REVIEW

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Penicillin allergy: Consider trying penicillin again

ABSTRACT

A history of allergy to penicillin does not necessarily rule out using penicillin again. With skin testing and, in some cases, desensitization, most patients with a history of penicillin allergy can safely receive the drug.

KEY POINTS

IgE-mediated penicillin reactions can be identified by skin testing with benzylpenicilloyl-polysine (Pre-Pen) and penicillin G. This test can help determine whether a patient with a history of penicillin allergy can safely use penicillin or a penicillin derivative, or whether penicillin is best avoided.

The risk of allergic reactions to cephalosporins is increased in patients with a history of penicillin allergy, especially in those with a positive penicillin skin test.

Skin testing can reduce unnecessary use of vancomycin and fluoroquinolones, helping to forestall the emergence of microorganisms that are resistant to multiple drugs.

YOUR PATIENT needs penicillin, but a red sticker on her chart declares that she is allergic to it. Must an alternative drug such as vancomycin be used instead?

Perhaps not. When we think of penicillin allergy, we worry most about the worst-case scenario: anaphylaxis and death. Indeed, penicillin is the most common cause of drug-induced anaphylaxis and drug-induced allergic reactions in general,[1] causing an estimated 75% of all anaphylactic deaths in the United States[2]: 500 to 1,000 deaths each year.[3]

Yet penicillin is one of the most useful antimicrobial drugs. It is highly effective and generally not toxic.[4] With skin testing we can determine if a patient with a history of penicillin allergy is among the minority at risk of a serious reaction if he or she receives it again, and even many who test positive can safely receive penicillin after undergoing desensitization.

In this article we review the allergic reactions to penicillin, the molecular basis of penicillin reactions, and the diagnosis and management of patients with a history of penicillin allergy. We conclude by discussing how penicillin skin testing might help in decreasing the emergence of multidrug-resistant microorganisms.

ADVERSE DRUG REACTIONS

Adverse drug reactions can be divided into those that are predictable and those that are not.

Predictable reactions

Predictable reactions are dose-dependent and are related to the pharmacology of the drug. Types of predictable reactions include overdos-

TABLE 1

Immunologic mechanisms of penicillin reactions

IgE-mediated (type 1)
- Asthma
- Urticaria
- Angioedema
- Anaphylaxis*

Not IgE-mediated
- Antibody-mediated (cytotoxic, or type 2)
  - Hemolytic anemia
  - Thrombocytopenia
- Immune complex-mediated (type 3)
  - Serum sickness
  - Vasculitis
- T lymphocyte-mediated (type 4)
  - Contact dermatitis
  - Morbilliform rash (possibly)

*Symptoms of anaphylaxis: urticaria, angioedema, generalized pruritus, flushing, wheezing, bronchospasm, laryngeal edema, tachycardia, arrhythmias, nausea, vomiting, diarrhea, abdominal pain, headache, seizures, uterine contractions

Penicillin anaphylaxis causes 500–1,000 deaths each year

es, side effects, secondary or indirect effects, secondary effects related to the underlying disease, and drug interactions.[5,6]

Unpredictable reactions

Unpredictable reactions occur in only a small subset of patients and are not related to the pharmacology of the drug. These reactions include allergic reactions, drug intolerance, idiosyncratic reactions, and pseudoallergic reactions.[5,6]

Allergic reactions are exaggerated immunologic reactions to an otherwise innocuous nonself molecule,[7] and can be classified as immediate, accelerated, or late.

Immediate reactions, such as anaphylaxis, usually occur within 1 hour of receiving the drug. Anaphylaxis is an acute systemic reaction that results from the IgE-mediated release of chemical mediators from mast cells and basophils. Urticaria and angioedema are the most common clinical manifestations; others are listed in TABLE 1. These clinical manifestations can occur singly or in various combinations.[2]

Accelerated reactions occur 1 to 72 hours after receiving the drug and include urticaria and maculopapular rashes.

