

Proving penicillin allergy

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Preview

Allergic reactions to penicillin are usually short-lived and reversible, but they can be fatal. What causes these reactions? Can they be avoided? How is the risk of penicillin allergy evaluated? Drs Erffmeyer and Blaiss describe the full spectrum of allergic, immune, and nonimmune reactions to penicillin and discuss how to assess and treat patients with suspected penicillin allergy.

Penicillin, semisynthetic penicillins, and cephalosporins are among the most commonly prescribed medications worldwide. These drugs all share a common beta-lactam ring, which is an integral component of the molecular nucleus. Despite the continued introduction of new pharmacologic agents in the United States, penicillin remains the most common drug to cause allergic reactions in humans.

Although the precise prevalence of allergic reactions to the penicillins is unknown, estimates range from 1% to 10% of all patients treated.¹ The majority of such adverse reactions are dermatologic.

Penicillin is one of the most common causes of anaphylaxis, with a reported frequency of 1 to 5 reactions per 10,000 patient courses of treatment.² According to a 1979 report by the National Institute of Allergy and Infectious Diseases Task Force,³ penicillin-induced anaphylaxis may cause as many as 400 to 800 deaths per

year in the United States. About 75% of patients who die from anaphylaxis following penicillin administration have no history of allergic reactions to penicillin.

Risk factors

Sensitization to penicillin can occur with any route of administration, but especially with the topical route. Multiple short courses of therapy are the most likely to result in sensitization.⁴ Once a person is sensitized, exposure to penicillin by any route may provoke an allergic response. However, reactions are more frequent and severe when the drug has been given parenterally.

The interval between the original anaphylactic episode and readministration of penicillin is also an important factor. The risk of a subsequent episode decreases as the interval between the original attack and readministration increases.

Anaphylactic reactions to penicillin occur most commonly in persons between 18 and 40 years of age; however, neither extreme of the age spectrum is exempt.⁵ Race, sex, a personal or family history of

atopic disease, and allergy to other drugs do not appear to be predisposing factors. Thus, a person is not predisposed to penicillin allergy merely because a family member has such an allergy. Most deaths from penicillin-induced anaphylaxis have occurred in persons with no history of penicillin allergy. Persons allergic to the mold *Penicillium* are not at increased risk for an allergic reaction to penicillin.⁵

Types of reactions

Immediate allergic reactions following penicillin administration are mediated through IgE antibodies against the major or minor determinants (see box on page 34). Such reactions usually occur within 30 minutes of drug administration. The reactions may be strictly cutaneous, such as urticaria, or may be systemic, such as urticaria with laryngeal edema, wheezing, and hypotension. *Unusual reactions that are not immediate but occur within 72 hours of penicillin administration have been termed accelerated reactions; these reactions may also be IgE mediated.* Immediate systemic reactions have been attributed primarily to IgE antibodies directed against the minor determinants. IgE of major-determinant specificity has been linked to an increased risk of an accelerated reaction. However, even persons who possess IgE antipenicillin anti-

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Richard D. deShazo, MD, was the Editorial Board coordinator for this article.

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Penicillin allergy: How it happens

Penicillin is a hapten, a low-molecular-weight (300-d) compound, which by itself cannot elicit an immunologic response. It must first bind to a tissue macromolecule, usually protein, to form a complete antigen.¹ The beta-lactam ring of penicillin and its metabolites readily binds to tissue macromolecules, which explains why the incidence of immune reactions is higher for penicillin than for other drugs.

The major penicillin metabolic product, referred to as the major determinant, is the penicilloyl group,⁸ which makes up about 85% of penicillin breakdown products. The majority of antibodies formed in penicillin allergy are specific for the penicilloyl group.

A small amount of penicillin (5% or less) is metabolized by several other pathways. The fact that these metabolites are formed in such small quantities has led to their designation as the minor haptenic determinants, or the "minor determinants."⁸ The minor determinants are composed of the parent penicillin molecule, penicilloate, penicillamine, penilloate, and other simple chemical products of penicillin degradation.

bodies directed only against the major determinant have experienced anaphylaxis after receiving penicillin.

