CME CREDIT *EDUCATIONAL OBJECTIVES:* Readers will be able to identify IgE-mediated and non–IgE-mediated reactions to penicillin and indications and contraindications for penicillin skin testing

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# Penicillin allergy: A practical guide for clinicians

## ABSTRACT

Penicillin allergy is the most commonly reported drug allergy in the United States. However, after undergoing a complete evaluation by a board-certified allergist, including skin testing, 90% of patients labeled as "penicillin-allergic" are able to tolerate penicillin. Clinical presentation is key in classifying reactions as either mediated by or not mediated by immunoglobulin E (IgE), and in determining which patients may benefit from penicillin skin testing, graded-dose challenge, or desensitization. Cross-reactivity between penicillin and other beta-lactams is less common than previously thought.

## KEY POINTS

The prevalence of reported penicillin allergy is 10% in the general population. However, more than 90% of these patients are found not to be allergic to penicillin after skin testing.

In patients found to have penicillin allergy, the frequency of positive results on skin testing decreases by 10% per year of avoidance. Therefore, 80% to 100% of patients are expected to test negative for penicillin allergy by 10 years after their reaction.

Skin testing for penicillin allergy is only useful for type 1 IgE-mediated reactions. However, in properly selected patients, the negative predictive value of penicillin skin testing is nearly 97%.

The rate of cross-reactivity between penicillin and cephalosporins is approximately 3%.

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Most patients who report that they are allergic to penicillin can ultimately receive penicillin or a penicillin-type antibiotic again after an appropriate evaluation and, possibly, treatment. This course of action decreases the need for broad-spectrum antibiotics,[1–4] reduces health care costs, and prevents the development of multidrug-resistant pathogens.[5]

About 10% of the general population say that they are allergic to penicillin.[1,6,7] Although the prevalence of life-threatening anaphylactic reactions to penicillin has been estimated to be between 0.02% and 0.04%,[6] the most common reaction is a cutaneous eruption. Since anaphylactic reactions are mediated by immunoglobulin E (IgE), evaluation of patients with a history of penicillin allergy by penicillin skin testing is recommended to rule out IgE-mediated reactions.

This review outlines a practical approach to evaluating a suspected IgE-mediated reaction to penicillin, with key points in the history and diagnostic testing. We also review subsequent management and cross-reactivity with other beta-lactam-containing antibiotics.

## EVALUATING ALLERGIC PATIENTS

Evaluation of patients with a history of penicillin allergy can be improved with an understanding of the classification of drug reactions, risk factors for allergy, and the pathophysiology of penicillin allergy.

### Classification of drug reactions

Adverse drug reactions include all unintended pharmacologic effects of a drug and can be classified as predictable (type A) or unpredictable (type B). Predictable reactions are dose-dependent, are related to the known pharma-



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TABLE 1

**Gell and Coombs classification of hypersensitivity reactions**

| Type of reaction | Hypersensitivity | Mediated by | Time of onset | Examples |
|---|---|---|---|---|
| **IgE-mediated** | Type I | IgE antibodies | Within 1 hour | Anaphylaxis |
| **Non–IgE-mediated** | Type II | Cytotoxic | Hours to days | Hemolytic anemia |
| **Non–IgE-mediated** | Type III | Immune complex | 7–21 days | Serum sickness |
| **Non–IgE-mediated** | Type IV | Cell-mediated | Days to weeks | Maculopapular rash<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis |

IgE = immunoglobulin E

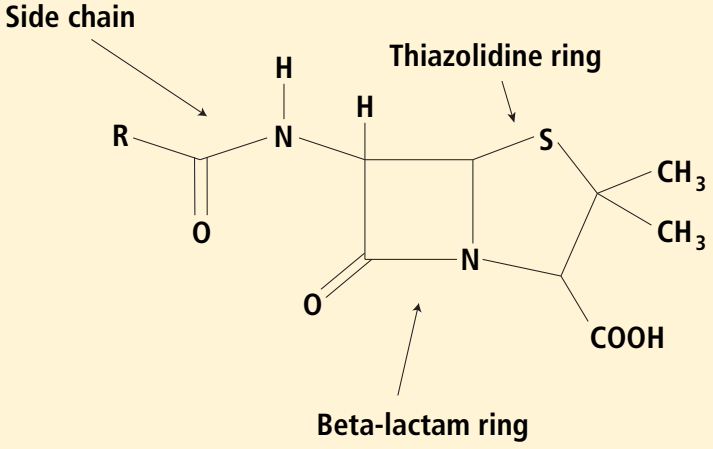


**FIGURE 1.** In a penicillin molecule, metabolites of the core ring structure, ie, the beta-lactam ring and the thiazolidine ring, can trigger immediate immunoglobulin E-mediated reactions. Reactions to the side chain may be responsible for cross-reactivity with other antibiotics.