Late reactions occur after 72 hours. Common manifestations are skin rashes, erythema multiforme, serum sickness, and hemolytic anemia.[7]

Allergic reactions are also classified by immunologic mechanisms

According to Gell and Coombs, these mechanisms are:
- Type 1: IgE-mediated
- Type 2: Antibody-mediated
- Type 3: Immune complex-mediated
- Type 4: T lymphocyte-mediated.[6]

ALLERGIC REACTIONS TO PENICILLIN

Penicillin can cause all four types of immunologic reactions proposed by Gell and Coombs (TABLE 1).[8,9] Although more than one immunologic mechanism may be involved in a reaction, one usually predominates.[8]

Allergic reactions are estimated to occur in approximately 2% of patients treated with penicillin.[5] Most of these are maculopapular or urticarial rashes. Severe allergic reactions to penicillin such as anaphylaxis are less common,[5] but are potentially life-threatening. Fortunately, fewer than 10% of these reactions are fatal.[10]

STRUCTURE OF PENICILLIN: MAJOR AND MINOR DETERMINANTS IN REACTIONS

Penicillin belongs to the beta-lactam group of antibiotics. All penicillin antibiotics contain a common nucleus (6-aminopenicillanic acid) composed of a beta-lactam ring and a thiazolidine ring; this complex is connected to a side chain (FIGURE 1). An intact beta-lactam ring is necessary for bacteriocidal activity, and the side chain determines the spectrum of antibacterial activity, the susceptibility to destruction when exposed to acids and beta-lactamases, and pharmacokinetic properties.[4]

Major determinants. Penicillin is a hapten, ie, it has a low molecular weight (300 d) and becomes immunogenic only when it binds to a tissue macromolecule, usually a protein.[11]

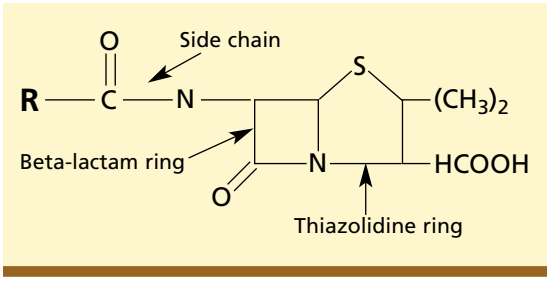

FIGURE 1. Chemical structure of penicillin

The beta-lactam ring of penicillin covalently binds to the lysine residues of proteins and forms the penicilloyl group, known as the *major determinant* because it is the major penicillin metabolic product, accounting for approximately 85%–90% of the penicillin breakdown products.[12]

Minor determinants. Penicillin metabolites also form disulfide bonds with sulfhydryl groups of cysteine, producing the *minor determinants*, so called because they are formed in smaller quantities.[12] The minor determinants are composed of the parent penicillin molecules, penicilloate, penicilloylamine, penilloate, and other simple chemical products of penicillin.[11]

Immediate allergic reactions to penicillin are mediated through IgE antibodies against either the major or minor determinants or both. Late reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, are usually not IgE-mediated and involve other immunologic mechanisms.[11]

RISK FACTORS FOR IgE REACTIONS

Specific risk factors have been identified for IgE-mediated reactions.

Multiple short courses of penicillin, via any route of administration, increase the risk of sensitization.[11] However, parenteral and topical administration are more likely to induce sensitization than oral administration.[13] Topical drug exposure can cause delayed hypersensitivity reactions.[14]

Allergic diseases (allergic rhinitis, allergic asthma, contact dermatitis) increase the risk that an immediate IgE-mediated reaction can be severe once an IgE antibody has developed to the drug.[13]

Age. Anaphylactic reactions most commonly develop between the ages of 20 and 49 years. However, they have also been reported in children and in the elderly.

