotic syndrome
Liver	Hepatitis
Heart	Myocarditis

Large-scale reviews of cutaneous adverse drug reactions have found beta-lactams to be the most frequent culprit drugs. For example, the Boston Collaborative Drug Surveillance Program analyzed data from 37,665 consecutive inpatients and determined the frequency of beta-lactam-associated cutaneous reactions to be: 5.1% of exposed patients (amoxicillin), 4.5% (ampicillin), 1.6% (penicillin G), and 1.5% (cephalosporins) (7,8). The majority of reported reactions consisted of maculopapular/morbilliform eruptions and urticaria, but it is unknown how many were in fact caused by drug-specific IgE antibodies.

Retrospective data on penicillin-induced anaphylaxis have revealed remarkably consistent results, which show that these reactions are rare. In 1968, Idsoe et al. reviewed over a

dozen published and unpublished reports from around the world, and they found that penicillin-induced anaphylaxis occurred in 0.015–0.04% (1.5–4/10,000) of treated patients (9). More recently, in a study of 1740 children and young adults who received monthly intramuscular (im) injections of penicillin G for an average of 3.4 yr, the incidence of anaphylaxis was 1.23 per 10,000 injections (10). Similarly, 2 of 9203 healthy military recruits developed anaphylaxis after prophylactic treatment with a single dose of im benzathine penicillin, which translates to an incidence of 2.17/10,000 (11). The incidence of anaphylaxis to cephalosporins and other beta-lactams has not been studied in large-scale surveys, but limited data suggest that it is at least one order of magnitude lower than with penicillin (12).

Risk Factors for the Development of Beta-Lactam Allergies

Most of the information we have about potential risk factors for the development of allergies to antibiotics is derived from studies on penicillin allergy. For this reason, the following discussion focuses primarily on penicillin, but presumably many of the results can be extended to other beta-lactams.

Age

Patients between the ages of 20 and 49 appear to be at greatest risk of having acute allergic (particularly anaphylactic) reactions to penicillin (9). This observation may reflect age-dependent differences in immune responses to medications. For example, children with hymenoptera sensitivity are known to lose specific IgE antibodies more rapidly than adults (13), and a similar mechanism may be operative in penicillin allergy. Conversely, the higher rate of allergy may simply be the result of more frequent exposure, and therefore a higher chance of sensitization in this age group.

Atopy

Atopy was initially believed to be a predisposing factor for the development of allergic reactions to penicillin (14,15). Later large-scale studies have not substantiated these earlier reports (1,16), whose findings were probably biased by the referral population evaluated. However, patients with asthma may be more likely to develop life-threatening or fatal anaphylactic reactions, as has been described with food allergies (17,18).

Concurrent Infection

Ampicillin is widely known to cause a morbilliform eruption in more than 90% of patients who are treated with the medication while infected with Epstein-Barr virus (EBV) (19). When evaluated, these patients are invariably found to lack penicillin-specific IgE antibodies, and can tolerate future courses of the medication without difficulty. Infection-associated drug reactions such as this and others are presumably the result of a modification of the immune response to the medication, although the mechanism has not been delineated. One theory is that viral infections result in a release of interferons, which in turn cause increased expression of major histocompatibility complex (MHC) receptors (along with processed drug) on antigen presenting cells in the skin (20). In contrast to reactions such as ampicillin with EBV, there is no clear evidence that IgE-mediated reactions are associated with particular infections (21,22).

Route and Frequency of Administration

The route of administration of antigens is known to be important in determining the type of immune response generated (20). In the case of penicillin, the parental route seems to be most sensitizing for the development of Type I allergies, and it is also most likely to result in anaphylaxis. The vast majority of deaths secondary to penicillin-induced anaphylaxis have occurred in patients treated with intramuscular (im) or intravenous (iv) rather than oral

penicillin (9). It is also believed that allergic sensitization is most likely to occur in individuals who receive frequent, repeated courses of similar antibiotics (22,23). Although the theories about route and frequency of administration have never been studied in prospective fashion, they are supported by the observation that patients with cystic fibrosis—who undergo frequent treatments with iv antibiotics—are particularly prone to developing IgE-mediated beta-lactam allergies (24).

Hereditary Factors

There is limited evidence that genetic or familial factors may play a role in the expression of antibiotic allergies, including beta-lactams. In two separate survey-type studies, children of parents who reported an antibiotic allergy were 15 times more likely to also be antibiotic-allergic (25), and patients with a history of drug allergy were 9 times more likely to report a family history of drug allergy among first-degree relatives (26). The results of both investigations are limited by a lack of confirmatory testing or provocative challenges and their reliance on patient history, which is known to be a poor predictor of true allergy. Furthermore, the reactions reported by the subjects included a variety of both IgE- and non-IgE-mediated reactions. To explain the fact that the familial predilection occurs across different classes of medications, it has been theorized that these patients are more likely to mount an allergic immune response against drug-protein complexes that are normally formed during therapy (27). Given the limitations of the available data, further research is needed to clarify whether and by what mechanism hereditary factors may play a role in beta-lactam allergies.

