

Penicillin Allergy

Mechanisms, Diagnosis, and Management



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KEYWORDS

• Penicillin allergy • Hypersensitivity • Skin testing • Drug challenge • Desensitization

KEY POINTS

- Penicillin allergy is common and can occur through multiple types of hypersensitivity mechanisms.
- History and physical examination are key to evaluation of penicillin allergy.
- Penicillin allergy is most often lost over time.
- Allergy skin testing and/or drug provocation challenge can accurately diagnose penicillin allergy.

INTRODUCTION

The discovery of penicillin in 1928 by Sir Alexander Fleming changed the course of modern medicine. Once fatal diseases such as sepsis, meningitis, and endocarditis could now be cured. Penicillins have saved countless lives since then and continue to be the first-line treatment of many infectious diseases. It is still the only recommended treatment of prevention of mother-to-child transmission of syphilis. However, allergic reactions are common, and the first case of anaphylaxis was reported in 1945.¹

The prevalence of penicillin allergy in the United States is approximately 10%.² In part, this is driven by the high rate of use of this drug because the vast majority of the population has received this antibiotic (often multiple times by adulthood). The chemical nature of penicillin also plays a large role in susceptibility to allergic reactions. The carbonyl group of the beta-lactam ring is an excellent electrophile (**Fig. 1**, labeled *), which provides the ability to covalently bind to proteins and is the basis

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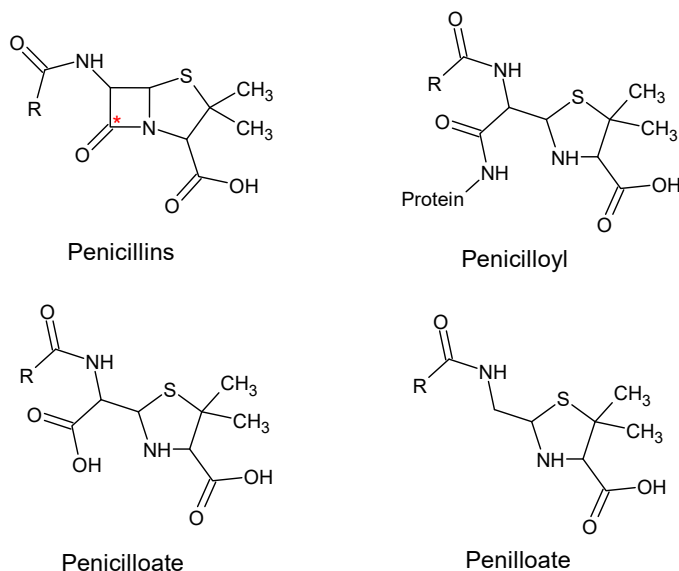


Fig. 1. Chemical structure of penicillins. Asterix indicates carbonyl group that is the site of covalent bond to carrier protein. Penicilloyl is the major determinant of allergic reactions. The penicillin ring can isomerize into minor determinants (penicilloate and penilloate) that less commonly cause reactions.

for its ability to block bacterial cell wall synthesis by inhibiting bacterial transpeptidase. However, this also allows the drug to act as a hapten, by covalently binding to circulating proteins (carriers) and forming a neoantigen that looks foreign to the immune system.

Drug allergies occur across a spectrum of reaction severities that range from benign rashes to life-threatening reactions. Some reactions warrant lifelong avoidance of the allergenic medication, while the drug may be safely used again in other cases. As a result, it is important to develop a framework to not only manage acute reactions, but to determine when it is appropriate to test for drug allergies, when to use an allergenic medication again, and when it is appropriate to refer to an allergist.

For many years, our approach to penicillin allergy was to simply have drug-allergic patients avoid the medication, often lifelong. However, recent data in the past few years have demonstrated potential harm in doing this. First, only about 10% of the population with a penicillin allergy listed on chart is actually allergic.² The majority of patients (~80%) lose their penicillin allergy during a 5 to 10-year period.² Second, many patients with a chart listing of penicillin allergy may not have been allergic to begin with. In some cases, they could have had a viral exanthem or idiopathic urticaria that was blamed on the medication. In other cases, patients developed side effects (eg, vomiting and diarrhea) that were recorded as allergies.