Factors that do not appear to increase the risk of reactions are race, gender, personal or family history of atopic disease, allergy to other drugs, and allergy to the mold *Penicillium*.[11]

TABLE 2

Penicillin skin test reagents*

Benzylpenicilloyl-polylysine (Pre-Pen full strength)†
Penicillin G (10,000 U/mL)
Penicillin minor determinants (mixture, 10–2 M‡)
Ampicillin (1–3 mg/mL)
Amoxicillin (1–3 mg/mL)
Cephalosporin (1–3 mg/mL)
Saline solution (negative control)
Histamine (positive control)

*One drop of each reagent is used for the prick tests; 0.02 mL is used for the intradermal tests.
†Penicillin G concentration of 10,000 U/mL needs to be prepared daily.
‡Penicillin minor determinant mixtures are available only at some research centers. Ideal concentration for skin test may vary.

PENICILLIN SKIN TESTING

Skin testing demonstrates the presence or absence of specific IgE antibodies against major and minor penicillin determinants.

IgE antibodies against major determinants can be tested by using benzylpenicilloyl-polysine (Pre-Pen, Kremers Urban, Milwaukee, Wis). Reagents for minor determinants are not commercially available, but methods of preparation have been published.[15,16] Most clinicians use penicillin G at a concentration of 10,000 U/mL as a partial source of minor determinants.[11] The use of aged penicillin as a source of minor determinants is not recommended.[5,15]

Histamine is used as a positive control, and saline is used as a negative control.

Prick (epicutaneous) testing is done first, and results are read 15 to 20 minutes later. If the prick tests are negative, intradermal testing follows (TABLE 2).

Skin testing will not detect non-IgE reactions

Interpreting the results

The skin test is positive if the major or minor determinant produces a wheal larger than 3 mm compared with the negative saline control.

Although a response to the minor determinants has been associated with an increased risk of more severe reactions, patients who test positive to any of the reagents should be considered at high risk for penicillin-induced anaphylaxis.[17]

Using major determinants and a mixture of minor determinants, 99% of patients who test negative will tolerate penicillin. Using benzyl penicilloyl and penicillin G (as a source of minor determinants), approximately 97% of patients who test negative will tolerate penicillin.[2] However, a small percentage of patients at risk for anaphylactic reaction will be missed with this testing method.[2]

Of patients with a negative skin test to the major and minor determinants, 1% to 4% will develop non-life-threatening allergic reactions if they receive penicillin.[18] Severe allergic reactions to penicillin, such as anaphylaxis, in patients who test negative have not been reported.[8] Some authorities believe that penicillin skin testing with benzyl penicilloyl and penicillin G has a lower sensitivity (90%–95%) for detection of IgE antibodies to penicillin because penicillin G does not contain all the minor determinants.[19]

Skin testing is safe if done properly

Conversely, if a patient has a history of penicillin allergy and a positive skin test, he or she has at least a 50% chance of an immediate reaction if penicillin is given again. These patients should receive an alternative antibiotic or be desensitized.[2]

After an allergic reaction, the chance of having a positive response on skin testing diminishes with time. In one study,[20] the response rate decreased by 10% per year. Therefore, an estimated 50% of patients who had immediate reactions to penicillin will have a negative skin test after 5 years, and 75% to 80% will be negative at 10 years. However, some authors suggest that these patients face a higher risk of sensitization if they receive penicillin again compared with the rest of the population.[21]

After an episode of anaphylaxis from penicillin, the skin test may give false-negative results for 1 to 2 weeks or longer.[2] This point is pertinent in patients who were taking multiple drugs at the time of the anaphylactic episode, in whom the offending agent may not be obvious.

