
SKIN TESTING IN THE EVALUATION OF HYMENOPTERA ALLERGY AND DRUG ALLERGY

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HYMENOPTERA ALLERGY

Allergic reactions to insect stings are a major medical problem. Most insect stings are associated with local reactions, including pain, swelling, and redness. These reactions usually subside in a few days. Systemic reactions that can lead to potentially life-threatening manifestations occur in certain individuals. Approximately 50 deaths per year result from insect anaphylaxis in the United States.⁸ Retrospective population studies show an incidence of at least 0.4%,^{14, 74} and one study suggests that this incidence may be as high as 3%.²² Several older studies have outlined the clinical features of individuals with insect sting anaphylaxis.^{12, 19, 44} A study by the American Academy of Allergy and Immunology confirmed these findings.⁴² About 33% to 40% of individuals who have insect sting anaphylaxis are atopic. There is a 2:1 male-to-female ratio. The majority of reactions occur under the age of 20, although the number of deaths is greater in adults. The reason for increased mortality in adults might be the presence of cardiovascular disease and the greater likelihood that they are taking a medication that puts them at risk for anaphylaxis, such as a β blocker.

Severe insect sting anaphylaxis may occur at any age. Review of a large patient population with potentially fatal anaphylaxis as defined by symptoms of hypotension, loss of consciousness, upper airway edema,

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and marked respiratory distress showed a fairly uniform age distribution.³⁶ The majority of individuals with the most severe reactions had no warning of their sensitivity. Most patients who die of insect sting anaphylaxis have not had previous generalized allergic reactions.⁸

Natural History

Understanding the natural history of insect allergy is important in managing certain issues of this disease process, such as selection of patients for treatment, type of treatment, and duration of treatment. Studies suggest that insect sting allergy is a self-limiting process for most individuals.⁶¹ This conclusion also is the only explanation for the presumed effectiveness of insect whole-body extracts used for over 40 years for the treatment of insect sting allergy and now recognized to lack potency.⁶⁰ Several studies employing intentional sting challenges have shown that only 50% to 60% of unselected patients who have had previous systemic reactions and positive venom skin tests react again following a re-sting in the absence of venom immunotherapy.^{10, 15}

Factors such as age and the nature of the anaphylactic symptoms have been identified as relative to the natural course of the disease process. Children who have skin manifestations (hives, edema) as the only sign of venom hypersensitivity are a selected subpopulation.⁷¹ These patients have a low incidence of reactions with repeat stings, and when symptoms do occur, they tend to be mild. Patients of all ages who have more severe anaphylactic symptoms, such as loss of consciousness and hypotension, are much more likely to react again when re-stung, and the reactions are likely to be of similar intensity.³⁶ Reisman analyzed 220 patients with a history of venom anaphylaxis, positive venom skin test results, and subsequent field re-stings in the absence of venom immunotherapy. He found that when re-sting reactions did occur, the severity of the symptoms were very similar to the severity of symptoms of the initial reaction. Reisman also found, contrary to his earlier findings, that the incidence of re-sting reactions was unrelated to the time interval since the initial sting reaction.⁵⁹

Following an insect sting reaction, serum venom-specific immunoglobulin (IgE) usually rises and peaks in 2 to 3 weeks. In the absence of further venom exposure (stings or immunotherapy), these antibody titers decline at a variable rate with marked individual differences in the change of titers over time. It should be emphasized, however, that the absolute titer of serum venom-specific IgE is not related to the occurrence or severity of a re-sting reaction.⁶⁰

Almost all patients who have had large local reactions continue to have similar reactions following subsequent stings.⁴³ These local reactions are not dependent on IgE antibody, which is present in more than half the individuals following large local reactions. The use of venom immunotherapy does not modify the large local reaction. In a small minority of patients (less than 5%), anaphylaxis will develop with subsequent stings. These patients with large local reactions are not candidates for venom immunotherapy and do not require venom skin tests.

