

Dilemmas and controversies in penicillin allergy

Arveen K. Thethi, MD*, R.G. Van Dellen, MD

*Division of Allergic Diseases and Internal Medicine, College of Medicine, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA*

Since the initial reports of penicillin and beta-lactam drugs causing allergic reactions, much has been elucidated regarding their pathophysiology and mechanism of action. Despite advances in testing for penicillin allergy, with IgE antibodies and skin tests available for the major and minor determinants of penicillin, these reactions remain a challenge to all physicians. They have characteristically been classified according to mechanism [1] and time [2]. Herein, the authors propose a classification system of penicillin allergy based on immunologic mechanisms, as outlined in [Box 1](#). Topics discussed include the controversies and unknowns surrounding penicillin allergy.

Background

Ever since penicillin was first introduced as a therapeutic agent in the 1940s, allergic reactions, including death, have been reported. In a recent study, Markus et al [3] found that 12.7% of persons admitted to the hospital reported an allergy to penicillin. Two studies that looked at deaths from anaphylaxis to penicillin reported that one-quarter to one-third of those patients who died owing to the administration of penicillin had histories of penicillin allergy ([Table 1](#)) [4,5]. Both of the studies were retrospective, and historical information was incomplete. Given these data, on hearing of a history of penicillin allergy, a physician may eliminate the use of penicillin and possibly other beta-lactam antibiotics in an individual when a beta-lactam antibiotic might be the drug of choice.

* Corresponding author.

E-mail address: thethi.arveen@mayo.edu (A.K. Thethi).

Box 1. Reactions to penicillin based on immunologic mechanism

IgE-mediated reactions

Anaphylaxis

Urticaria

Possibly some exanthems (at times difficult to differentiate from urticaria)

IgG/IgM antibody causing direct toxicity (with complement)

Hemolytic anemia

Possibly other cytopenias

Interstitial nephritis

Immune complex disease

Serum sickness

Possibly some exanthems

Possibly drug fever

Delayed hypersensitivity

Contact dermatitis

Some exanthems

Fixed drug eruption at sites of previous tinea infections

Toxic epidermal necrolysis

Other immunologic mechanisms, mechanism unknown, or mechanism poorly documented

Some exanthems

Hepatitis

Eosinophilia

Other severe skin reactions

Stevens-Johnson syndrome

Exfoliative dermatitis

Acute generalized exanthematous pustulosis

Bullous skin disease

Clostridium difficile colitis

Table 1
Anaphylaxis from penicillin

Parameter	Number of patients	
	Study 1 [4]	Study 2 [5]
Deaths from penicillin	151	32
Information regarding previous exposure	104	22
History of previous reaction	37	5

With the more widespread use of penicillin skin testing, subsequent studies have shown that many patients with a history of penicillin allergy can take penicillin safely [6]. The following observations have been made:

- Of those patients with a history of penicillin allergy who are skin tested with major and minor determinant reagents, 40% to 90% have negative immediate allergy skin tests [6]. More recent experience suggests that less than 10% of persons with a history of penicillin allergy have positive skin tests [7]. This observation may be explained in part by the longer time elapsed between the reaction to penicillin and the testing.
- In patients with a history of penicillin allergy and negative immediate allergy skin tests who are then treated with penicillin, adverse reactions occur in as many as 12% [6,8]. IgE-mediated reactions occur in 4% or less [6,8]. This incidence is probably no greater than in patients who receive a penicillin drug with no history of penicillin allergy.
- Some patients are exquisitely sensitive to penicillin. Systemic reactions and death may occur from minute amounts of penicillin in these rare individuals. These persons need to avoid penicillin and should not be tested for penicillin allergy. Giving even minute amounts is life threatening. One of the authors (RVD) knows of several deaths from penicillin skin testing. There are reports of systemic reactions in penicillin-allergic patients after intercourse with a partner who had received dicloxacillin [9] and after a passionate kiss from a person who had just received bacampicillin [10], and an anaphylactic reaction after exposure to an intradermal injection of 3×10^{-6} U [11].
- Despite these findings, penicillin skin testing in the United States has generally been safe. All patients should have a history taken before proceeding with penicillin skin testing, and those who give a history suggestive of such exquisite sensitivity should not be tested or tested only cautiously by diluting the usual concentration of skin test reagents. In a review of the authors' experience testing 1710 patients, all of them with a history of penicillin allergy, the incidence of systemic reactions in the entire group was 0.12%. In patients who had positive allergy skin tests, the incidence was 2.3% [12]. Other researchers have found slightly higher rates of systemic reactions. Gadde et al [13] reported 13 systemic reactions in 5063 patients tested who had positive and negative histories, for an overall reaction rate of 0.26% including positive and negative skin tests. This finding is similar to the authors' results; however, 1.2% with positive histories and 9.4% with positive skin tests had systemic reactions to skin testing.
- Patients with previous reactions suggesting hepatitis, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a severe exfoliative dermatitis should not be tested or given penicillin.
- Patients with a history of penicillin allergy and positive penicillin skin tests have been successfully desensitized to penicillin. It is possible for these patients to experience delayed immunologic reactions other than IgE-