Multiple Drug Allergy Syndrome

The term “multiple drug allergy syndrome” refers to patients who have experienced allergic reactions to two or more non-crossreacting medications. Some investigators believe that the syndrome is caused by an individual’s

underlying heightened propensity to develop hypersensitivity reactions (both IgE- and non-IgE-mediated) (27). According to this theory, a patient who develops an allergy to one medication is more likely to develop a second allergy to an unrelated compound. Multiple drug allergy syndrome has been described in both pediatric and adult patients (28–31). For example, Smith et al. prospectively followed inpatients who received treatment with penicillin, and found that patients who developed an allergic reaction to the antibiotic were about 3 times more likely to report a history of prior drug allergy (30). Similarly, hospitalized patients with a history of antibiotic allergy were found to be 9 times more likely to develop an allergic reaction to another antibiotic, compared with inpatients without a history of antibiotic allergy (29). Other investigators have disputed the existence of the multiple drug allergy syndrome. Khoury et al. compared the frequency of reactions to non-beta lactam antibiotics in age- and sex-matched groups of patients with and without positive penicillin skin tests (32). There were no significant differences in reaction rates between the groups, and penicillin-allergic patients were least likely to react to another antibiotic.

Beta-Lactam Immunochemistry

Beta-lactam antibiotics, like many medications, are structurally too small to act as complete antigens, and therefore cannot independently elicit an immune response (21). Instead, they covalently bind to a larger carrier molecule, such as tissue or serum proteins, to form a multivalent antigen that is capable of stimulating the immune system. This process is known as haptentation, and the low molecular-weight compounds are known as haptens (33). The elicited immune response may be a humoral one with the production of specific antibodies, a cellular one with the generation of specific T-lymphocytes, or both. In general, immediate-type reactions correlate with the presence of specific IgE antibodies, and recent evidence

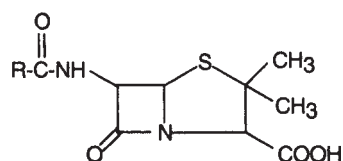
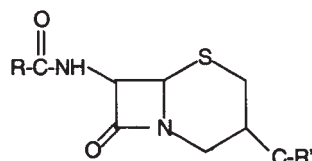
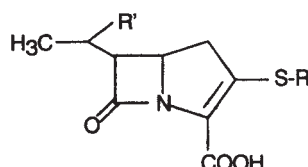
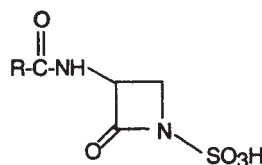
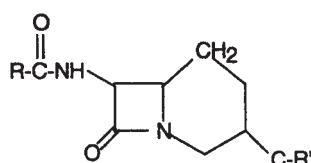
**Penicillins****Cephalosporins****Carbapenems****Monobactams****Carbacephems**

Fig. 1. Structures of major and minor penicillin antigenic determinants. Adapted from Kishiyama, J. L. and Adelman, D. C. (1994), The cross-reactivity and immunology of beta-lactam antibiotics. *Drug Safety* **10**, 318–327.

has implicated drug-specific T-lymphocytes in delayed cutaneous reactions (34).

Beta-lactams, like most antibiotics, are chemically inert in their native state. They are able to haptenate proteins only after undergoing conversion to reactive intermediates. Beta-lactams

differ from other antibiotics in that they undergo spontaneous degradation under physiologic conditions to form reactive intermediates. Most other antibiotics must be metabolized enzymatically to produce intermediates that are capable of binding to host proteins.

Among beta-lactams, only the immunochemistry of penicillin has been well-characterized. Penicillin has a core bicyclic nuclear core made up of a four-membered beta-lactam ring and a five-membered thia-zolidine ring (Fig. 1). In the 1960s, Parker and Levine independently showed that under physiologic conditions, the beta-lactam ring of penicillin opens spontaneously, allowing the carbonyl group to form an amide linkage with amino groups of lysine residues on nearby proteins (35,36). This newly created bond—the penicilloyl group—is called the major antigenic determinant because about 95% of tissue-bound penicillin exists in this form. The remaining portion of penicillin degrades to a variety of derivatives that are also capable of acting as haptens (37). Of these, the most important intermediates to induce allergic responses are penicilloate and penilloate. These two compounds, along with benzyl-penicillin itself, are collectively known as the minor antigenic determinants. The minor determinants cover all clinically relevant allergic determinants not covered by penicilloyl, and are not crossreactive with each other (37).

Non-penicillin beta-lactam antibiotic families include the cephalosporins, carbapenems, monobactams, and carbacephems (Fig. 2). Like penicillin, each contains a common four-membered beta-lactam ring. With the exception of monobactams, a second five- or six-membered ring comprises a bicyclic core structure. Unlike penicillin, the immunogenic determinants that are produced by degradation of these compounds are unknown. Although the beta-lactam ring may open to create intermediates that are analogous to the penicilloyl moiety (such as a cephalosporoyl group in the case of cephalosporins), these products do not