Causative Agents

In the United States, there are four major winged stinging insects: the honeybee, wasp (*Polistes*), yellow jacket, and hornet.⁸⁰

Taxonomy of Hymenoptera

Hymenoptera

Apidae

Honeybees

Bumblebees

Vespidae

Hornets

Yellow jackets

Wasps

Formicidae

Fire ants

Harvester ants

These insects are members of the order Hymenoptera of the class Insecta. The honeybee and bumblebee belong to the superfamily Apoidea. These insects are docile and sting only when provoked. Multiple stings have occurred from honeybees if their hive, which contains thousands of insects, is in danger. As a rule, the honeybee loses its stinging mechanism in the sting process, thereby inflicting self-evisceration and death.

The yellow jacket, hornet, and wasp are members of the superfamily Vespoidea. In most areas, the yellow jacket is the major cause for insect sting reactions. These insects nest in the ground, under logs, or in walls and frequently are disturbed in the course of activity such as gardening and lawn mowing. Because vespids feed on sugary sources, these insects are attracted to foods and commonly are found around garbage and at picnics. The hornets build nests that hang in trees and shrubs. Wasps usually build a honeycomb nest under eaves and rafters and are relatively few in number in such nests.

The imported fire ant *Solenopsis invicta*, a nonwinged stinging insect, is responsible for increasing numbers of acute allergic reactions.^{78, 79} This insect is found predominantly in the Southeastern United States, particularly along the Gulf Coast, and is gradually spreading westward and northward. The fire ant attaches itself to its victim by biting with its jaws and pivoting around its head, stinging in multiple sites in a circular pattern with the stinger located on the abdomen. Within 24 hours of the sting, a sterile pustule develops that is diagnostic of the fire ant sting.

Venom Constituents

Insect stings are painful because of the injection of a complex mixture of small peptides, vasoactive amines, and proteins. Major venom

constituents include phospholipase, hyaluronidase, and other enzymatic proteins that may contribute to the tissue damage associated with insect stings. Honeybee venom contains a large amount of mellitin, a relatively small peptide that is highly toxic and destructive to cells.⁶⁵

Protein and Peptide Components of Venoms of Honeybee and Vespids

Honeybee Venom

Proteins

Phospholipase A2

Hyaluronidase

Acid phosphatase

Peptides

Melittin

Apamin

Mast-cell-degranulating peptide

Vespid venoms

Proteins

Phospholipase A1

Hyaluronidase

Antigen 5

Peptides

Mast-cell-degranulating peptide

Kinin

There have been extensive studies of the cross-reactivity of venom antigens. Within the vespid family, there is extensive cross-reaction between the two hornet venoms⁴⁵ and between the yellow jacket and hornet venoms,⁶⁴ and there is limited cross-reactivity between wasp venom and other vespid venoms.⁶³

Fire ant venom is unique among the Hymenoptera venoms in its composition (primarily alkaloids) and its very low protein content (approximately 1%). In contrast, venoms from honeybees, yellow jackets, hornets, and wasps contain about 50% protein by dry weight. Fire ant venom has bactericidal, hemolytic, cytotoxic, and insecticidal properties.³⁴ Characterization of fire ant antigens has revealed allergens ranging in molecular weight from 13,000 to 42,000, a range similar to that of important aeroallergens.⁴⁹

Diagnosis

The diagnosis of an insect sting reaction is usually obvious, and in contrast to insect bites, insect stings are always associated with pain. The allergic symptoms tend to occur within a short period, usually 10 to 15 minutes following insect sting. This relationship may not be apparent when there is a delay in the onset of symptoms following the sting. The identification of the insect responsible for the sting may be difficult. Details concerning the location of the nest may help identify the insect.