mediated reactions. Multiple desensitization protocols have been published [14–17].

This article discusses the following dilemmas and controversies surrounding penicillin allergy and testing for penicillin allergy:

- What minor determinants should be used in skin testing?
- Is history alone reliable enough without performing allergy skin testing to penicillin?
- What is the incidence of resensitization after negative penicillin skin tests in a patient with a previous positive history of penicillin allergy who is treated with penicillin?
- Is it safe to give a cephalosporin drug in patients who have histories of penicillin allergy?
- What is the role of delayed hypersensitivity and testing for this reaction in penicillin allergy?

Controversies in penicillin allergy and skin testing

What minor determinants should be used in skin testing?

Since the late 1960s, penicillin skin tests have been performed with major and minor determinants of penicillin. Penicillin is a small molecular weight molecule and functions as a hapten. The hapten adheres to a protein, and this hapten-protein complex is antigenic [2]. The terms *major* and *minor* do not refer to the clinical importance of these reagents or determinants but rather their in vitro activity. When penicillin G is mixed in vitro with a protein, most of the protein combines with penicillin G through the beta-lactam ring at a lysine amino acid of the protein. This complex is called the benzylpenicilloyl determinant. The reagent is commercially available as benzylpenicilloyl polylysine (Pre-Pen), but it is unknown whether this reagent will always be readily accessible. The minor determinants are less well characterized biochemically. Multiple minor determinant mixtures have been used in various studies (Box 2). Except for penicillin G, these reagents are not commercially available in the United States and will not be soon. A minor determinate mixture is commercially available in Germany. The

Box 2. Minor determinant mixtures

Penicillin G, benzylpenicilloate, and benzylpenilloate
 Penicillin G, benzylpenicilloate, and benzylpenicilloyl-N
 propylamine
 Penicillin G and benzylpenicilloate
 Penicillin G alone

mixtures used in the United States are locally made. If penicillin skin testing is negative to the major and minor determinants, the patient has a low risk of having a reaction should a subsequent penicillin drug be used.

All of the studies reviewed herein have used the major determinant plus the different minor determinants listed.

Penicillin G, benzylpenicilloate, and benzylpenilloate

In 1969, Levine and Zolov [18] reported on a series of patients who underwent skin testing with the major determinant of penicillin (benzylpenicilloyl-polylysine) and a minor determinant mixture containing penicillin G, benzylpenicilloate, and benzylpenilloate. Of 185 patients who had a positive history of penicillin allergy but negative skin tests, 7 had reactions when they were subsequently treated with penicillin. Six of the seven reactions were judged to be non-IgE. The reaction rate including all reactions (7 of 185 treated) was 3.8%.

Mendelson et al [19] initially reported on 240 patients and subsequently an additional 700+ for a total of 1025 patients [20] who had positive histories but were skin test negative to the major determinant and the previously listed minor determinants. These patients were then treated with 10 days of oral penicillin whether they needed the treatment or not. Only 20 of the 1025 patients had a rash, a reaction rate of 1.9%. These patients were mostly children and adolescents.