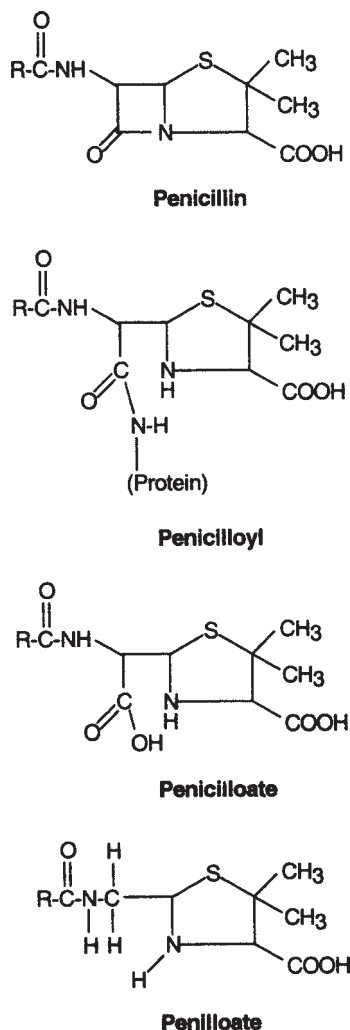


Fig. 2. Structures of commonly used beta-lactam antibiotics. Adapted from Kishiyama, J. L. and Adelman, D. C. (1994), The cross-reactivity and immunology of beta-lactam antibiotics. *Drug Safety* **10**, 318–327.

appear to lead to allergic responses. Recent evidence suggests that non-penicillin beta-lactams generally induce immune responses directed at their side chains, rather than the core portion of the molecule. The clinical relevance of these findings is discussed in the Clinical Management section of this article. Table 2 summarizes side-chain identities of commonly used beta-lactams.

Skin Testing: Penicillins

Reagents

Insight into the immunochemistry of penicillin has allowed for the development of validated skin test reagents to detect penicillin-specific IgE antibodies (Table 3). Ideally, both the major (benzyl-penicilloyl) and minor (benzylpenicillin, penicilloate, and penilloate) antigenic determinants are used in skin testing. Benzyl-penicilloyl is conjugated to a polylysine carrier molecule to produce a multivalent “complete” antigen. This compound is known as penicilloyl-polylysine (PPL), and since the 1970s it has been commercially available in an aqueous form in the United States as Pre-Pen®. Among the minor determinants, only penicillin G is widely available in the United States. Penicilloate and penilloate, which are frequently produced in a mixture (minor determinant mixture or MDM), continue to lack FDA approval, and thus are not commercially available to the general medical community. Since a number of medical centers synthesize minor determinants for local use, many allergists do have access to these reagents (38). Because penicilloate and penilloate are unstable in solution, they are lyophilized and used for skin testing after reconstitution (39). Efforts to conjugate minor determinants to a carrier molecule (analogous to PPL) have been unsuccessful. Consequently, in order to crosslink IgE antibodies and produce a wheal-and-flare skin-test response, these compounds presumably bind to host proteins at the skin-test site.

“Aged” penicillin should not be used as a substitute for MDM in testing for penicillin allergy. Although it was previously believed that penicillin left in solution degraded to form minor determinants, structural analytic studies of “aged” penicillin have revealed penicilloate and penilloate to be absent, or present in insignificant amounts (39,40).

In addition to the major and minor penicillin determinants, the addition of amoxicillin or ampicillin should be considered in the skin-

Table 2

[illegible]

Modified from Poley G.E and Slater J.E (1999), Drug and vaccine allergy. *Immunol. Allergy Clin. North Am.* **19**, 409–422

testing panel of patients who report reactions to these extended-spectrum penicillins. Although a majority of patients who are allergic to these compounds have IgE antibodies directed against the core beta-lactam portion of the molecule, some patients (especially those with cystic fibrosis) appear to mount an

immune response only to particular R-group side chains present in these medications. Patients with selective side-chain reactivity have negative skin-test responses to PPL and MDM, but test positive to non-irritating concentrations of the culprit extended-spectrum penicillin (24,41–44). Amoxicillin and ampicil-

Table 3
Reagents Used in Penicillin Skin Testing

Reagent	Concentration
Penicilloyl-polylysine (Pre-Pen)	6×10^{-5} M
Penicillin G	10,000 units/mL
Penicilloate/penilloate (MDM)	0.01 M
Ampicillin/amoxicillin	12.5 mg/mL

lin have each been reported to be non-irritating for intradermal testing in non-allergic control subjects up to a concentration of 25 mg/mL (42,45–47). For simplicity of preparation, the author dilutes commercially available iv ampicillin (125 mg/mL) ten-fold to produce a 12.5 mg/mL solution. Since iv amoxicillin (for human use) is unavailable in the United States, it is reasonable to substitute ampicillin because the two medications crossreact extensively.

Procedure and Interpretation

Penicillin skin testing, like any allergen skin testing, should be performed only by experienced personnel, and in a setting prepared to treat possible allergic reactions. Appropriate positive and negative controls should be utilized. For safety reasons, epicutaneous testing should always precede intradermal tests. When such a protocol is used, penicillin skin testing rarely provides systemic allergic reactions (1,3,16,48). Most experts agree that a positive response is defined by the size of the wheal, which should be 3 mm or greater than that of the negative control (for either prick or intradermal testing) (49).

Predictive Value

When both PPL and MDM are utilized, a negative penicillin skin test essentially rules out any potential for a serious immediate-type reaction. In large series, the negative predictive value of penicillin skin testing has been reported to be 97–99% (1–3,50). When reactions did occur in skin test-negative patients, they were mild and self-limited (1–3,50). Penicillin-

induced anaphylaxis has never been reported in a skin test-negative patient challenged with the medication (51).