Most reactions to penicillin are not IgE-mediated and tend to occur 72 hours or more after initial therapy. Many of these reactions involve other types of immunologic mechanisms.⁶ Cytotoxic reactions involve IgG or IgM antibodies to penicillin antigens on tissue cell membranes and interaction with serum complement. These reactions (eg, penicillin-induced hemolytic anemia) can lead to cell damage. Immune complex reac-

tions are due to soluble complexes of penicillin with IgG or IgM that bind to blood vessel walls and trigger the complement cascade. Serum sickness is an example of this type of immune reaction. Cell-mediated reactions to penicillin, such as contact dermatitis, require activated T cells that recognize penicillin or its metabolites as foreign and release lymphokines that induce an inflammatory response. Less well defined from a precise pathophysiologic basis are penicillin-induced reactions such as leukopenia, neutropenia, thrombocytopenia, acute interstitial nephritis, drug fever,

and a wide variety of nonurticarial cutaneous disorders.

The incidence of maculopapular rash is higher with ampicillin therapy (5% to 10%) than with the other penicillins (2%).¹ Patients who have infectious mononucleosis, cytomegalovirus infection, or lymphocytic leukemia or who require allopurinol (Lopurin, Zyloprim) therapy are at increased risk for a rash if they receive concomitant ampicillin therapy. The cause of maculopapular rash is unknown but does not appear to be IgE-mediated. Therefore, a maculopapular rash does not carry the risk of severe allergic reaction on reexposure to ampicillin, as does a previous urticarial reaction to ampicillin.⁶

Patient evaluation

When patient history suggests the likelihood of a penicillin hypersensitivity reaction in a patient who needs penicillin therapy, it is useful to assess the risk of a potentially serious allergic reaction to penicillin. Allergy skin testing has stood the test of time. However, skin testing for penicillin allergy only detects IgE-mediated reactions to penicillin and does not predict the possibility of hemolytic anemia, serum sickness, contact dermatitis, or nonimmune reaction.⁷

Skin tests to assess the presence of IgE antibodies to the major determinant, penicilloyl, can be done with benzylpenicilloyl-polylysine

When patient history suggests penicillin hypersensitivity, allergy skin testing is useful to assess the risk of a potentially serious allergic reaction to penicillin.

(Pre-Pen*). Standardized minor-determinant preparations will likely be available in the future. Many physicians use fresh penicillin G as a partial substitute for a minor-determinant mix for skin testing. Skin tests with benzylpenicilloyl-polylysine and penicillin G detect about 90% of potential reactors. With the addition of a minor-determinant mix, this figure approaches 100%.⁸

Skin tests are initially performed by the prick method. If prick tests are negative, intradermal tests are done (table 1). The tests should be performed by a physician who is knowledgeable in skin-testing techniques and in a setting where anaphylaxis can be treated. A histamine skin test is performed as a positive control and a saline skin test as a negative control. Penicillin allergy is present if a wheal and flare reaction larger than that of the negative control reaction occurs at any dilution of the penicillin reagents during prick or intradermal testing.⁷

The value of skin testing is readily apparent. A negative test indicates that the risk of an immediate or accelerated reaction is quite low, probably the same as or less than that in the general population. A positive skin test, with any reagent, indicates the presence

Table 1. Skin-testing protocol for penicillin allergy*

Method	Benzylpenicilloyl-polylysine (Pre-Pen) concentration	Penicillin G concentration (U/mL)
Skin prick (1 drop)	6×10^{-5} M	10
		1,000
		10,000
Intradermal (0.02 mL)	6×10^{-5} M	10
		1,000
		10,000

* Skin testing should be done in setting where anaphylaxis treatment is available. Patient should be observed for 15 min for reaction at test site before next highest concentration is administered.

Modified from Blaiss and deShazo.⁷

of IgE antibodies, which definitely increases the risk of an immediate or accelerated reaction.

In vitro assays, such as the radioallergosorbent test (RAST), can detect some, but not all, of the allergenic penicillin determinants.⁸ Also, the RAST is not as sensitive as skin testing in detecting allergy. This fact underscores the value of

penicillin skin testing in proving the presence or absence of penicillin allergy.

Routine skin-testing procedures with semisynthetic penicillins have not been perfected to the same degree as those with penicillin G. However, modified procedures can be performed. Some studies^{9,10} have demonstrated that when skin tests are performed with the actual drug to be used, the number of allergic patients detected increases.

Penicillin desensitization

If use of an alternative antibiotic is not possible in a patient with positive skin tests to penicillin reagents, or if penicillin skin testing was not available or not performed, penicillin can be administered via a formal desensitization protocol. Until

continued on page 39

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* Available from Schwarz Pharma, Kremers Urban Co, Milwaukee.