Penicillin G, benzylpenicilloate, and benzylpenicilloyl-N propylamine

Sogn et al [21] in a multicenter study sponsored by the National Institute of Allergy and Infectious Diseases reported on 1134 patients, roughly half of who had a positive history of penicillin allergy. All of the patients had negative skin tests and were subsequently treated with a penicillin drug. Seven had what was considered an IgE-mediated reaction, but an additional 33 had other untoward reactions, for a total reaction rate of 3.5%.

Penicillin G and benzylpenicilloate

Solley et al [22] found that, of 290 patients with positive histories of penicillin allergy but negative skin tests who were treated with a penicillin drug, 12 (4.1%) experienced a reaction. These effects included IgE and non-IgE-mediated reactions.

Penicillin G alone

Green et al [23] in a multicenter study sponsored by the American Academy of Allergy challenged 346 skin test-negative patients with penicillin using only penicillin G as the minor determinant and not benzylpenicilloate, benzylpenilloate, or benzylpenicilloyl-N propylamine. All but 96 of the 346 patients had positive histories of penicillin allergy. Twelve of 346 (3.5%) subjects experienced a reaction. Three of the 12 reactions were thought to be IgE mediated.

Shepherd [24] also used penicillin G as the only minor determinant. Of 388 hospitalized patients with positive histories and negative skin tests who were subsequently treated with penicillin drugs, four had what were thought to be IgE-

mediated reactions, and 18 had rashes later, for a total reaction rate of 5.7%. Shepherd has subsequently expanded her studies to include outpatients and indicates that she has now tested and treated over a thousand patients with similar results (G. Shepherd, MD, personal communication, October 2003).

Use of any of the minor determinants described previously results in a low incidence of reactions on administration of a penicillin drug if skin tests are negative; however, the reaction rate is not zero. The difficulty arises in patients who have positive skin tests to the benzylpenicilloate, penicilloate, or benzylpenicilloyl-N propylamine minor determinants alone without having positive skin tests to the major determinant or penicillin G. The estimated incidence of patients who have positive skin tests to one or the other of these determinants alone ranges from 7.2% to 15.8% [22,25]. The significance of these solitary skin tests to one of the minor determinant reagents other than penicillin G remains unknown. Gorevic and Levine [26] described one patient who was positive to benzylpenicilloate alone who had a history of a morbilliform rash to penicillin. The patient was then desensitized to carbenicillin, and the skin tests became negative. That observation suggests there was some clinical relevance to the positive skin tests, at least in this one patient. Further investigation is needed to assess the positive predictive value of skin tests to these minor determinant reagents. The positive predictive value, that is, the number of patients with positive skin tests who would have a reaction if given penicillin, is not known. Only a few patients have been so treated, and the estimated reaction rate is around 50% [18,22,23], but the numbers are small. Penicillin G is the only minor determinant currently available commercially. Establishing the positive predictive value of each of the different minor determinants would be helpful to allergists and others who skin test to penicillin.

Is history alone adequate to determine penicillin allergy without the need to perform skin tests to penicillin?

The recommendation has been made that history is an adequate method of determining penicillin allergy, and skin testing may not be needed. Salkind et al [27] reviewed a Medline search for relevant English language articles from 1966 to October 2000. Bibliographies were searched to identify additional articles. Fourteen studies met the criteria of using both minor and major determinants to perform allergy skin testing, provided an explicit definition of penicillin allergy, and listed the specific criteria necessary for a positive skin test result. In performing their analysis, Salkind and coworkers concluded “taking a detailed history of a patient’s reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive a penicillin” without any testing. They suggested that 10% to 20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing, and that a concerning history of type 1 penicillin allergy is the only compelling need for skin testing. This is an attractive hypothesis owing to the fact that skin testing for penicillin allergy is not widely available, is performed mainly by allergists, and

relies on minor determinate reagents that are not commercially available (except penicillin G) and will likely not be available in the near future. The authors disagree with the previous hypothesis. The conclusion in this study is based on the findings using skin testing. Other studies do not agree that history correlates well with positive skin tests. Although Green et al [23] found a correlation between history and positive skin tests, other studies have shown that a vague or uncertain history can be associated with positive skin tests [22,28].