There are significant consequences to needlessly avoiding penicillin. As penicillin is still the first-line treatment of many infections, penicillin-allergic patients may receive second-line medications that are less effective. This could result in more treatment failures, infections that are more difficult to treat, and longer hospital stays.³⁻⁵ Moreover, patients with penicillin allergy may receive stronger antibiotics or those with broader spectrum than would be needed for their infection. Patients with penicillin allergy are more likely to receive IV antibiotics in the hospital, have higher utilization of

vancomycin, and as a result, more likely to develop vancomycin-resistant enterococcus.^{6,7} We and others also demonstrated that penicillin-allergic patients were more likely to develop difficult-to-treat infections such as methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*, possibly due to receiving nonpenicillin, broad-spectrum antibiotics.^{4,5,7} Macy and Shu demonstrated that removing the penicillin allergy label decreased outpatient visits, ER visits, and days of hospitalization.³ Moreover, these patients were exposed to less clindamycin and macrolides during future hospital stays.³

Health-care cost may be significantly higher for penicillin-allergic patients. In the Kaiser Permanente system, penicillin allergy was associated with 30,433 additional hospital days during a 3-year period, resulting in more than US\$64 million in additional health-care expenditures.⁷ A recent study sought to determine financial benefits of penicillin testing. They determined that penicillin allergy testing (combining data from United States and Europe) would reduce inpatient costs by US\$657 per patient (US\$1440 in United States and US\$489 in Europe) and outpatient costs by US\$2476 (US\$256 in United States and US\$6045 in Europe).⁸

It is therefore beneficial to accurately determine whether a patient truly has a penicillin allergy because this has significant influence on current and future management of infections, health-care utilization, and health-care costs. This review article will focus on the clinical presentation of penicillin hypersensitivity reactions and their acute management, in addition to approaches to diagnosis and clearing penicillin allergy when appropriate. These approaches will include those that can be performed in the primary care office as well as those for which referral to an allergist would be indicated. Although this review focuses on managing patients with penicillin allergy, this approach can be extended to almost any other drug allergy.

MECHANISMS OF PENICILLIN ALLERGY

Type I Immediate Hypersensitivity (IgE-Mediated)

Type I hypersensitivity, or immediate reactions, are mediated by IgE antibodies in response to proteins perceived as foreign by the immune system. Although lone penicillin molecules are too small to drive an immunologic antibody response, they can covalently bind to proteins in plasma and form immunogenic hapten-carrier complexes.⁹ The most common hapten, penicilloyl (see [Fig. 1](#)), is created when the penicillin beta-lactam ring covalently binds to common serum proteins' lysine residues. Penicilloyl, also called the "major determinant," is responsible for 60% to 85% of penicillin reactions.^{10,11} Additionally, penicillin can isomerize and form other hapten complexes such as penicilloate and penilloate (see [Fig. 1](#)). These molecules are also known as "minor determinants" and account for 10% to 20% of penicillin allergies.¹⁰ Reactions to minor determinants are more often associated with anaphylaxis as opposed to the major determinant. Ultimately, the penicillin moiety (hapten) and protein (carrier) form a neoantigen—"new" antigen that is recognized as foreign by the immune system ([Fig. 2](#)). The penicillin hapten-carrier protein is taken up by antigen-presenting cells (APCs), such as dendritic cells, and presented to naive CD4+ T cells through MHC-II complexes in lymph nodes, which results in type 2 helper T (Th2) cell differentiation. Th2 cells then induce the differentiation and isotype switching of naive B cells into plasma cells producing IgE antibodies specific to the penicillin hapten-carrier complex. These IgE bind to the constant region (Fc) of epsilon receptors on the surface of basophils and mast cells, which will subsequently activate on reexposure.^{1,10} Because this sensitization process typically takes weeks, patients are generally asymptomatic during the last course of penicillin.¹⁰ On reexposure of