For example, yellow jackets tend to nest in the ground, and hornets tend to build their nests in shrubs. The honeybee may be identified more easily because it usually leaves its stinger in place.⁶⁰

Confirmation of stinging insect allergy is made by the detection of venom-specific IgE, which is carried out most easily by the simple immediate skin test. Persons who experience a severe systemic reaction to a Hymenoptera sting should undergo venom skin testing after an interval of at least 2 to 4 weeks. Most of the studies in support of this delay in skin testing were performed while using whole-body extracts.^{9, 51, 73} A study by Goldberg and colleagues suggests that the combination of skin test and serum venom-specific IgE performed within 1 week after the systemic reaction may yield positive results in more than three quarters of the patients, thus preventing a delay in treatment of certain high-risk individuals.²¹

Venom skin tests are indicated only for individuals who have had a history of a systemic reaction following an insect sting, such as generalized urticaria, angioedema, upper airway obstruction, circulatory collapse with shock and hypotension, cardiac arrhythmias, nausea, vomiting, diarrhea, and rarely uterine contractions. Skin tests are not indicated for individuals with large local reactions or for children with dermal reactions only. There is no current rationale for performing routine venom skin tests in an insect-nonallergic population such as individuals who are being evaluated for other allergic problems.⁶²

Since 1979, commercial venoms have been available for diagnosis and treatment. The commercial products include freeze-dried venom of honey bees and venom protein of yellow jackets, yellow hornets, white-faced hornets, and wasps. A mixed vespid venom protein is also available for treatment only—not for diagnosis. Because of the difficulty in collecting all species of yellow jackets and wasps, the venom raw materials for these two insects may vary in species composition from lot to lot. A listing of the exact species content for any particular lot may be obtained by contacting the supplier. Final containers of freeze-dried venom products are sealed under vacuum. This practice forcibly draws the diluting fluid into the sealed vial when the syringe needle penetrates the seal during reconstitution. The venom must be reconstituted accurately with a special diluent containing human serum albumin as a macromolecular stabilizing agent. The exact amount of diluent is provided in the product information for the specific venoms. After reconstitution, the initial concentration contains 100 µg of venom or venom proteins per milliliter. The mixed vespid venom solution contains 300 µg venom protein/mL after reconstitution. Diluted solutions of stinging insect venoms injected intradermally produce wheal and erythema reactions in patients who have significant IgE-mediated, Type I immediate hypersensitivity to stings of these insects.³⁰ Dilutions of these venom products help judge the sensitivity of the patient and whether the patient should be treated.

Skin testing should be carried out with all five individual venoms, as many patients have multiple sensitivities and patients often cannot

identify the specific insect responsible for the sting. Epicutaneous testing should be done before intradermal testing (see article by Dolen elsewhere in this issue). In both the epicutaneous and intradermal tests, a negative control test with diluent alone must be performed. The flexor surface of the forearm is the usual location for skin testing. It is important that a separate sterile syringe and needle be used for each extract and each patient.

The authors use the prick method in their practice. Prick tests are accomplished using a solution of 1 μg venom protein/mL. Instructions are included in the package insert on proper dilution and storage of diluted venoms. One part of the extract concentration of 100 $\mu\text{g}/\text{mL}$ is combined with nine parts of diluent. This step is then repeated using the new concentration to achieve the proper concentration to perform prick tests (i.e., 1 $\mu\text{g}/\text{mL}$). One drop of the venom protein solution is applied to the forearm, and the skin is pricked through the surface of the drop with a sterile 27-gauge needle. For prick test, a positive reaction (reaction greater than diluent control) at the 1 $\mu\text{g}/\text{mL}$ concentration indicates a high level of sensitivity to the test venom. Patients showing a positive reaction to the prick test at this concentration should begin intradermal tests at concentrations of no more than 0.0001 to 0.001 $\mu\text{g}/\text{mL}$. Patients with negative prick tests may begin intradermal tests at a concentration of 0.001 $\mu\text{g}/\text{mL}$.