What is the incidence of resensitization after negative penicillin skin tests in a patient with a previous positive history of penicillin allergy who is treated with penicillin?

Possibly some allergists who perform penicillin skin tests have seen patients with negative skin tests who were given a first course of penicillin without difficulty but in whom a reaction developed on the next administration of penicillin. Accumulating evidence suggests that, although resensitization occurs, the incidence of resensitization is low.

Mendelson et al [20] studied 1025 history-positive patients, predominantly children and adolescents, with negative skin tests who were treated with a 10-day course of penicillin. Nine hundred of these patients were subsequently skin tested, and the incidence of positive skin tests was 1.29%. Nevertheless, performing skin tests is not quite the same as giving a course of penicillin, because the positive predictive value of the skin tests is not well defined.

Pichichero and Pichichero [29] treated children with positive histories but negative skin tests and found that 26 of the 247 children experienced positive skin tests (10.5%). Solensky et al [30] treated 46 adult patients who were history positive but skin test negative with a course of Penicillin VK. The subjects subsequently received two additional courses of penicillin without reactions, and skin testing after the third course of penicillin remained negative.

Perencevich et al [31] observed 38 patients over a 2-year period who had positive histories for penicillin allergy but negative skin tests and who received penicillin safely. This group had 48 subsequent hospital re-admissions, of which 35 required antibiotics. Beta-lactam antibiotics were prescribed in 86% of the admissions, a penicillin drug in 35%, and a cephalosporin drug in 51%; none of these patients had reactions. Similarly, Pichichero and Pichichero [29] observed 163 patients who had positive histories of penicillin allergy but negative skin tests over 6 months to 8 years. These 163 patients received 513 courses of beta-lactam antibiotics, and only three had mild reactions.

Lopez-Serrano et al [32] reported on 207 history-positive but skin test–negative patients who had negative challenges with intramuscular benzylpenicillin and oral amoxicillin. They retested and rechallenged these patients 10 to 30 days later. Ten patients (approximately 5%) had reactions.

Nugent et al [33] recently examined the incidence of skin test sensitization after penicillin skin testing. Of 239 subjects with initial negative skin tests, 2.5% converted to positive skin tests on testing 4 weeks later. None had a prior history

of penicillin allergy. The significance of this finding remains unknown. It is not too surprising that a small percentage of patients would become sensitized by penicillin skin testing, because these individuals are exposed to small doses of penicillin.

Macy et al [8] reported on 1246 individuals with a history of penicillin allergy but negative penicillin skin tests who were observed for 4 years. From that group, 568 received one or more courses of penicillin. Of those who received penicillin, 65 had an adverse reaction (11.4%). Only 4.8% had a reaction on first penicillin exposure, and 3.2% of penicillin courses were associated with a reaction. None of these reactions was life threatening. Less than 1% was thought to be IgE mediated. If the researchers included only those persons with clinically significant adverse drug reactions and a positive penicillin skin test after the reaction, the rate of true IgE-mediated penicillin allergy fell to 0.38% in the cohort.

Based on the previous studies, one can say with some confidence that re-sensitization does occur after negative penicillin skin tests and subsequent treatment with penicillin or other beta-lactam antibiotics, but this re-sensitization is uncommon. The situation may be different in hospitalized patients who are given high doses of parenteral penicillin. Parker et al [34] reported that 3 of 15 hospitalized patients treated with high doses of intravenous penicillins had subsequent positive skin tests. Earl et al [35] reported that 6 of 10 patients treated with high-dose intravenous penicillins in the hospital had subsequent positive skin tests.

Is it safe to give a cephalosporin drug in patients who have histories of penicillin allergy?

The incidence of reactions to cephalosporins is greater in persons who have a history of penicillin allergy (14.6%) than in persons who do not (1.9%) [6,36]. For a third-generation cephalosporin, ceftazidime, the relative risk was less than for first- and second-generation cephalosporins [6].