Some studies indicate that skin testing with PPL and penicillin G alone (without penicilloate and penilloate) may fail to identify approx 10–20% of patients who have a positive skin test to any penicillin determinant (1,2). If one considers the fact that only about 10% of all patients labeled penicillin-allergic by history have positive skin tests, the omission of MDM misses about 1–2% of truly allergic patients (10–20% of 10%). As a result, lack of access to MDM should not necessarily dissuade physicians from evaluating patients with possible penicillin allergy (52).

For ethical reasons, it is unusual for penicillin skin test-positive patients to be challenged with the medication. Consequently, the positive predictive value of penicillin skin testing is based on a relatively small number of patients. Studies (in which appropriate concentrations and volumes of reagents were used) have reported 40–100% of skin test-positive patients to have immediate allergic reactions after being challenged with penicillin (2,6,16,43,53,54). This positive predictive value is comparable to that observed in hymenoptera skin testing (55).

Skin Testing: Other Beta-Lactams

Unlike penicillin, there are no reliable skin-testing reagents for all other beta-lactam antibiotics. The lack of proper diagnostic testing is largely the result of our inadequate knowledge of the relevant allergenic drug determinants that elicit immune responses. Skin testing with native beta-lactams can be of some help in the evaluation of patients with allergies to these medications. Although the sensitivity and specificity of such tests is unknown, most experts agree that a positive skin test (using a concentration proven to be non-irritating) strongly suggests the presence of drug-specific IgE antibodies (49). It is equally important to real-

ize that a negative skin test with the free drug does not rule out the presence of immediate-type allergy.

Cephalosporins

Skin testing with native cephalosporins has been performed since the 1960s. As part of many studies, a non-irritating concentration was determined in healthy, non-allergic control subjects (3,56–60). For intradermal testing, concentrations of 1–25 mg/mL have been reported to be non-irritating. This wide range of values probably results from the fact that, in a given study, once a non-irritating concentration was found, no additional attempts were made to test with higher concentrations (since this concentration also gave positive skin-test responses in allergic patients). In a recent report whose sole objective was to find the highest non-irritating concentration of 16 antibiotics—including 5 cephalosporins—in 25 non-allergic subjects, all cephalosporins were found to be non-irritating for intradermal testing when diluted 10-fold from the full-strength commercially available solution (61). Concentrations of these 10-fold dilutions ranged from 9–33 mg/mL.

Monobactams and Carbapenems

Skin testing with native monobactams and carbapenems also may be of value in selected patients. Aztreonam and imipenem have been reported to be non-irritating for intradermal skin testing at concentrations of 6×10^{-3} M (about 2.6 mg/mL) and 5×10^{-3} M (about 1.6 mg/mL), respectively (62,63). The predictive value of such skin testing is unknown, but a positive response suggests IgE-mediated allergy. Major and minor determinants (analogous to penicillin) of aztreonam and imipenem have been synthesized and used in research settings (62,63), but their relevance is unclear, and they are not available to the practicing allergist.

Clinical Management: Penicillins

When to Skin Test

Historically, evaluation of possible penicillin allergy was limited to acute situations in which patients with a history of penicillin allergy required penicillin and an alternate antibiotic could not be substituted (64). The “Disease management of drug hypersensitivity: a practice parameter” of the Joint Task Force on Practice Parameters also suggests that penicillin skin testing in adults be used primarily when there is an acute need for the medication (49). For the pediatric population, “elective” testing of patients when they are well and not in immediate need of the medication is recommended because of their frequent outpatient need for penicillin treatment and the impracticality of testing children when they are sick (49).

This author believes that elective penicillin skin testing of history-positive adults as well as children makes clinical sense, in light of emerging new data and the increasing prevalence of multiple antibiotic resistance. As mentioned earlier, although penicillin allergy is self-reported by up to 10% of the population, the vast majority of these patients are not truly allergic and could receive penicillin-class antibiotics. It is also common practice to deny these patients access to cephalosporins and other beta-lactams, in addition to penicillins. Instead, patients labeled as penicillin-allergic are needlessly treated with broad-spectrum antibiotics (65,66), and the use of these drugs contributes to the development and spread of multiple drug-resistant bacteria (67–69). Thus, an important and often under-appreciated aspect of penicillin allergy is the morbidity, mortality, and economic cost associated with the unnecessary withholding of appropriate therapy in patients who are assumed to be penicillin-allergic (70). More judicious use of broad-spectrum antibiotics can help reduce the spread of antibiotic resistance (67,69,71), and one way to achieve this goal is to penicillin skin test and identify the many patients erroneously labeled

as “penicillin-allergic.” In recent years, a number of medical centers in the United States have reported on successful efforts to carry out penicillin skin testing and decrease the utilization of broad-spectrum antibiotics (72–76).

In the “real world” practice setting, patients who have negative penicillin skin tests frequently find it difficult to trust the result after having been told their entire lives to avoid penicillin. Likewise, the referring physician or other future prescribing physicians may be reluctant to treat patients with a beta-lactam antibiotic simply based on a skin-test result. To alleviate patients’ and physicians’ fears and to unequivocally prove the medication’s safety, an elective oral challenge (with the same antibiotic implicated in the previous reaction) can be performed.