The skin test does not predict reactions caused by other immune mechanisms, such as cytotoxic antibody-mediated reactions, antibody-antigen immune-complex-mediated reactions, or delayed-type cell-mediated reactions. It determines only the presence of specific IgE antibodies to penicillin.[13]

Safety of penicillin skin testing

Skin testing is safe if done properly; the rate of systemic reactions is less than 1%,[22] although serious reactions, including anaphylaxis and death, have been reported. Severe reactions to penicillin skin testing are usually caused by violations of the test protocols, such as giving doses higher than recommended or doing intracutaneous testing without first doing prick or puncture testing.[23]

Skin testing is not recommended for a patient with a history of exfoliative dermatitis (Stevens-Johnson syndrome, or toxic epidermal necrolysis) from penicillin or any other beta-lactam antibiotic.[2]

RAST and ELISA testing

The radioallergosorbent test (RAST) and the enzyme-linked immunosorbent assay (ELISA) detect IgE antibodies to the major penicillin determinant only, with a sensitivity of approximately 80%.[24]

Therefore, RAST or ELISA testing does not reliably rule out allergy to penicillin.[2,11,13] However, a positive RAST indicates the presence of IgE antibodies to penicillin, and patients with a positive test should be considered at increased risk for allergic reactions.[18]

EVALUATION AND MANAGEMENT OF PENICILLIN ALLERGY

Patients with a history of penicillin allergy are more likely to experience a reaction to penicillin on subsequent courses than are those without a history.[21] However, 80% of these patients do not have penicillin-specific IgE antibodies as detected by skin testing and can safely take penicillin.

TABLE 3

Intravenous protocol for penicillin desensitization

STEP*	SOLUTION (U/mL)†	DOSE (mL)	DOSE (U)
1	100	0.1	10
2	100	0.2	20
3	100	0.4	40
4	100	0.8	80
5	1,000	0.15	150
6	1,000	0.30	300
7	1,000	0.60	600
8	1,000	1.00	1,000
9	10,000	0.2	2,000
10	10,000	0.4	4,000
11	10,000	0.8	8,000
12	100,000	0.15	15,000
13	100,000	0.30	30,000
14	100,000	0.60	60,000
15	100,000	1.00	100,000
16	200,000	25	200,000
17	400,000	25	400,000
18	800,000	25	800,000
19	1,600,000	25	1,600,000
20	3,200,000	25	3,200,000
21	5,000,000	25	5,000,000

*Each step is administered at 15-minute intervals
†Use penicillin G for dilutions in 0.9% sodium chloride

Nevertheless, any patient with a history of penicillin allergy—either vague (maculopapular rash, isolated gastrointestinal symptoms, unknown details) or convincing (anaphylaxis, angioedema, urticaria, bronchospasm)—who requires penicillin needs a skin test before he or she receives the drug.[2] Up to 33% of patients with a vague history of penicillin allergy will test positive.[25]

Skin testing should preferably be done in a hospital and shortly before the penicillin is to be given.[13] Some researchers recommend waiting no longer than 72 hours after a negative skin test before giving penicillin, because of the theoretical concern of sensitization from environmental penicillin products (such as food items) or from the minute amounts of penicillin G introduced during skin test.[15]

However, from a practical point of view, in some situations the test can be done on an outpatient basis, eg, in a patient with cardiac valve disease who needs prophylactic antibiotics before a dental procedure.[13]

Reported allergic reactions that occurred when penicillin was reintroduced to patients with a positive history and a negative skin test have all been mild and self-limited; no life-threatening false-negative reactions have been documented.[26]

On the other hand, a patient who had an allergic reaction to penicillin and a positive skin test reaction to either a major or minor determinant should receive an alternate antibiotic. If penicillin is essential, desensitization is required.[2]

Test-dose challenge

Because no complete mixture of minor determinants is commercially available, some authorities recommend giving a test-dose challenge if the patient has a convincing history of severe IgE-mediated reaction to penicillin (anaphylaxis) and negative skin tests using major determinant and penicillin G.[8]

A test-dose challenge might be done using 1/100 of the therapeutic dose (or 1/1000 of the therapeutic dose if the previous reactions was severe), followed by 1/10 of the dose and then the full therapeutic dose if there is no reaction.[8]

If a reaction occurs during the test-dose challenge but the patient absolutely needs penicillin and no acceptable alternative antibiotic is available, then penicillin desensitization is recommended.[8]

Desensitization

In desensitization, we give increasing amounts of a drug to a patient who has or is believed to have IgE antibodies to it.[1] Desensitization is believed to work by making mast cells unresponsive to the specific antigen used, in this case penicillin.[27] However, the specific mechanism is still unresolved.