cologic actions of the medication, and occur in otherwise healthy individuals. Unpredictable reactions are further classified into drug intolerance, drug idiosyncrasy, drug allergy, and pseudoallergic reactions.[8,9]

Penicillin allergy can manifest as any hypersensitivity reaction of the Gell and Coombs classification (TABLE 1).[9] Type I (immediate) and type IV (delayed) reactions are the most common types of reactions that occur with antibiotics and should be classified based on the onset of symptoms as immediate (within 1 hour) or delayed (days or weeks).[8]

## Risk factors for IgE-mediated reaction

Risk factors for a hypersensitivity reaction include frequent or repetitive courses of penicillin[10] and high-dose parenteral (rather than oral) administration.

Age and atopy are not risk factors for penicillin allergy.[7] However, atopy increases the risk of a more severe anaphylactic reaction to penicillin, and anaphylactic reactions are most commonly reported between the ages of 20 and 49.[6]

## Pathophysiology of penicillin allergy

All penicillins share a common core ring structure (beta-lactam and thiazolidine rings) but differ in their side chains (R group) (FIGURE 1).

Under physiologic conditions, the core ring structure is metabolized into major (penicilloyl) and minor (penicillin itself, penicilloate and penilloate) antigenic determinants that may trigger an immediate IgE-dependent response.[9] In the United States, commercial forms of antigenic determinates for skin testing exist in the form of penicillin G (minor determinant) and penicilloyl-polylysine, better known as Prepen (major determinant).

Immediate-type reactions to similar antibiotics such as aminopenicillins and cephalosporins may be caused by IgE antibodies against the R-group side chain rather than the core penicillin major and minor determinants.[11]

## Questions to ask patients who have a history of penicillin allergy

Patients should be questioned closely about previous and current reactions to penicillin



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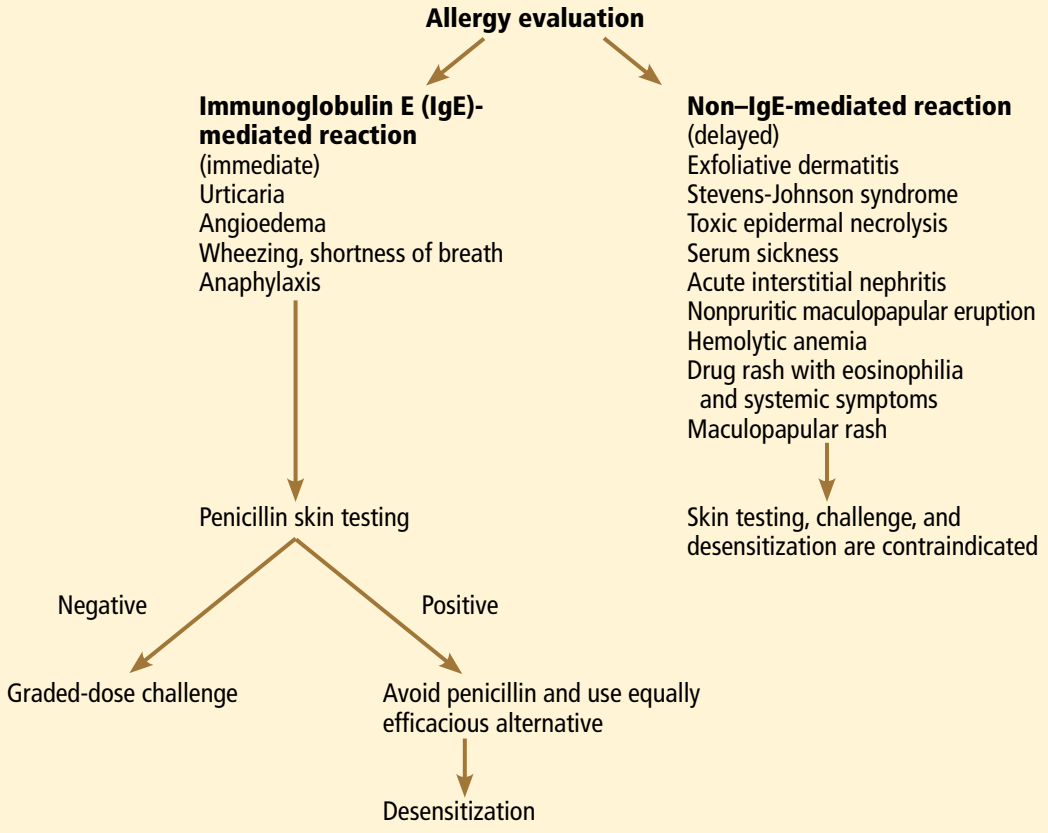