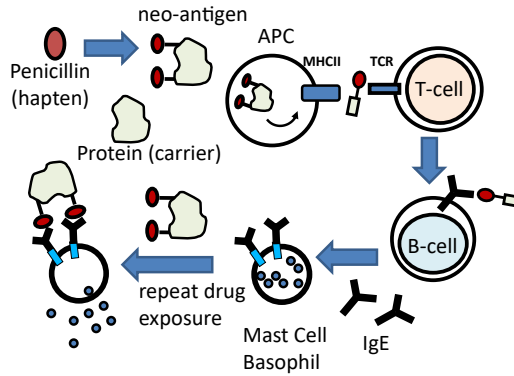


Fig. 2. IgE-mediated drug allergy. Penicillin (hapten) covalently binds to a circulating protein (carrier), forming a neo-antigen. This is taken up by APC, processed, and presented to CD4+T-cells via the MHCII complex. T-cells then stimulate B-cells that have antibodies specific to the neoantigen, leading to IgE production. The IgE then binds to mast cells and basophils. On repeat exposure to penicillin, the IgE on mast cells/basophils bind the neo-antigen, triggering allergic mediator release, which produces the clinical symptoms of an allergic reaction.

the drug, hapten–carrier complexes activate basophils and mast cells by binding to IgE, which cross-links the Fc epsilon receptors and induces the degranulation of basophils and mast cells. The release of inflammatory mediators such as tryptase, histamine, prostaglandins, and leukotrienes drive the clinical manifestation of type 1 hypersensitivity, which includes urticaria, angioedema, bronchospasm, gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), cardiovascular collapse, and anaphylaxis. These symptoms typically have an onset of minutes to hours following reexposure.¹⁰ Because penicillin-specific IgE antibodies decrease over time, patients with past reactions may lose sensitivity following a period of avoidance. In fact, ~50% of patients with IgE-mediated penicillin can lose the sensitivity after 5 years; this increases to 80% after 10 years.^{12–14}

Type II Cytotoxic Hypersensitivity (IgM and IgG-Mediated)

Type II hypersensitivity, or cytotoxic reactions, are mediated by IgM or IgG antibodies binding to cellular surface antigens. Major and minor penicillin determinants covalently bind to cell surface proteins (typically on white blood cells, red blood cells, or platelets) and together, they act as antigens. IgG, or less commonly IgM, is the predominant antibody involved in this type of reaction. When exposed to penicillin, the preformed antibodies bind to the penicillin-surface protein complexes and induce cellular destruction via complement activation and/or phagocytosis by macrophages, leading to hemolytic anemia (as the case illustrated above), neutropenia, or thrombocytopenia.¹⁵ Typical onset is 1 week to months after drug initiation. Although reactions typically resolve after penicillin discontinuation, symptoms can develop within hours after reexposure because IgM and IgG antibodies can persist for years.^{15,16} It is therefore crucial to avoid the drug permanently.

Type III Immunocomplex Hypersensitivity

Type III hypersensitivity, or immune complex reactions, are mediated by immune complexes consisting of a soluble antigen (ie, circulating protein) bound by an antibody. A similar hapten–carrier as discussed above generates IgG or IgM antibodies. Binding of

these antibodies to the penicillin-soluble protein leads to immune complex formation, which can deposit in tissues (blood vessels, kidneys, and joints). The penicillin–IgG complex then activates the complement system, which releases chemotactic agents that recruit inflammatory cells (neutrophils and macrophages). These inflammatory cells release lysosomal enzymes and free radicals causing inflammatory tissue damage. Symptoms can vary with the site of the penicillin–IgG complex deposition. Namely, complexes deposited in blood vessels, kidneys, and joints, will result in urticarial, vasculitis, nephritis, and arthritis, respectively. Symptoms typically occur 1 to 3 weeks after drug initiation since a significant quantity of antibodies is required to generate this type of reaction, which takes weeks to be produced.^{17,18}