Patients with a history of penicillin allergy have experienced serious anaphylactic reactions with the first administration of a cephalosporin drug, and fatalities have occurred from reactions to cephalosporins [36]. Many of those reactions occurred soon after the introduction of cephalosporins.

Several studies have shown that patients with a history of penicillin allergy and negative skin tests to penicillin G can tolerate cephalosporin drugs with a low incidence of reactions [7,22,37]. This observation was one of the unexpected findings when the authors analyzed data from patients with positive histories to penicillin but negative skin tests. Of 151 patients in this setting who were given a cephalosporin drug, two had reactions, an incidence of 1.5% [22]. Shepherd and Burton [37] reported that 159 patients given cephalosporins in this setting had no reaction in the first 24 hours. Four of these patients had delayed reactions. More recently, at the authors' center, Severson et al [7] reported on 395 patients who had positive histories of penicillin allergy but negative skin tests who were given cefazolin for preoperative prophylaxis before orthopedic surgery. Two (0.5%) of

these 395 patients had drug-related skin rashes within 72 hours of cefazolin administration. This reaction rate is about the same or possibly even less than that occurring in patients who have negative skin tests and receive a penicillin drug.

Accumulating evidence suggests that patients with a positive history of penicillin allergy and a positive skin test or positive serum IgE antibodies or a positive challenge have a low incidence of allergic reactions if subsequently challenged or treated with a cephalosporin (Table 2) [38–43]. Among a group of approximately 279 patients with a history of allergy to penicillin, positive testing, or challenge to penicillin who have been treated or challenged with a cephalosporin, the reaction rate has been 3.2%. The study by Macy et al [8] was particularly instructive. Of the 42 patients with positive skin tests to penicillin who were subsequently treated with a cephalosporin, only one had a reaction on the first administration. Six additional patients had reactions on subsequent

Table 2
Cephalosporin challenge/treatment in patients with positive histories of penicillin allergy

Number of patients treated or challenged	Reactions	Reference and year	Comments
3	3	Assem and Vickers, 1974 [38]	All 3 received cephaloridine
3	0	Warrington et al, 1978 [39]	
27	0	Solley et al, 1982 [22]	
62	1	Saxon et al, 1987 [40]	
19	2	Blanca et al, 1989 [41]	Given subcutaneous, then intramuscular dose of cephamandole, then oral cephaloridine for 3 days
9	0	Shepherd and Burton 1993 [37]	
30	0	Audicana et al, 1994 [42]	Challenged with cephalexin and ceftazidime; four patients excluded because of positive skin tests to the cephalosporin
43	2	Pichichero and Pichichero, 1998 [29]	
41	1	Novalbos et al, 2001 [43]	Challenged with three different cephalosporins (cefazolin, cefuroxime, ceftriaxone) with different side chains than with penicillin reaction; one patient had delayed onset, fixed drug eruption
42	1 (7)	Macy et al, 2002 [8]	Only 1/7 had reaction on first course of cephalosporin; other 6 had multiple courses of cephalosporins before a reaction
279	10 (18) Reaction rate, 3.6% (6.5%)		

courses; some received multiple courses before a reaction. Macy and Burchette [25] found that patients who were labeled penicillin allergic had a lower incidence of adverse reactions to beta-lactam antibiotics than to alternative unrelated antibiotics independent of penicillin skin test results.

When treating patients with a history of penicillin and cephalosporin allergy, the current recommendations include using an alternative antibiotic. The package inserts or product labels for all cephalosporin antibiotics contain a similar warning—before therapy with the cephalosporin, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to the cephalosporin, other cephalosporins, penicillins, or other drugs. If this product is to be administered to penicillin-sensitive patients, caution should be exercised, because some clinical cross-reactivity between penicillins and cephalosporins may occur. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures. Anaphylaxis may occur.

The practice parameter published jointly by the American College of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology states the following: “Only 15% of patients with a history of allergy to penicillin have positive skin tests and, of those, 98% will tolerate a cephalosporin. However, those patients who react (less than 1%) may have fatal anaphylaxis” [44].