Radioallergosorbent testing is not as sensitive as skin testing in detecting penicillin allergy.

a standardized, commercially prepared minor determinant mix is available, penicillin also may be given to selected patients with negative skin tests by means of a modified procedure of gradual administration.²

Optimally, any desensitization procedure should be performed in a setting where anaphylactic reactions can be diagnosed and treated immediately. Many allergists place all patients in intensive care units for desensitization. A consent form indicating the risk of anaphylaxis must be signed by the patient or appropriate family members before desensitization. A physician must be in attendance throughout the procedure.

Various methods of desensitization have been developed, including oral, subcutaneous, intramuscular, and intravenous administration.⁸ The oral route of desensitization exploits the relative safety of this method of administering penicillin (table 2).¹¹

Regardless of the method of desensitization, the basic principles are similar.⁷ Initially, small doses of the drug are administered. The dose is usually doubled at 15-minute intervals. This process continues until a full therapeutic dose can be given. The patient is then observed for 30 minutes, after which treatment is begun with the therapeutic dose of penicillin needed. The protocol can be modified for

Table 2. Oral desensitization protocol for penicillin*

Dose	Penicillin V elixir (units)	
1	100	
2	200	
3	800	
4	1,600	
5	3,200	
6	6,400	
7	12,000	Observe patient for 15 min between each dose
8	24,000	
9	48,000	
10	80,000	
11	160,000	
12	320,000	
13	640,000	Observe patient for 30 min, then start full-dose parenteral penicillin

* Procedure should be performed in intensive care unit under strict observation.

From Wendel et al.¹¹

semisynthetic penicillins and cephalosporins.

In the vast majority of instances, penicillin desensitization can be done with little or no difficulty.² If a systemic allergic reaction occurs during desensitization, prompt treatment with epinephrine, antihistamines, corticosteroids, and other appropriate measures should be instituted, according to the situation. Once such a reaction has been successfully treated, the procedure may be resumed at one dose below the dose that caused the reaction.

Penicillin desensitization is not permanent. Therefore, any patient

who has undergone the procedure should have skin tests before receiving penicillin in the future.

Desensitization can only be used in situations where IgE-mediated mechanisms are thought to be involved in producing penicillin allergy. The procedure does not prevent non-IgE-mediated immune or other adverse reactions resulting from penicillin administration.

Cross-reactivity

The exact incidence of IgE-mediated reactions to cephalosporins in patients with penicillin allergy or a history of penicillin allergy has not been established. Although it may

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vary among individuals and may not be extensive, some degree of cross-reactivity between penicillins and cephalosporins does exist.⁸ Allergic reactions to first-generation cephalosporins in penicillin-allergic patients reportedly range from 5% to 16%.¹⁷ Few data are available about the cross-reactivity of penicillin with second- and third-generation cephalosporins. A recent review article¹³ suggested that the risk of reaction with use of a cephalosporin in patients suspected of having penicillin allergy may be about 2%. Nevertheless, cephalosporins cannot be considered a uniformly safe substitute for penicillin.

Precise determination of cephalosporin allergy would require the production of cephalosporin haptenic determinants and the development of reliable skin-test reagents. With use of penicillin skin tests to evaluate cephalosporin allergy, a positive test may place the patient at higher risk for a reaction to cephalosporin, but a negative test does not rule out a reaction to cephalosporin.^{7,13}

Aztreonam (Azactam), a monobactam, and imipenem-cilastatin (Primaxin), a carbapenem, represent two new classes of antibiotics that have become available for therapeutic use in recent years. Initial research indicates that aztreonam does not exhibit cross-reactivity with other bicyclic beta-lactam antibiotics.¹⁴ Consequently, aztreo-

nam can be given safely to patients with documented IgE-mediated penicillin allergy. In contrast to aztreonam, imipenem-cilastatin has exhibited extensive skin-test cross-reactivity with penicillin.¹⁴ Therefore, any person who has a positive skin test to any of the penicillin reagents is at risk for an allergic reaction to imipenem-cilastatin.

Conclusion

Patients with a history of reaction to penicillin should, if possible, be given an antibiotic that does not cross-react. If penicillin must be used, skin testing should be done if possible. Ideally, penicillin should be given orally be-

cause of the much lower incidence of allergic reactions with this route. When penicillin is given intramuscularly, the patient should be observed in the physician's office for 30 minutes for systemic reactions. Patients with known penicillin allergy should wear a Medic-Alert bracelet, and their medical charts should clearly indicate a penicillin allergy. PGM

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