Penicillin Resensitization

Initially, elective penicillin skin testing was discouraged because of a fear that patients who tested negative may become resensitized, or redevelop their allergy, following future treatment courses with penicillin. In children, the resensitization rate in 240 history-positive/skin test-negative patients was found to be about 1%, following a course of oral penicillin (50). An additional 1500 unreported patients evaluated by the authors of this study have confirmed these results (Louis Mendelson, personal communication). In adults, recent evidence suggests that resensitization is also rare. Solensky et al. challenged 46 skin test-negative patients with a convincing history of penicillin allergy with three separate courses of oral penicillin, and none converted to a positive skin test (77). Although resensitization following oral penicillin appears to be low, limited data indicate that it may be more common following parenteral administration (78,79). Therefore, pending additional studies, history-positive patients who have tolerated a parental course of penicillin should have skin testing repeated prior to receiving additional penicillin.

Testing Only with PPL and Penicillin G

The previous discussion assumes that the evaluating allergist has access to both major and minor penicillin determinants. Skin testing with PPL and penicillin G alone (without MDM) can be successfully used to evaluate patients with a history of penicillin allergy (52), but because such testing may miss some allergic patients, it requires a more cautious approach. It is recommended that these skin test-negative patients first be given a test dose of approx 1/100th of the full therapeutic dose (49). If no reaction occurs during a brief observation period (e.g., 1 h), the full dose may be administered (49).

The Role of Allergic History

It is difficult to decide based solely on a patient’s history (e.g., without skin testing) which patients may be safely treated with penicillin. Some patients report reactions that were clearly mislabeled as being allergic in nature, and they may not need to be skin-tested. More often, patients report reactions (such as various skin eruptions) that could indicate allergy, or they cannot remember appropriate details of their reaction because it occurred in the distant past. Often, patients simply do not recall the reaction, but were told by their parent or pediatrician to always avoid penicillin. Patients with convincing histories of penicillin allergy are more likely to have positive skin tests than those with vague histories (1,16,53). However, vague allergic histories should not be disregarded, because, as a recent review of the literature revealed, one-third of all history-positive/penicillin-skin test-positive patients had a vague history of a previous reaction (80).

Skin Test-Positive Patients

Patients who have a positive penicillin-skin test to any antigenic determinant should avoid all penicillin-class compounds and be treated with alternate antibiotics that do not crossreact

Table 4
Administration of Cephalosporins to Patients with Positive Penicillin Skin Tests

Ref.	No. of Patients	No. of Reactions (%)	Comment
Girard (56)	23	2 (8.7)	Both reactions to cephaloridine*
Assem (82)	3	3	All reactions to cephaloridine*
Warrington (88)	3	0	
Solley (43)	27	0	
Saxon (89)	62	1 (1.6)	Specific cephalosporin not reported
Blanca (90)	17	2 (11.8)	
			Both reactions to cefamandole*
Shepherd (91)	9	0	
Audicana (92)	12	0	
Novalbos (60)	23	0	
TOTAL	179	8 (4.5)	

*These cephalosporins have side chains similar to benzylpenicillin. All patients had positive skin-test responses to PPL, penicillin G, and/or MDM. Patients negative to the major and minor determinants but positive to amoxicillin/ampicillin are not included.

with penicillin. The only exception to this rule is if a patient has a positive response only to an extended-spectrum penicillin. For example, if a patient tests positive to amoxicillin but is negative to PPL, penicillin G, and MDM, he/she can likely tolerate other penicillins that do not share the same side chain (to which the IgE is presumably directed) (41,42,44). When skin test-positive patients require treatment with penicillin, they should undergo desensitization (discussed in detail later in this article).

Clinical Management: Cephalosporins

Patients with a History of Penicillin Allergy

In vitro studies with penicillin and cephalosporins have shown a high degree of immunologic crossreactivity that is suggested by the presence of a common beta-lactam ring (81–85). Although clinical crossreactivity occurs much less frequently, the exact incidence is still not known. A retrospective review of treatment courses with first-generation cephalosporins in 701 patients with a history of penicillin allergy and 15,007 patients without a

history of penicillin allergy revealed “allergic reactions” in 8.1–1.9% of patients, respectively (86). In 1975 Dash reviewed the international literature for allergic reactions to first-generation cephalosporins and found similar results—a reaction rate of 7.7% in penicillin allergy history-positive patients, and 0.8% in history-negative patients (87). Neither report commented on the type of penicillin allergy history the participants had or on the type of reactions elicited by the cephalosporins, and none of the patients underwent penicillin skin testing. In contrast to these findings, a review of over 600 hospitalized inpatients with a history of penicillin allergy who received cephalosporins revealed only one non-immediate reaction (unpublished observation by author).

The major weakness of the studies discussed here is a lack of confirmation of penicillin allergy by skin testing, since it is likely that the vast majority of these patients did not have penicillin-specific IgE antibodies. There are a limited number of reports of penicillin-skin test-positive patients challenged with cepha-

losporins, and they reveal a very low reaction rate (Table 4). Additionally, the frequency of reactions to cephalosporins in skin test-positive patients does not appear to differ from that in penicillin history-positive/skin test-negative patients (3,43,91,92). It is also important to point out that in virtually all reported positive cephalosporin challenges, the culprit cephalosporin shares a similar R-group side chain with benzylpenicillin (Table 4). Therefore, the observed crossreactivity may have been the result of side chain-specific determinants rather than the core beta-lactam portion of the molecules. Several investigators have described selective allergic crossreactivity between particular penicillins and cephalosporins that share similar or identical side chains (46,47).