Type IV Delayed Cell-Mediated Hypersensitivity

Type IV hypersensitivity, also known as cell-mediated or delayed reactions, are mediated by CD4+ (helper) and CD8+ (killer) T-cells. There are 4 subtypes of delayed reaction that are characterized by the effector cells involved and clinical phenotypes (Fig. 3): Type IVa (Th1 helper T-cell and macrophages), Type IVb (Th2 helper T-cell and eosinophils), Type IVc (CD8+), and Type IVd (CD8+, Th17 helper T-cell and neutrophils).¹⁰ They all consist of a sensitization (exposure leading to activation of allergic cells) followed by an elicitation phase (allergic cells producing the reaction). There are 2 proposed hypotheses for the sensitization phase: the hapten model and the “p-” (primary interaction) model.¹⁹ In the hapten model, penicillin haptens bind to self-proteins and form a penicillin protein–hapten complex that is taken up and proteolytically processed by APCs, and presented on MHC to T-cells specific to the penicillin hapten–protein complex. In the p-i model, penicillin directly binds to T-cell receptors and MHC protein (p-i HLA) without the need for covalently binding to a protein. This directly activates T-cells leading to differentiation of helper and effector T-cells.^{19–21} In both models, CD4+ T-cells stimulate other cells (eg, macrophages, eosinophils, neutrophils), which lead to tissue damage, and/or CD8+ T-cells induce apoptosis in cells.¹⁹

TYPE IVa

Type IVa hypersensitivity is mediated by a Th1 helper T-cell immune response resulting in macrophage activation. The sensitization phase involves priming of Th1 cells (via

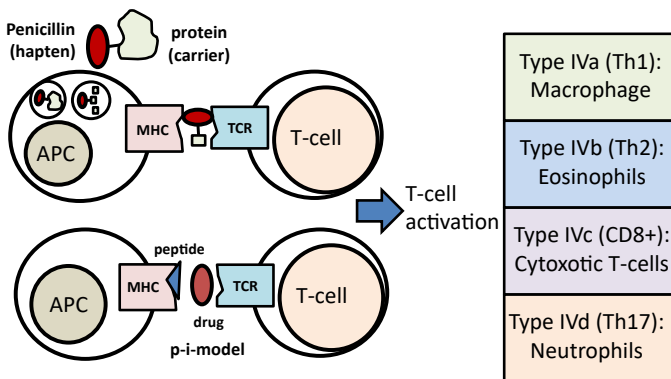


Fig. 3. Type IV drug hypersensitivity. T-cells can be stimulated via 2 pathways, presentation by APC of penicillin-covalently linked to a protein, or direct interaction of penicillin with a T-cell receptor and MHC (p-i model). T-cells may differentiate via 4 main pathways (Type IVa–d), which produce different cellular responses and distinct drug hypersensitivity conditions.

the hapten or p-i model). During the elicitation phase, Th1 cells are recruited to the skin where they secrete inflammatory cytokines (mainly IFN- γ and TNF- α) leading to macrophage activation and inflammatory response.^{10,20} The typical rash is either macular or maculopapular. These generally occur 1 to 2 weeks following initial drug exposure and commonly manifest toward the end of a course of penicillins. If someone receives a subsequent course of penicillin, the rash could develop within 24 to 72 hours of reexposure. In general, these reactions tend to be of mild-to-moderate severity and usually go away quickly after the offending drug is removed. This allergy may also be lost quickly, potentially within months. Mill and colleagues²² demonstrated that 94.1% of children challenged after this type of drug allergy are able to tolerate it without any reactions.