Intradermal test dilutions are made in the same manner used to obtain the prick-skin test dilutions, and directions are included in the package insert with the specific venoms. The venom product brochure recommends injecting a volume of 0.05 mL slowly into the superficial skin layers until a small bleb occurs. Some authors feel this volume is excessive and may cause irritant reactions and suggest using 0.02 mL volumes instead.⁶² Intradermal tests should be started with the most dilute solution, usually a concentration of 0.001 $\mu\text{g}/\text{mL}$. If after 20 minutes no skin reaction is obtained, the intradermal testing should be continued using 10-fold increments in the concentration until a reaction of 5- to 10-mm wheal and 11 to 20 mm erythema is obtained or until a concentration of 1 $\mu\text{g}/\text{mL}$ has been tested, whichever occurs first. A patient should be considered sensitive to the test venom when a skin response occurs at a concentration of 1 $\mu\text{g}/\text{mL}$ or less, provided that this reaction is greater than that of the diluent control. It has been suggested that the 1 $\mu\text{g}/\text{mL}$ venom concentration may produce an irritant reaction in some patients, and it is recommended that caution be used in attributing a positive skin test response at this concentration to the presence of IgE antibody to venom.²⁰ On the other hand, there is an increasing amount of data to support the clinical significance of a positive skin test response at this concentration.^{31, 84} Interpretation of skin test results always requires correlation with the patient's history. In patients who have a positive history of stinging insect hypersensitivity, skin tests with a concentration of 1 $\mu\text{g}/\text{mL}$ are recommended if skin test responses at lower concentrations are negative. There are patients who have severe systemic reactions after an insect sting and have barely

detectable venom IgE levels as determined by skin tests or RAST. A substantial number of such patients may have skin test responses that are negative at 0.1 $\mu\text{g/mL}$ but that are positive at 1 $\mu\text{g/mL}$.²³ There have been occasional reports of individuals who have experienced anaphylaxis to an insect sting and have had negative skin test responses for stinging insect venom but positive venom-specific IgE antibodies demonstrated by specific IgE immunoassays such as RAST. It may be reasonable to consider blood testing for those rare patients who have a convincing history of anaphylaxis after an insect sting and who have negative skin test responses before concluding that venom immunotherapy is not necessary.

Imported fire ant whole-body extract is the only reagent currently available for diagnostic testing in patients with suspected fire ant hypersensitivity. If screening prick test responses are negative, intracutaneous testing should be performed with initial concentrations of approximately 1×10^{-6} weight/volume (w/v). Intracutaneous skin test concentration should be increased by increments until a positive response is elicited or a maximum concentration of 1×10^{-3} or 2×10^{-3} w/v is reached.^{16, 82, 83} Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.^{29, 68} If the patient is able to positively identify fire ant as the stinging insect, testing with other stinging insect venoms is not required. The presence of a pustule at the sting site at 24 hours after the sting is diagnostic of a fire ant sting. This type of reaction should be looked for carefully, especially if the sting occurred in an area where fire ant mounds have been sighted.

Patients on nonselective β blockers may be more reactive to allergens given for testing or treatment and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.³³ Certain medications may lessen the skin-test wheal and erythema responses elicited by allergens and histamine for varying time periods. Conventional antihistamines should be discontinued at least 5 days before skin testing. Topical steroids should be discontinued at the skin test site for at least 2 to 3 weeks before skin testing.^{6, 55} Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.⁵⁸ Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.⁵⁶

IgE antibodies reacting with venom also have been measured by specific IgE immunoassays such as the radioallergosorbent test (RAST). The RAST is not as sensitive as the skin test. Approximately 15% to 20% of the patients who have positive venom skin tests do not react with RAST. RAST and related assays should not be used as a routine diagnostic test. As noted previously, it may be of use when skin tests cannot be performed or when the reaction to skin tests is equivocal.⁶⁰