Another factor to consider when evaluating early reports of reactions to cephalosporins in patients with a history of penicillin allergy (56,93–98) is that initial cephalosporin preparations contained trace amounts of penicillin (99). Such contamination may have confounded the findings and resulted in an overestimate of the allergic crossreactivity. Furthermore, as mentioned previously, patients who are allergic to one medication may be more likely to react to a non-cross-reacting agent (28–31). Thus, in some penicillin-allergic patients, “multiple drug allergy syndrome,” rather than immunologic cross-reactivity, may be responsible for their cephalosporin allergy.

The approach to patients with a history of penicillin allergy who require treatment with cephalosporins is outlined in Fig. 3. Ideally, if penicillin-skin testing is available, it should be utilized in the evaluation. Patients whose skin-test responses are negative can receive any cephalosporin safely. Alternatively, if skin testing is positive, the “practice parameter” suggests one of three options (Fig. 3). Based on the evidence discussed here, this author recommends a graded challenge. The pace and degree of caution exercised in such incre-

mental challenges depend on the side chain similarity (or lack thereof) between the cephalosporin and the penicillin to which the patient reacted previously. In the absence of penicillin-skin testing, since less than 1% of patients will have a reaction, direct administration of the cephalosporin can be considered (Fig. 3), but is generally discouraged (49). Under these circumstances, this author recommends an initial test dose or a graded-dose challenge.

Patients with a History of Cephalosporin Allergy

The lack of standardized validated skin testing makes evaluation of possible cephalosporin allergy more difficult than penicillin allergy. As stated previously, skin testing with native cephalosporins can be of some value, but its predictive value is unknown. A positive skin-test response using a non-irritating concentration is suggestive of IgE-mediated allergy, but a negative result does not rule out sensitivity.

Little is known about the extent of cross-reactivity among different cephalosporins, and thus the safety of administering a particular cephalosporin to a patient who has previously experienced an allergic reaction to another cephalosporin. Case reports of patients who are allergic to a particular cephalosporin being able to tolerate other cephalosporins seem to suggest that the immune response is directed against R-group side chains, rather than the core portion of the molecules (45,57,58,100). These data and clinical experience led to the recommendation that patients with a history of cephalosporin allergy may safely receive other cephalosporins as long as they have dissimilar side chains (Fig. 3). The results of a recent study by Romano et al. places some doubt on this practice, however (59). The investigators skin-tested 30 cephalosporin-allergic patients with several different cephalosporins. About half of the subjects reacted only to the culprit cephalosporin, and the other half had positive skin responses to various cephalosporins, including