TYPE IVb

Type IVb hypersensitivities are mediated by Th2 immune response resulting in eosinophilic activation. The sensitization phase involves priming of Th2 cells. During the elicitation phase, Th2-cells secrete IL-5, which is a potent cytokine that drives eosinophil proliferation and survival. Eosinophils traffic to diverse tissues, including skin, kidney, liver, in addition to lungs, nervous system, and heart. When activated, eosinophils release cytotoxic granule proteins resulting in systemic inflammation and organ damage.²³

A clinical syndrome associated with this reaction is drug reaction with eosinophilia and systemic symptoms (DRESS).²³ It has been suggested that B-cell secretion of IL-10 during the sensitization phase may induce viral reactivation and subsequent inappropriate systemic immune response in the context of DRESS. Namely, members of the human herpes viridae family (primarily HHV-6, EBV, and CMV) are thought to trigger uncontrolled T-cell activation. In turn, T-cells release cytokines that drive eosinophilia, leading to systemic inflammation features found in DRESS patients.²³ Symptoms include maculopapular eruption, edema, fever, lymphadenopathy, and systemic organ (more commonly heart, lung, liver, kidney) damage, which can lead to death.²⁴ They generally occur 2 to 8 weeks after the initiation of penicillin.²⁵ DRESS is considered a severe, life-threatening rash that requires immediate discontinuation of the culprit drug, hospital admission, and prompt treatment.

TYPE IVc

Type IVc hypersensitivities are mediated by CD8+ T-cells resulting in extensive epithelial cell apoptosis and necrosis. The sensitization phase involves priming of CD8+ T-cells. During the elicitation phase, CD8+ T-cells release cytotoxic proteins (granulysin, perforin, Fas ligand, TNF- α , and IFN- γ) leading to keratinocyte necrosis, ranging from partial to full-thickness necrosis of the epidermis. Clinical syndromes associated with this reaction are Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).^{26,27} Both conditions are characterized by significant necrosis and detachment of the epidermis; less than 10% epidermal involvement is classified as SJS, more than 30% epidermal involvement is classified as TEN, and 10% to 30% involvement is classified as SJS/TEN overlap.¹⁰

In SJS and TEN, a prodrome of fever and influenza-like symptoms may develop 1 to 3 days before the mucocutaneous reactions (vesicles, bullae, skin detachment). Severe epidermal detachment may lead to fluid loss, electrolyte imbalance, sepsis, and multiorgan failure.^{26,27} Mucosal involvement is common and patients frequently have oral lesions. Any mucosal surface can be involved, including eyes, lungs, gastrointestinal tract, and genitourinary tract. Generally, symptoms occur 4 days to 4 weeks

following drug initiation. SJS and TEN are severe reactions with an overall mortality rate ranging from 10% for SJS to 50% for TEN.²⁸

TYPE IVd

Type IVd hypersensitivities are mediated by CD8+ and Th17 immune responses resulting in neutrophilic inflammation. The sensitization phase involves priming of CD8+ and Th17 cells. During the elicitation phase, CD8+ T-cells and Th17 migrate to the skin where they release chemokines (CXCL8, IFN- γ , GM-CSF) leading to neutrophil recruitment and sterile pustule formation.^{29–31} A clinical syndrome associated with this reaction is acute generalized exanthematous pustulosis (AGEP). Clinical manifestation includes fever, neutrophilic leukocytosis, erythema, and development of numerous small sterile pustules. Symptoms typically develop within 24 to 48 hours of drug exposure and resolve spontaneously in 1 to 2 week following drug discontinuation.³¹

DISCUSSION

Management of Allergic Reactions

Type I hypersensitivity

Most commonly, urticaria and angioedema are the primary symptoms from IgE-mediated drug allergies, and they typically occur within minutes of drug administration. Although rare, anaphylaxis due to penicillin allergy can occur. The medication should be stopped immediately and treatment should be sought immediately.³² Anaphylaxis is defined as an allergic reaction that involves multiple organ systems, or a severe reaction involving the cardiovascular or respiratory system. Immediate epinephrine administration, followed by antihistamines, is the key to combating anaphylaxis. Epinephrine is lifesaving in these circumstances and should be injected intramuscularly into the outer thigh at a concentration of 0.01 mg/kg of body weight, not exceeding 0.5 mg.³³ Administration of epinephrine activates adrenergic receptors that help increase peripheral resistance and cardiac output and can therefore mitigate hypotension and shock.^{34,35} Additionally, its administration produces bronchodilation and may inhibit mast cell and basophil release of inflammatory mediators, which help alleviate pulmonary symptoms, such as shortness of breath.³⁴ The vasoconstrictive effects also help to relieve angioedema and urticaria. Potential adverse events (tachycardia, elevated blood pressure) should be considered especially for individuals at high-risk (eg, elderly and those with comorbidities) but these should not prevent the use of epinephrine.^{36,37}