The algorithm published in the practice parameters for administration of a cephalosporin to a patient with a history of penicillin allergy states that one should first skin test to penicillin. If the skin test is negative, one should give the cephalosporin, and less than 1% will have mild reactions within 24 hours. If the skin tests to penicillin are positive, one should give an alternative drug, or give the cephalosporin via graded challenge or desensitize to the cephalosporin. If graded challenges are used, less than 2% of patients will react in 24 hours, but reactions are anaphylactic [44].

What is the role of delayed hypersensitivity and its testing in penicillin allergy?

Allergic reactions to penicillin and its derivatives are often classified as immediate, accelerated, or delayed according to the time interval between drug administration and onset of the reaction. Immediate reactions occur within the first hour after drug administration and are manifested clinically by urticaria or angioedema, wheezing, hypotension, or shock. Accelerated reactions occur within 1 to 72 hours of drug administration, whereas delayed reactions take 72 hours or longer to appear. The latter reactions include manifestations such as maculopapular rashes, toxic epidermal necrolysis, interstitial nephritis, and serum sickness [2,45].

There has been limited understanding of the pathophysiology behind non-immediate reactions. Maculopapular rashes seen days after initiating treatment with penicillin or its derivatives have often been classified as idiopathic in nature. Researchers have now shown that such rashes often represent a type IV cell-mediated hypersensitivity reaction dependent on sensitized T lymphocytes [46].

Romano et al [47] have shown that adverse reactions to aminopenicillins are related to particular genes in the HLA region, and that presentation of penicillin-hapten determinants to lymphocytes is major histocompatibility restricted. The lymphocyte transformation test, an *in vitro* test, has been used as part of the diagnostic work-up in patients with possible delayed drug allergies [48–50]. An enhanced proliferative response of an individual's peripheral blood lymphocytes in the presence of the suspected drug is considered a sign of drug-specific, T-cell sensitization. Patch testing and delayed (>6 hours after administration) intradermal skin tests have also been proposed as diagnostic tools to identify offending drugs in delayed hypersensitivity reactions [51–54].

In a study performed by Romano et al [54] to evaluate the diagnostic value of delayed skin tests and patch tests, 193 adults with a history of nonimmediate cutaneous eruptions to penicillin or its derivatives underwent prick and intradermal skin tests, patch tests, radioallergosorbent tests (RASTs), and oral challenges. Agents used for the prick and intradermal tests included penicilloyl-polylysine, benzylpenicillin, ampicillin, amoxicillin, and a minor determinant mixture (MDM) consisting of benzylpenicillin and benzylpenicilloate. If the prick test was negative at 20 minutes, intradermal skin tests using 0.02 mL were performed and read at 20 minutes and 48 hours. Patch testing was administered to individuals who experienced nonimmediate reactions with benzylpenicillin, ampicillin, and amoxicillin. Of 119 subjects with either maculopapular rashes or erythematous reactions to aminopenicillins, 62 (52%) demonstrated delayed hypersensitivity as indicated by positive patch or delayed reading intradermal test responses. Most of these individuals had positive results with both tests. Some subjects who had negative patch test responses had positive delayed intradermal tests, suggesting that intradermal testing may be more sensitive.

Most delayed hypersensitivity reactions can be identified through patch or delayed reading intradermal skin tests. Occasionally, the exanthema can be associated with a delayed positive prick test. Ortiz-Frutos et al [55] described a patient in whom an erythematous nodule developed that persisted for a month after the patient was intradermally tested to penicillin. The patient presented 25 years later for further evaluation. Prick and intradermal tests showed no reaction 15 minutes later, but by 36 hours, papuloerythematous lesions appeared at the site of prick tests to benzylpenicillin, ampicillin, and amoxicillin. These lesions lasted approximately 6 days, and biopsy revealed dermal edema with massive eosinophilic infiltration consistent with an allergic response. Delayed reading intradermal and patch testing were also positive in this patient.

Although delayed hypersensitivity reactions to aminopenicillins, mostly in the form of maculopapular rashes, have been identified, Dolovich et al [56] described an isolated late cutaneous skin test response to ampicillin that started and ended earlier than would be expected for a classic delayed hypersensitivity reaction. A woman received intramuscular and oral ampicillin for treatment of a fever. Two days later, she had a diffuse erythematous papular rash, and ampicillin was stopped. The rash resolved after approximately 2 weeks. The patient recalled a similar rash after receiving ampicillin when she had infectious mononucleosis.