Protocols for penicillin desensitization have been published (**TABLE 3**).[8,28–32] Oral desensitization is apparently safer than parenteral desensitization,[26] though the basic principle is similar for either method. The starting dose is very small, usually 1/10,000 of the recommended dose. The dose is usually

doubled every 15 minutes until the full therapeutic dose is achieved.[2]

Mild reactions such as pruritus, rhinitis, wheezing, or urticaria occur in 30% to 80% of patients during and after the procedure.[1,26] These reactions require symptomatic treatment, and the dose of penicillin is repeated until it is tolerated. Severe reactions such as laryngeal edema may require epinephrine, diphenhydramine, and even intubation until the patient is stable. If penicillin desensitization is absolutely necessary, the next dose of penicillin should be reduced by one third or more of the previous provoking dose.[8]

When desensitization is achieved, continuous treatment with penicillin is required to avoid the return of the IgE-sensitive state. A delay of more than 12 hours may allow such sensitivity to return, and desensitization should be repeated if penicillin is still needed.[8]

Desensitization does not prevent non-IgE-mediated immune reactions such as serum sickness or hemolytic anemia.[1] Penicillin desensitization should be done in a hospital, with intravenous access, resuscitative equipment available, and a physician experienced in the procedure available at all times.

Repeat skin testing after penicillin treatment

Repeat skin testing is recommended before subsequent courses of beta-lactam antibiotics, even after a patient has tolerated a course of penicillin, with or without desensitization.[8]

Parker et al[33] reported that, of 18 hospitalized patients who had a history of penicillin reaction, had negative penicillin skin tests, and had successfully completed penicillin treatment, 3 (16%) had a conversion to a positive penicillin skin test when retested after their penicillin treatment.

Solensky et al[34] reported that 46 outpatients with a history of penicillin allergy and negative penicillin skin tests were given three 10-day courses of oral penicillin V, with each course followed by a repeat penicillin skin test, and no patients became resensitized.

This well-designed study suggests that adult patients with a history of penicillin allergy and an initial negative penicillin skin test are not at risk for resensitization to penicillin with subsequent courses of oral penicillin. It is important to recognize that this study used penicillin G and penicilloic acid (one penicillin minor determinant) for testing and that the penicillin challenge was oral.

The rate of resensitization to semisynthetic penicillins given parenterally has not been studied in patients with a past history of penicillin allergy with initial negative penicillin skin tests.

Morbilliform rashes due to ampicillin or amoxicillin do not require skin testing because the immunologic mechanism is not thought to be IgE-mediated.[11] However, if the rash is urticarial, the patient should undergo testing before receiving another course of penicillin.[2] Amoxicillin or ampicillin skin tests, although not well standardized, can be included in these patients because some may have a positive skin test reaction to ampicillin or amoxicillin but no test reaction to penicillin, implying the presence of IgE antibodies specific to the side chains in these compounds.[35]

CROSS-REACTIVITY WITH OTHER BETA-LACTAMS

In vitro studies have shown allergic cross-reactivity between penicillins and cephalosporins, which also share a common beta-lactam ring. Cross-reactivity in clinical practice appears less common.[36] Nevertheless, severe allergic reactions, including deaths, have occurred when a cephalosporin was given to penicillin-allergic patients.[1]

After desensitization, start penicillin within 12 hours

The exact mechanism of cross-reactivity between penicillin and other beta-lactam antibiotics remains unresolved. The specific haptens involved in allergic reactions to cephalosporins are still unknown, and both chain and nuclear components may participate in the development of hypersensitivity reactions.[37]