Antihistamines can be used to supplement epinephrine therapy. Antihistamines help resolve cutaneous associations of anaphylaxis (eg, urticaria and pruritus) and can be used with epinephrine or as monotherapy in nonanaphylactic reactions if only the skin is involved (mostly to provide symptomatic comfort).^{38–40}

Type II hypersensitivity

Although rare, drug-induced hemolytic anemias to penicillins (and also cephalosporins) are possible.^{41–43} The mainstay treatment of drug-induced hemolytic anemia is removal of the causative agent.^{41,43–45} Depending on the severity, patients can be given blood transfusions.^{43,45} Glucocorticoids have negligible effects on improving the anemia.^{44,46,47}

Type III hypersensitivity

Serum sickness or serum sickness-like reactions are typically self-limiting as long as the offending agent is removed.⁴⁸ If no contraindication to non-steroidal anti-

inflammatory drugs (NSAIDs) (eg, renal failure, history of NSAID allergy), these can help to symptomatically improve arthralgias. Antihistamines can be considered to treat the rash, although its efficacy has not been studied and may be low. In more severe cases (eg, disabling arthralgias or angioedema), glucocorticoids can be given.⁴⁸ Responses may be variable, and in some cases, the symptoms may start to wane in as little as a day.⁴⁸

Type IV hypersensitivity

Type IVa Reactions: These reactions tend to be primarily cutaneous, typically with a macular or maculopapular rash of varying pruritic intensity that is usually mild-to-moderate severity. There is little published data on optimal regimens but our group utilizes cetirizine 10 mg BID in addition to hydroxyzine 25 to 50 mg at bedtime. These rashes typically self resolve within a few days, and glucocorticoids (0.5 mg/kg) with a tapering dose during 1 week can be considered in cases refractory to antihistamines.

Drug reaction of eosinophilia and systemic symptoms

The mainstay treatment is removal of the offending agent and glucocorticoids.⁴⁹ A typical starting dose is 1 mg/kg, with a very slow taper during 1 to 3 months. In refractory cases, higher doses can be used initially, 250 to 500 mg for the first few days, followed by a decrease to 1 mg/kg and then a slow taper. In refractory cases, cyclosporine can be considered.^{25,49}

Stevens-Johnsons syndrome and toxic epidermal necrolysis

Immediate removal of the causative agent is the first step. These disorders can involve dramatic loss of skin barrier, and patients typically need to be transferred to a burn center. It is imperative to initiate this as quick as possible. Patients are susceptible to damage of any mucosal surface—ocular, oral, gastrointestinal, genitourinary; hence, these all need to be considered. It is essential to consult ophthalmology to perform a slit lamp eye examination (even if the patient has no ocular complaints) because these reactions can produce corneal scarring and blindness. Supportive therapy is also recommended to achieve proper fluid, nutritional, pain, and oxygenation statuses.^{50–52} Skin assessment and antibiotic treatment of infections should be performed.^{53,54} Several different treatments have been proposed: glucocorticoids, IVIG, cyclosporine, plasmapheresis, and TNF inhibitor.⁵⁴ However, data is inconclusive. Glucocorticoids may increase mortality, particularly later in the course of the reaction, so these are generally avoided. IVIG in high doses (2 g/kg given over 2 days) may be beneficial.⁵⁵

Acute generalized exanthematous pustulosis. Mainly, AGEP will resolve on its own once the inciting agent is removed, although supportive therapy (eg, emollients, keeping the skin dry and clean) can be used.⁵⁶ Glucocorticoids have not been shown to be useful.^{57–59}