Prick and intradermal skin tests to benzylpenicillin, ampicillin, cephalothin, and penicilloyl-polylysine were all negative at 15 minutes. Two hours later, a pruritic erythematous indurated area developed at the site of the intradermal ampicillin skin tests. The reaction site became less erythematous within 24 hours and completely resolved after 2 days. Serum tests for IgE and IgG antibodies to ampicillin were negative. An intradermal ampicillin skin test was repeated 3 months later; there was no detectable reaction after 15 minutes, but a large erythematous wheal developed within 2 hours. A skin biopsy specimen was obtained 6 hours after the intradermal skin test was placed. No IgG, IgA, IgM, or complement deposition was observed. The tissue was infiltrated primarily with mononuclear cells and some neutrophils. There was no increase in eosinophils, basophils, or mast cells to suggest an allergic reaction. The pathology indicates this was not an Arthus-type reaction, but little is known about the mechanism or incidence of this late cutaneous response. Could the positive skin tests have been a delayed hypersensitivity reaction that occurred earlier than usual?

Another unusual nonimmediate reaction caused by penicillins is a fixed allergic reaction at the site of a pre-existing dermatophyte infection. Dennison et al [48] described a patient with a history of chronic fungal infections of the groin and interdigital spaces of the toes who received phenoxymethylpenicillin followed by penicillin G for pneumonia. Two days after penicillin therapy was initiated, an erythematous macular eruption developed that was localized to the groin. Despite the rash, penicillin treatment was continued. The eruption reached maximum intensity on the third day but never extended beyond the initial borders. The patient recalled having a similar reaction when he last received penicillin. As was true for the most recent presentation, the previous reaction appeared shortly after treatment when penicillin was started, but did not extend beyond its original borders, and faded once penicillin was discontinued. Scrapings of the groin area revealed hyphae.

Intradermal tests were performed using 0.1 mL of penicillin G and penicilloyl-polylysine. There were no reactions when tests were performed on the forearm, but both responses were positive in the groin area, suggesting hypersensitivity localized to the area. The responses peaked at 24 hours and faded by 48 hours. Testing for trichophytin (the antigenic factor of fungi) showed the classic delayed response at 48 hours in the forearm and groin. The mechanism by which some individuals with a history of dermatophyte infection develop penicillin hypersensitivity and a positive trichophytin test has to do with the capacity of dermatophytes to produce small amounts of penicillin. In theory, any patient who sustains a superficial fungal infection risks becoming sensitized to penicillin; however, this is uncommon.

Although maculopapular rashes are the most common delayed hypersensitivity reaction to semisynthetic penicillins, other more severe responses have been documented. Romano et al [49] described two cases of toxic epidermal necrolysis caused by delayed hypersensitivity to aminopenicillins. The first patient developed erythema of the lower limbs after receiving an intramuscular injection of ampicillin. As treatment continued, the reaction progressed to toxic epidermal

necrolysis and was associated with fever and eosinophilic leukocytosis. In the second case, the patient developed a diffuse maculopapular rash that advanced to toxic epidermal necrolysis following oral amoxicillin therapy. Symptoms in both individuals resolved after steroid administration. Skin prick tests to penicilloyl polylysine, MDM, penicillin, amoxicillin, and ampicillin were negative in both subjects. Intradermal skin tests to penicillin, amoxicillin, and ampicillin were positive after 6 hours. Patch tests were positive after 48 to 72 hours (for amoxicillin, ampicillin, and penicillin in the first case, and for amoxicillin and ampicillin in the second).

Tagami et al [50] reported on another patient with drug-induced toxic epidermal necrolysis caused by delayed hypersensitivity to ampicillin. Upon recovery from severe toxic epidermal necrolysis, the patient had positive late intradermal and patch tests to ampicillin. A lymphocyte transformation test was positive for ampicillin.