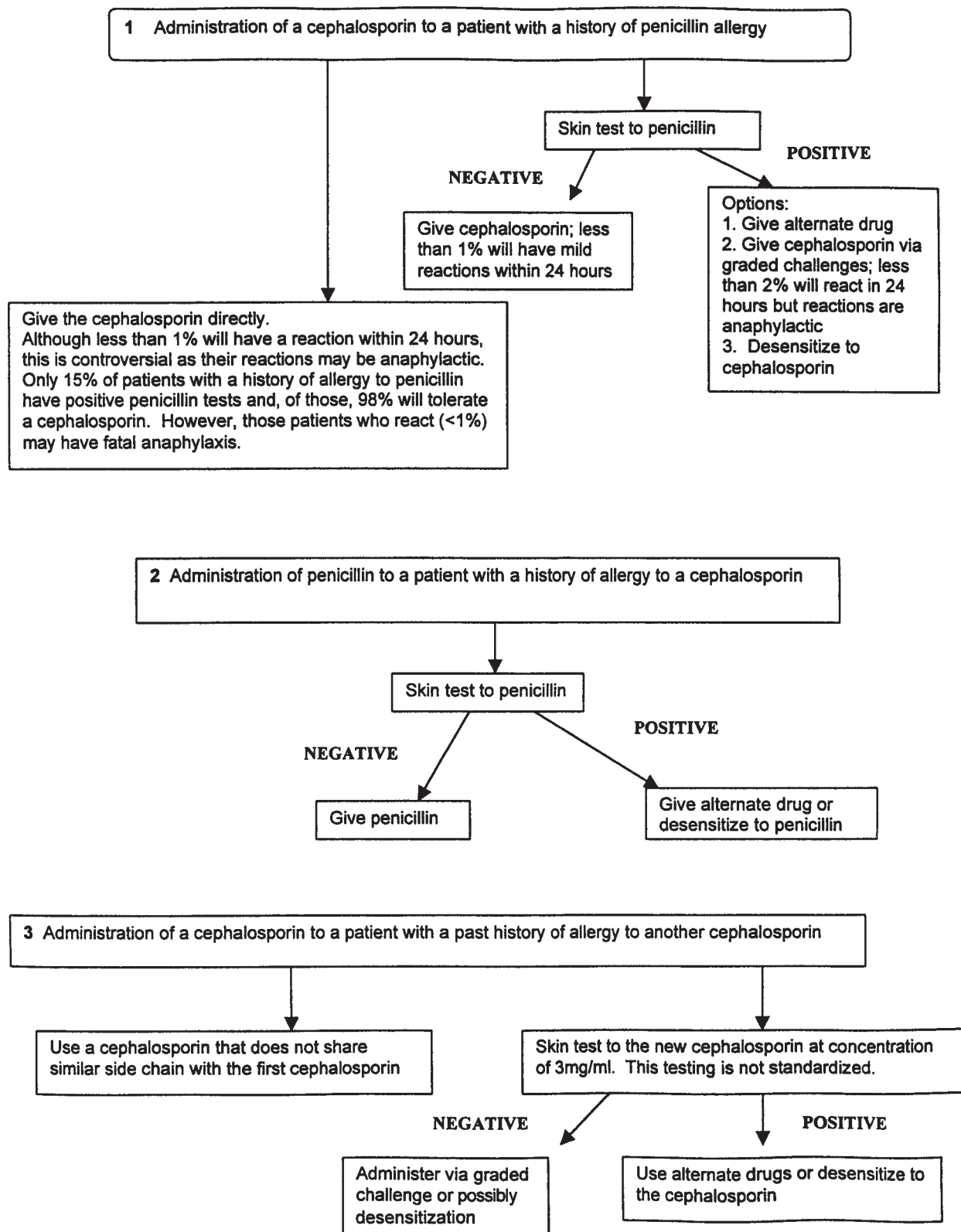


Fig. 3. Algorithms for the evaluation and management of patients with histories of penicillin/cephalosporin allergies. Adapted from Bernstein, I. L., et al. (1999), Disease management of drug hypersensitivity: a practice parameter. *Ann. Allergy Asthma Immunol.* **83**, 665–700.

ones with different side chains. These results suggest that some cephalosporin-allergic patients form IgE antibodies to crossreacting core deter-minants (rather than R groups), but none of the patients was challenged to confirm this suspicion.

The management of patients with a history of cephalosporin allergy who require treatment with penicillin is straightforward, and it is based on the result of penicillin-skin testing (Fig. 3). Skin test-negative patients may receive penicillin, whereas skin test-positive patients should receive an alternate agent or undergo desensitization. If penicillin-skin testing is not available, penicillin can be given via a graded challenge.

Clinical Management: Other Beta-Lactams

Monobactams

Aztreonam is a newer beta-lactam antibiotic that contains a monocyclic ring structure, in contrast to the other bicyclic core beta-lactams (Fig. 2). There are no standardized aztreonam skin-test reagents, making evaluation of possible allergy difficult. Native aztreonam is non-irritating for intradermal skin testing up to a concentration of 2.6 mg/mL (62,101,102), but its predictive value is unknown. Patients with a history of immediate reactions to aztreonam who require re-administration should undergo desensitization.

The immunogenicity of aztreonam and its potential allergic crossreactivity with penicillin and cephalosporins were extensively studied in cooperation with the drug's manufacturer during the preclinical development and early clinical trials (103). A prospective and comparative randomized trial of aztreonam, cefotaxime, and procaine penicillin in the treatment of gonococcal urethritis showed aztreonam to be least immunogenic (e.g., least likely to result in the development of drug-specific IgG and IgE antibodies) (104). In vitro studies demonstrated virtually no immunologic crossreactivity between either penicillin or cephalosporins

and aztreonam (104–106). The only exception to this was ceftazidime, which shares an identical side-chain R group with aztreonam (105,106). These findings indicate that the immunologic response to aztreonam is directed at its side chain, rather than the core beta-lactam portion of the molecule.

In vivo studies and challenges of penicillin-allergic patients have confirmed a lack of crossreactivity between these agents (62,102–104,107). Of 41 penicillin-skin test-positive patients, none had a reproducible positive skin test to aztreonam determinants analogous to penicillin major and minor determinants (which were synthesized for research purposes only) (62). Subsequently, these investigators challenged 20 penicillin skin test-positive patients with aztreonam, and none experienced an adverse reaction (103), a finding confirmed by Vega et al. in 19 additional penicillin-skin test-positive patients (102). Graninger and colleagues treated 23 penicillin and/or cephalosporin-allergic patients (by history only) with aztreonam; 22 tolerated the medication, and one patient developed urticaria after 3 wk of treatment (108). Finally, there is a case report of a penicillin-allergic patient who failed penicillin desensitization but was able to tolerate aztreonam (109).

To summarize, available data indicate a lack of allergic crossreactivity between aztreonam and other beta-lactam antibiotics. Therefore, patients who report previous reactions to penicillins and cephalosporins can safely receive aztreonam, with the exception of patients who are allergic to ceftazidime (which has an identical side chain). Conversely, patients who have experienced Type I allergic reactions to aztreonam are able to tolerate penicillins and cephalosporins (except for ceftazidime) (101,110,111).

Carbapenems

Imipenem is the prototype agent in this newer class of beta-lactams that contain a bicyclic nucleus similar to penicillin (Fig. 2). As with other non-penicillins, skin testing can be performed only with the native drug. Intradermal skin testing with native imipenem was non-irritating at 1 mg/mL and 1.6 mg/mL (in two separate groups of 20 control subjects) (63,112).

Skin testing with imipenem determinants (prepared in a similar fashion to penicillin determinants) showed extensive cross-reactivity in penicillin-allergic patients (63). Of 40 patients with a history of penicillin allergy, 20 were found to be penicillin-skin test-positive, and 10 of these individuals also had positive responses to imipenem determinants. In contrast, all 20 history-positive/penicillin-skin test-negative patients failed to respond to imipenem. The 50% skin test crossreactivity is similar to that found with first-generation cephalosporins (56,82). None of the patients was given imipenem, and there are no other published reports of imipenem challenges in penicillin-skin test-positive patients.