Venom Selection

Since the introduction of commercial venoms, the product brochure recommendations for venom selection have not changed. Treatment with

all venoms for which there are positive skin test reactions is recommended. As a result, many patients are treated with multiple venoms, particularly mixed vespid venom (yellow hornet, white-faced hornet, and yellow jacket). Reisman analyzed the issue of venom cross-reactivity versus individual venom sensitivity through experiments using RAST inhibition and precipitation experiments with antivenom IgG antibodies raised in rabbits. He summarized the results as follows⁶²:

- There is extensive cross-reactivity between the two major North American hornet venoms, bald-faced hornet and yellow hornet.⁴⁵
- There is extensive cross-reactivity between the yellow-jacket venom and the hornet venoms.⁶⁴
- There is limited cross-reactivity between yellow-jacket and *Polistes* venoms.⁶³
- The relationship between honeybee venom and yellow-jacket venom is more complex.

RAST inhibition studies have shown four different patterns of reactivity⁶⁶:

- Specific sensitivity to each venom with no cross-reaction
- Extensive cross-reaction between the two venoms
- Reaction to a major allergen in yellow-jacket venom cross-reacting with a minor allergen in honeybee venom
- Reaction to a major allergen in honeybee venom cross-reacting with a minor allergen in yellow-jacket venom

The majority of patients with allergic reactions caused by yellow-jacket or hornet stings most likely will have positive skin test reactions to both venoms. About half of the patients will react to *Polistes* venom. About half of individuals with *Polistes* sting reactions will have positive skin-test reactions to yellow-jacket and hornet venoms. Patients who have had reactions caused by yellow-jacket stings also may have positive skin-test reactions, usually to a lesser degree, to honeybee venom and vice versa. Patients who have had honeybee sting reactions occasionally will have positive skin-test reactions to vespid venoms, again usually to a lesser degree.⁶²

It has been suggested that if the responsible insect can be identified accurately or if there is a significant difference in the degree of skin test reactivity, knowledge of these cross-reactions can lead to a single venom therapy whenever possible, despite the presence of multiple positive venom skin test results.⁶² Experience with immunotherapy with single venoms confirms the effectiveness of this approach.⁶⁷

Summary of Insect Sting Testing

Insect sting anaphylaxis is a relatively common problem estimated to affect at least 0.4% of the population and is responsible for at least 50

deaths per year in the United States. Along with a suggestive clinical history, the most sensitive measure for accurate diagnosis is the venom skin test. Venom extracts are available commercially for testing and treatment for the five important flying stinging insects (honeybee, wasp, yellow jacket, yellow hornet, white-faced hornet). Whole-body extract is the only available skin test reagent for imported fire ant diagnosis and treatment. Patients with a history of a systemic reaction to a stinging insect with a positive intradermal skin test to venom at a concentration of 1 $\mu\text{g}/\text{mL}$ or less are considered to have a diagnosis of venom allergy. There is some controversy over whether the 1- $\mu\text{g}/\text{mL}$ concentration only causes an irritant reaction, so positive skin tests at this concentration must be correlated closely with clinical history. There is extensive cross-reactivity among the yellow jacket and hornet and, to a lesser degree, to wasp and honeybee. Knowledge of this cross-reactivity can aid in choosing the correct venom or venoms for venom immunotherapy. Venom immunotherapy is indicated in patients with positive skin tests with a history of insect sting anaphylaxis. It has been shown to be as high as 97% effective in some studies.