**FIGURE 2.** Clinical decision algorithm for penicillin allergy

and should undergo skin-prick and intradermal testing, followed by graded-dose challenge or drug tolerance desensitization (FIGURE 2).

Questions to ask patients who have a history of penicillin allergy (TABLE 2)[9,12] include the following:

**Do you remember the details of the reaction?** These include the route of administration, the time between the dose of penicillin and the appearance of symptoms, and how the reaction was managed.

Immediate reactions (ie, IgE-mediated, or Gell and Coombs type I) usually occur within the first hour after the first dose of the antibiotic, although they occasionally take up to 2 hours to occur, especially if the medication is taken orally and is taken with food. Symptoms consistent with IgE-mediated reactions include urticaria (most common), pruritus, angioedema, laryngeal edema, wheezing, shortness of breath, presyncope or syncope, hypotension, and cardiorespiratory collapse.

In contrast, symptoms of a non–IgE-mediated reaction are delayed in onset, occurring after days of treatment. They include nonpruritic maculopapular eruptions, hemolytic anemia, serum sickness, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, acute interstitial nephritis, and toxic epidermal necrolysis.[9]

If the patient has had severe non–IgE-mediated reactions to penicillin (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute interstitial nephritis, hemolytic anemia, or serum sickness) in the past, skin testing, graded-dose challenge, and desensitization are contraindicated.

**How many years ago did the reaction occur?** Most patients lose their sensitivity to penicillin over time.[7,13–15] Nearly 50% of patients with IgE-mediated penicillin allergy lose their

**Ask about previous and current reactions to penicillin**



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**TABLE 2**

**Questions to ask patients who have a history of penicillin allergy**

| |
|---|
| Do you remember the details of the reaction? |
| How many years ago did the reaction occur? |
| How was the reaction managed? What was the outcome? |
| Why were you given penicillin? |
| Have you tolerated other forms of penicillin since the reaction? |

sensitivity within 5 years of the reaction,[15] increasing to 80% or more by 10 years.[13]

**How was the reaction managed? What was the outcome?** Use of and positive response to epinephrine and histamine 1 receptor antagonists (antihistamines) with resolution or significant improvement of symptoms within a few hours may indicate an IgE-mediated reaction.

**What was the indication for penicillin?** Many cutaneous reactions are a result of an underlying viral or bacterial infection. For example, up to 90% of patients with Epstein-Barr virus infection develop a maculopapular rash when given penicillin.[16]

**Have you tolerated other forms of penicillin since the reaction?** Sometimes the patient has already tolerated other beta-lactams such as aminopenicillins, cephalosporins, and semisynthetic penicillins (piperacillin-tazobactam). Patients who tolerate other beta-lactams without adverse reactions are not allergic to beta-lactams.

**The skin-prick test is the only validated test for IgE-mediated reactions to penicillin**

### Diagnostic tests

**Skin testing.** The only validated test for diagnosing IgE-mediated reactions caused by penicillin is the immediate hypersensitivity skin test,[9] which should be performed by a board-certified allergist. The test consists of skin-prick and intradermal testing with the major determinant (penicilloyl-polylysine), the minor determinant (penicillin G), a negative control (normal saline), and a positive control (histamine). Minor-determinant mix is not commercially available in the United States.