A recent retrospective study reviewed records of 63 patients with reported penicillin allergies who received imipenem during hospitalization (113). Six of the 63 patients (9.5%) developed reactions that were possibly allergic (mostly cutaneous eruptions), and none was serious in nature. Two of the six patients received penicillin immediately prior to imipenem and had reactions that persisted (e.g., did not begin) while on imipenem, making their significance questionable. No patients underwent skin testing with either penicillin or imipenem. Thus, despite the observed skin-test crossreactivity between penicillin and imipenem, the clinical relevance remains unknown. Pending additional data, patients with positive penicillin skin tests (or patients with a history of penicillin allergy if skin testing is unavailable) should receive imipenem

cautiously—via desensitization or graded challenge, depending on the specific history. Patients with a history of penicillin allergy who are penicillin skin test-negative can safely be treated with imipenem.

Desensitization

Rapid desensitization with beta-lactams should be considered when a patient who has medication-specific IgE antibodies requires treatment with the same or a crossreacting antibiotic. Desensitization “fools” the immune system into accepting a medication, and it is achieved by administering progressively increasing doses of the drug. Desensitization somehow renders mast cells unresponsive to the allergic determinants of a medication, but the exact immunologic mechanism is poorly understood (114).

Among the beta-lactams, desensitization with penicillin has the largest body of evidence behind it (115–119), but the same principles can be applied to other beta-lactam antibiotics (115,120–122). Penicillin desensitization can be accomplished, and has been described via both the oral and intravenous routes (115–119). Representative penicillin desensitization protocols are shown in Tables 5 and 6. The starting dose is determined by the amount of drug the patient tolerated during skin testing, which is generally 1/10,000th or less of the full therapeutic dose. Doubling doses are administered every 15 min until the full dose is reached. Once desensitization is completed, the patient can safely receive the usual therapeutic course of the desired penicillin. If it is necessary for the patient to remain in a desensitized state, penicillin needs to be administered chronically on a BID basis (117,123). Once penicillin is discontinued for 48 h or more, the patient is again at risk of anaphylaxis, and desensitization must be repeated.

Acute desensitization should only be performed by a physician who is familiar with the procedure, in a hospital setting, with iv access, and preparedness to treat potential anaphylaxis.

Table 5
Penicillin Oral Desensitization Protocol

Step*	Penicillin (mg/mL)	Amount (mL)	Dose given (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5	1.2	6	12.35
9	5	2.4	12	24.35
10	5	5	25	49.35
11	50	1	50	100
12	50	2	100	200
13	50	4	200	400
14	50	8	400	800

Observe patient for 30 mins, then give full therapeutic dose by the desired route.

*Interval between doses is 15 min.

Adapted from Sullivan, T. J. Drug allergy, in *Allergy: Principles and Practice*. 4th ed. Middleton, E., Reed, C. E., Ellis, E. F., Adkinson, N. F., and Yunginger, J. W., eds. Mosby, St. Louis, 1993, pp. 1726–1746.

Table 6
Penicillin iv Desensitization Protocol with Drug Added
by Piggyback Infusion

Step*	Penicillin (mg/mL)	Amount (mL)	Dose given (mg)	Cumulative dose (mg)
1	0.1	0.1	0.01	0.01
2	0.1	0.2	0.02	0.03
3	0.1	0.4	0.04	0.07
4	0.1	0.8	0.08	0.15
5	0.1	1.6	0.16	0.31
6	1	0.32	0.32	0.63
7	1	0.64	0.64	1.27
8	1	1.2	1.2	2.47
9	10	0.24	2.4	4.87
10	10	0.48	4.8	10
11	10	1	10	20
12	10	2	20	40
13	100	0.4	40	80
14	100	0.8	80	160
15	100	1.6	160	320
16	1000	0.32	320	640
17	1000	0.64	640	1280

Observe patient for 30 min, then give full therapeutic dose by the desired route.

*Interval between doses is 15 min.

Adapted from Sullivan T. J. Drug allergy, in *Allergy: Principles and Practice*. 4th ed. Middleton, E., Reed, C. E., Ellis, E. F., Adkinson, N. F., and Yunginger, J. W., eds. Mosby, St. Louis, 1993, pp. 1726–1746.

Despite the potential for severe reactions, desensitization is generally a safe procedure; mild, transient, IgE-mediated reactions occur in up to one-third of patients, but life-threatening or fatal reactions have not been described (117). Patients should not be pretreated with corticosteroids or antihistamines because these medications do not prevent IgE-mediated anaphylaxis, and they may mask early signs of an allergic reaction. Patients with asthma, chronic obstructive pulmonary disease (COPD), or other lung diseases should be optimally controlled prior to undergoing desensitization. Treatment with beta-adrenergic-blocking medications should be discontinued prior to desensitization. Desensitization does not prevent non-IgE-mediated reactions, such as hemolytic anemia and interstitial nephritis, from occurring.

Summary

The management of patients with histories of allergic reactions to beta-lactam antibiotics is a common situation in clinical practice. Fortunately, severe and life-threatening reactions to these medications are rare. However, many patients are unnecessarily labeled as being allergic, and because of the fear that they may develop anaphylaxis, are denied access to indicated antibiotic therapy. The evaluation of patients with allergies to beta-lactam antibiotics by allergists/immunologists can lead to improved utilization of antibiotics and help decrease the spread of multiple drug-resistant bacteria.

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