Treating through a penicillin rash

Cutaneous manifestations are the most common manifestation of an allergic reaction to penicillin. In cases of mild-to-moderate drug reactions (most often Type IVa), there are indications where the allergenic medication may be continued despite the reaction. This would most often be considered in cases of moderate-to-severe infections when an alternative medication is not an option. In these cases, the antibiotic can be continued, and the patient treated with antihistamines as described above. Cetirizine 10 mg BID ± hydroxyzine 25 mg QHS ± prednisone 20 to 40 mg daily (depending on severity of the initial reaction).

Potential cross-reactivity of other antimicrobials

Historically, there is thought to be approximately 5% to 10% cross-reactivity between penicillins and cephalosporins (mostly with first-generation and second-generation cephalosporins) but the majority of patients with a penicillin allergy can tolerate cephalosporins.⁶⁰

A prudent approach in penicillin-allergic patients is to avoid first-generation or second-generation cephalosporins, or cephalosporins with side chains similar to penicillins (Table 1).⁶¹ There is not significant cross-reactivity with monobactams, and these are safe to use in penicillin-allergic patients.⁶¹ Cross-reactivity with carbapenems is low, approximately 1%, so these can also be safely used.⁶²

Diagnostic Testing for Penicillin Allergy

Skin testing

Penicillin skin testing should be done by personnel who are trained to interpret results and treat allergic reactions. In recent years, there has been an effort to train pharmacists and infection control groups to perform testing. Skin testing for penicillin is a highly sensitive test to evaluate IgE-mediated allergy.²

Skin testing with the major determinant (ie, penicilloyl polylysine, commercially available as PRE-PEN) and penicillin G is approximately 95% sensitive. A positive and negative control should be utilized (histamine and saline, respectively).² Initially, a skin prick to each of these is performed in duplicate, followed by intradermal testing if the former is negative. A positive test is a wheal that is 3 mm greater than the negative control. When the skin test is negative, an oral challenge to penicillin (250–500 mg) is performed, and the combination of the two is close to 100% sensitive to detect IgE-mediated reactions.^{63–65} The positive predictive value is estimated to be 40% to 100%; therefore, given the potential of false-positive tests, penicillin testing is not recommended as a screening test; it should only be done to determine whether the allergy is still present in patients with a history of reaction.^{63,65,66}

Patch testing

Patch testing may be performed to test for Type IV reactions. This is administered using a 5% or 10% concentration of penicillin in petroleum jelly (weight/volume) applied to the skin in a Finn chamber, worn for 48 hours, and is read 15 minutes after removal and again 24 hours after removal.⁶⁷ The specificity is high, approaching 100%, although the sensitivity is lower, approximately 50%.^{68,69}

Table 1 Beta-lactam antibiotics with similar side chains					
Amoxicillin	Ampicillin	Ceftraixone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

Each column represents drugs with identical R1 side chains.
From Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105(4):259-273.

Blood testing

There is no role for blood work in diagnosing IgE-mediated reactions. Although IgE assays for penicillin exist, these have poor sensitivity and specificity. Blood tests may be of utility in type II hypersensitivity reactions. A modified Coombs test can be used to confirm a drug reaction, by adding the culprit drug to patient blood during the assay. Blood testing may also be helpful in type III reactions. Often C3 and C4 levels are low due to complement consumption, and measuring kidney and liver function and inflammatory markers can help to assess the severity of reaction.

Blood testing can also be useful in Type IV reactions. In DRESS, blood eosinophils are typically 1500 cells/mcl or greater, and there is often liver or renal dysfunction. Although blood testing cannot be used to diagnose other Type IV reactions, it can help to assess severity by determining whether organ dysfunction is present.

Skin biopsy. Skin biopsies are not helpful to diagnose Type I or Type II hypersensitivity reactions and have a low diagnostic yield in Type III reactions. Skin biopsies are most helpful in diagnosing Type IVc reactions (SJS/TEN) because it can help to exclude several other rashes that may be in the differential (eg, bullous linear IgA dermatosis, autoimmune bullous skin conditions, scalded skin syndrome).