Results of skin-prick testing are read 15 minutes after application. A positive response is a wheal at least 3 mm larger in diameter (with equivalent erythema) than the negative control done simultaneously. Intradermal testing is only done after a negative skin-prick test. If the allergic reaction was severe (ie, anaphylaxis), skin testing should be done at least 4 to 6 weeks after the reaction.

A history of severe non–IgE-mediated reaction to penicillin is a contraindication to skin-prick testing for penicillin allergy. The positive predictive value of penicillin skin testing is 50%, and the negative predictive value is 97%.[3,7,9,13]

**Commercial in vitro testing** (serum-specific IgE assays) for IgE-mediated hypersensitivity to penicillin is inferior to skin testing in terms of the negative predictive value and is not a suitable substitute for penicillin skin testing.

## MANAGING PENICILLIN ALLERGY

### If skin testing is positive, use another antibiotic, or refer for desensitization

If penicillin skin testing is positive (FIGURE 2), use another antibiotic that is equally efficacious. Patients who absolutely need a beta-lactam may undergo drug desensitization, performed by a board-certified allergist.

During desensitization, patients receive progressively higher doses of the drug every 15 to 20 minutes subcutaneously or intravenously, or every 20 to 30 minutes orally, until a full therapeutic dose is tolerated. Most protocols begin with a dose ranging from 1/10,000 to 1/1,000 of the final dose, depending on the severity of the allergic reaction.[9,17]

Using modern protocols, the success rate for tolerance induction is extremely high (75% to 100% in patients with cystic fibrosis, a group with a high rate of drug allergy[18–20]).

Drug desensitization is contraindicated in patients with non–IgE-mediated reactions.

### If skin testing is negative, refer for graded-dose challenge

If skin testing is negative (FIGURE 2), graded-dose challenge is recommended. This procedure must be done by a board-certified allergist. If the original reaction was life-threatening, graded-dose challenge may entail giving 1/100



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of the therapeutic dose. Then, if no reaction occurs during a brief observation period (usually 30 minutes), a full dose is given. However, many patients can start with 1/10 or even a full dose of the drug, especially if the original reaction was limited to the skin and the penicillin skin test is negative.

Graded-dose challenge is contraindicated if the original reaction was a severe non–IgE-mediated reaction.

## UNDERSTANDING CROSS-REACTIVITY OF PENICILLIN

Penicillin is the only antibiotic for which skin testing is reliable and validated. If a drug that cross-reacts with penicillin is needed, it is important to know the rate of cross-reactivity (TABLE 3). The rate of cross-reactivity between penicillin and aminopenicillins (amoxicillin and ampicillin) is less than 1.3% in the United States.[10,21] However, the cross-reactivity rate among aminopenicillins and cephalosporins is between 10% to 40%. For that reason, patients with prior reactions to aminopenicillins should avoid cephalosporins that share identical R-chain side groups with aminopenicillins.[9,22]

The rate of cross-reactivity between penicillin and cephalosporins was reported as 10% 40 years ago.[23,24] But this was with early, first-generation cephalosporins that may have been contaminated with penicillin. The cross-reactivity rate with cephalosporins today is 3%.[25] In general, first- and second-generation cephalosporins cause more allergic reactions than third- and fourth-generation cephalosporins.[26]

Patients with a history of penicillin allergy who require a cephalosporin should still undergo penicillin skin testing. Skin testing with cephalosporins has not been validated. However, skin testing with nonirritating concentrations of cephalosporins[9] may be done to elucidate IgE reactions.

In a study by Romano et al,[27] 110 patients who had positive results on penicillin skin testing completed graded-dose challenge with the carbapenem antibiotic imipenem. The rate of cross-reactivity between penicillin and imipenem was less than 1%.

Monobactam antibiotics do not cross-react with other beta-lactams, except ceftazidime with aztreonam. This is probably because of similarities in their chemical structure.

**TABLE 3**

**Cross-reactivity of penicillin with other beta-lactam antibiotics**

| Beta-lactam antibiotic | Cross-reactivity rate |
|---|---|
| Aminopenicillins | < 2% |
| Cephalosporins | 3% |
| Monobactams [a] | 0% |
| Carbapenems | < 1% |

[a] Avoid aztreonam if the patient has had a previous reaction to ceftazidime.

**During desensitization, patients receive progressively higher doses up to a full therapeutic dose**

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