Another rare delayed response to penicillin derivatives is interstitial nephritis. In one of the early reports, Border et al [57] described a patient who experienced severe renal failure while receiving methicillin. Evaluation of the patient's serum identified antitubular basement membrane antibodies as detected by indirect immunofluorescence. A methicillin antigen assumed to be dimethoxyphenyl penicilloyl (DPO) was found in a linear pattern along the tubular basement membrane, as was IgG and C3. It was suggested that the DPO tubular basement membrane "hapten-protein conjugate" led to an immune response that was manifested as interstitial nephritis. Although this was a delayed reaction in time, the mechanism was most likely direct antibody toxicity with complement.

A recent publication by Pichler [58] discusses the cellular mechanisms associated with delayed hypersensitivity reactions. This review is not specific for penicillin drugs but presents new concepts of the role T cells have in delayed drug hypersensitivity reactions. Delayed hypersensitivity is thought to be a mechanism for some penicillin reactions, including various exanthemas and toxic epidermal necrolysis; however, no definitive routine diagnostic tools are available to evaluate the possibility of such a reaction. Delayed reading intradermal skin tests are not standardized, and in vitro tests are done for research purposes only. Currently, any testing for delayed hypersensitivity remains experimental.

Practical advice for physicians faced with a patient who gives a history of penicillin allergy and who needs a penicillin or beta-lactam drug

The following recommendations can be made when a patient with a history of penicillin allergy requires a penicillin or beta-lactam drug:

Take a careful history. Questions that should be asked include the following: When did the reaction to penicillin occur, and to what specific antibiotic if known? What kind of reaction occurred if known? Has the patient had any experience with beta-lactam antibiotics subsequent to the reaction? The

longer the reaction from the time the physician sees the patient, the less likely he or she is to still be allergic. Some of these patients may have taken a beta-lactam antibiotic without difficulty since their original reaction. Sometimes, reviewing the patient's chart gives that information. The patient might have been given a cephalosporin drug for preoperative prophylaxis and may not know it. Skin testing to penicillin would not be helpful in a patient who has a non-IgE reaction. If there is a history suggestive of an exfoliative dermatitis, Stevens-Johnson syndrome with mucosal blisters or ulcerations, hepatitis, or nephritis, the patient should not be tested or treated with penicillin; however, data to support this latter generally recognized recommendation are lacking. If necessary, one should determine whether the patient needs a penicillin or beta-lactam drug. If the patient gives a history of exquisite sensitivity, skin testing should not be done or should be performed only with diluted reagents.

- Perform skin tests to penicillin if they are available. When possible, patients should be referred to an allergy specialist for penicillin skin testing. Prick tests should always be done first, followed by intradermal tests if negative. If the skin tests to major and minor determinants are negative, the risk of a reaction to penicillin or one of the cephalosporin drugs is low but not zero. Consider giving a graded challenge or small test dose first, observing the patient for 30 to 60 minutes, and then proceeding with a full dose and observing for another 60 minutes. This strategy might provide added safety.
- If skin tests are not available, one could assay IgE antibodies. In the United States, such tests are only available for the major determinants of penicillin G, penicillin V, amoxicillin, and ampicillin (ImmunoCAP). Positive tests provide helpful information. The authors are not familiar with any large studies on the predictive value of IgE antibodies. One should remember that these assays test for the major determinants and not any of the minor determinants. If these tests are negative, the minor determinants have not been tested for, and skin testing is advisable.
- If skin testing is not available, and if the reaction to penicillin was mild and happened years ago, using a cephalosporin drug, if indicated, would likely be of lower risk than using a penicillin drug. Again, one should give a small test dose under medical supervision. If no reaction occurs after 30 to 45 minutes, a strategy of proceeding with a full dose and continuing observation for 60 minutes might provide additional safety.
- If the patient has positive skin tests, or a history of a more severe reaction to penicillin and skin tests are not available, desensitization could be considered.

For all of these patients, the physician should be prepared to treat an acute anaphylactic reaction and have the appropriate equipment available should this occur. Informed consent should be obtained for any or all of the previous recommendations. The discussion with the patient and the risks should be documented in the patient's record.

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