Graded challenge

The graded challenge is the gold standard of IgE testing, and involves administering a medication systemically (oral or injected).² This is done when the pretest probability of a true allergy is low. For oral medications, 10% of the therapeutic dose is given and the individual observed for 30 to 60 minutes. If someone were allergic, this dose is usually low enough that the reaction would be mild. Assuming no reaction, then 90% of the therapeutic dose is given with observation for 30 to 60 minutes. For intravenous medications where (there may be risk of a more severe reaction), the starting dose is often 1% of therapeutic dose, then 10%, and 100% with 30 minutes of observation between each dose.

There are instances where type IV hypersensitivity reactions can be evaluated with a graded challenge. In these scenarios, the 10%/90% protocol from above is implemented because some Type IV reactions may occur within an hour due to the presence of memory T-cells in the periphery. If negative, a daily therapeutic dose of the medication is given at home for 4 to 5 days. These challenges would be contraindicated in severe drug reactions (DRESS, SJS/TEN).

Testing in the Primary Care Clinic and When to Refer to Allergy

Not all drug reactions need to be referred to an allergist, and in fact, most penicillin allergies may be safely performed in a primary care office. First, many adverse effects are incorrectly labeled as an allergy. For expected side effects such as gastrointestinal symptoms, headache, and noncutaneous reactions, these can be delabeled as an allergy without the need for further testing. Side effects can be managed symptomatically if the patient needed penicillin.

In cases of mild delayed rashes (Type IVa reactions), the graded challenge, as described above, is safe and can be performed by primary care doctors. In many cases, penicillin allergy may be cleared by challenges without the need for skin testing or patch testing.

Referral to an allergist can be considered in several scenarios. Reactions that were recent (within past 5 years) and those associated with Type I/IgE symptoms (hives/angioedema, respiratory symptoms, cardiovascular symptoms) should be referred for skin testing. Reactions that involved drug-induced hemolysis or any other

cytopenia are considered severe and should be referred for further workup. Furthermore, any drug allergy reaction that produced fever, elevated blood eosinophils, oral (or other mucosal surface) lesions, elevated liver enzymes or altered renal function, or blistering rashes would be considered moderate-to-severe and would warrant referral.

SUMMARY

Allergy to penicillin can occur via any of the 4 types of Gel-Coombs hypersensitivity reactions, producing distinct clinical histories and physical examination findings. These range in severity from mild reactions where the culprit drug may be used again, to severe reactions that necessitate lifelong avoidance. For all drug reactions, immediate penicillin discontinuation is essential, and depending on the type of reaction, epinephrine, antihistamines, and/or glucocorticoids may be used. Most beta-lactams may be safely used in penicillin-allergic patients, with the possible exception of first-generation and second-generation cephalosporins. It is important to note that most patients lose Type I and Type IVa allergies over time, so testing can be extremely useful in these reactions. Penicillin testing includes skin testing, patch testing, and graded challenge. The selection of the type of testing depends on the clinical setting, equipment availability, and type of hypersensitivity reaction. Desensitization may be used in some cases where treatment with penicillins is essential.

CLINICS CARE POINTS

- History and physical exam are essential to characterize the type of hypersensitivity reaction.
- During an acute reaction, prompt discontinuation of penicillin and appropriate treatment are essential.
- Anaphylaxis should be treated with epinephrine.
- Prednisone is the mainstay of treatment of Type IVb reactions (DRESS).
- Type IVc reactions (SJS/TEN) require supportive care and possible transfer to a burn center.
- Type IVa reactions are often mild and penicillins may be used again if needed.
- Most patients lose Type I-mediated and Type IVa-mediated hypersensitivities to penicillin during a 5 to 10-year period.
- Penicillin skin testing and/or graded challenges can be helpful to determine whether the allergy has been lost.

DISCLOSURE

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