Before 1980, cross-reactivity between penicillin and cephalosporins was estimated to occur in approximately 10% to 20% of patients. Since then, the rate has decreased to 2%.[13] The decrease may be due to less contamination of cephalosporin preparations with trace amounts of penicillin, and less frequent use of cephalothin and cephaloridine, both of which share a similar side chain with benzyl penicillin.[13] Cross-reactivity between peni-

cillin and second-generation and third-generation cephalosporins appears to be less common than with first-generation cephalosporins.[36]

Of importance: the risk of allergic reactions to cephalosporins is increased in patients with a history of penicillin allergy, especially in those with a positive penicillin skin test as compared with those with a negative penicillin skin test.

Kelkar et al[37] recently reviewed 11 studies and concluded that approximately 4.4% of patients with positive penicillin skin tests would be at increased risk for reaction if they received a cephalosporin. Patients who had a history of penicillin reaction but negative penicillin skin tests were at a much lower risk. Therefore, penicillin skin tests are helpful in determining patients who are at risk for a reaction to cephalosporin, if there is a history of penicillin reaction.[37]

Reactions to cephalosporin may still occur despite negative penicillin skin tests, because IgE antibodies may be directed to side-chain structures rather than to the beta-lactam ring.[38,39] In this situation a penicillin skin test will be negative. Unfortunately, cephalosporin skin testing has limited benefit because it is not well studied and the predictive value of this test is unknown.[36,37]

Carbapenems (eg, imipenem) should be considered cross-reactive to penicillin.[2,13] On the other hand, aztreonam, a monobactam, rarely cross-reacts with penicillin, possibly because it does not have a second nuclear ring structure.[2,13]

FORESTALLING RESISTANCE TO VANCOMYCIN, QUINOLONES

Penicillin skin testing can be used to decrease the use of broad-spectrum antibiotics such as vancomycin and fluoroquinolones.

A history of penicillin allergy alone is not reliable in predicting immediate allergic reactions to the drug.[21] As discussed above, most patients lose their IgE-mediated sensitivity over time and can safely receive penicillin antibiotics. Penicillin skin testing identifies the presence or absence of IgE antibodies to penicillin, information that will allow the physician to determine if penicillin or an alternative antibiotic should be given.

Patients with history of penicillin allergy are usually given an alternative antibiotic such as vancomycin or a fluoroquinolone.[40] Excessive use of these antibiotics is associated with emergence of pathogens that are resistant to multiple drugs.[41–45] The development of these pathogens causes infections that are associated with higher rates of morbidity and mortality.

Prescribing alternative antibiotics not only increases the risk of infections with multidrug-resistant pathogens but also increases the risk of treatment failure due to suboptimal therapy.[40] Lee et al[40] analyzed the antimicrobial therapy prescribed to patients with specific antimicrobial allergies. Patients who were labeled allergic to penicillin or cephalosporin were more likely as a group to have received vancomycin (39.7%) compared with those who did not report any antimicrobial allergy (17.4%). Levofloxacin was also prescribed more commonly in patients labeled allergic to penicillin or cephalosporins than in patients who did not report any allergies (21% vs 8.0%).

A person with a history of penicillin allergy and a negative penicillin skin test can use a penicillin compound. The appreciation of this clinical concept has the potential to reduce the use of certain broad-spectrum antibiotics and to decrease the emergence of resistant microorganisms.[41]

Our group found that intensive care physicians changed their antibiotic coverage to a penicillin in 48% of cases after penicillin skin tests were negative.[46] There were no adverse events during the testing or during the penicillin administration.

Li et al[47] recently reported a decrease in vancomycin use for prophylaxis as a result of a negative penicillin skin test in orthopedic patients with a history of penicillin allergy undergoing elective orthopedic surgery.

Allergic reaction to a cephalosporin is more likely if the patient has history of penicillin allergy

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