DRUG ALLERGY

With the multitude of pharmacologic agents in use, adverse drug reactions represent a significant health care problem in the United States. The incidence of drug reactions is increasing secondary to several factors, including the use of multiple medications in the same patient and short, intermittent dosing of drugs that favors sensitization on subsequent re-exposure. Host factors such as immunosuppression, presence of atopy, and specific genetic polymorphisms also play a role.¹¹

Allergic drug reactions account for approximately 10% of all adverse reactions.²⁹ The terminology *allergic drug reactions* is reserved for those untoward reactions known or suspected to be mediated by immunologic mechanisms. The most important characteristics that determine whether a drug induces an immune response are related to the chemical properties and molecular weight of the drug. Large-molecular-weight drugs are referred to as *complete antigens* and are more likely to be associated with a significant number of allergic reactions. Low-molecular-weight drugs must first combine with carrier proteins before they are capable of inducing an immune response. These substances, which are not allergenic or immunogenic by themselves, are called *haptens*, and the immunologic response is directed against the carrier protein-hapten complex. Antisera and insulin (beef and pork types) are complete antigens; penicillin and its metabolites are haptens.⁴¹

With rare exceptions, a stable covalent bond is necessary to produce an effective carrier-hapten combination.⁵² The higher the bonding affinity of a drug in vitro, the more likely it is to induce an allergic reaction.

Clinical Evaluation and Diagnosis of Drug Hypersensitivity

In view of the diverse immunopathologic, toxic, and pharmacologic effects of the multitude of medications used in medical practice, the tasks of identifying and characterizing allergic reactions to drugs are formidable. The average hospitalized adult receives more than eight drugs simultaneously, and the outpatient management of chronic conditions often requires polypharmacy, making candidates for hypersensitivity abundant.

Cardiovascular or respiratory compromise, urticaria, angioedema, rhinitis, vomiting, or diarrhea may be symptoms of acute drug allergy. A complete listing of medications should be obtained from patients with suspected drug allergy with focus on previous and current drug use, allergy or toxicity related to previously or currently used drugs, and the temporal sequence of events between initiation of therapy and onset of symptoms.¹³ A thorough physical examination should be performed with careful attention to all systems that could possibly account for the clinical presentation.

Laboratory studies can be used to determine the extent of immunologic activation to aid in the characterization of allergic drug reactions. Serum tryptase levels provide a specific biochemical marker of mast-cell-mediator release, facilitating the diagnosis of anaphylaxis.³⁷ Complement 3a (C3a), C4a, and C5a anaphylatoxin levels permit assessment of the presence and degree of complement activation. The immediate hypersensitivity skin test is the most useful test for detecting IgE-mediated drug reactions caused by penicillin and many large-molecular weight drugs, but has little use with low-molecular-weight agents.

Patch testing is the most reliable technique for the diagnosis of contact dermatitis. Lymphocyte proliferation assays may be useful as retrospective indicators of cell-mediated drug reactions, but they are not available in most medical centers, and their positive and negative predictive values have not been determined.⁵⁰

Skin Tests with Penicillin

Penicillin and its derivatives may cause more allergic drug reactions than any other drug or drug class, which are estimated to occur in 1% to 10% of treated patients.³² Penicillin has been deemed responsible for the majority of all drug-mediated anaphylactic drug deaths in the United States and is a frequent cause of nonfatal anaphylactic reactions. The risk of death from penicillin anaphylaxis is approximately 0.0015% to 0.002% (one death per 50,000 to 75,000 cases).⁸⁶ In the 1960s, this statistic was estimated to translate to 400 to 800 deaths per year in the United States.

Anaphylactic reactions to penicillin occur most frequently in the 40-

to 49-year age group and when the drug is given parenterally.⁴¹ Penicillin-specific IgE diminishes over time; therefore, the greater the interval since the previous reaction, the less likely the sensitivity still exists. Approximately 70% of adults with documented penicillin allergy have no detectable IgE when tested 10 years later.³² Similar results were found in one study among pediatric patients, suggesting that up to 75% lose their skin-test positivity within 3 to 5 years.⁴⁷ If a patient with a history of penicillin allergy requires penicillin, it is necessary to skin test the patient for the presence of penicillin-specific IgE antibodies to determine the risk of immediate hypersensitivity reaction.

Immune Response to Penicillin

Penicillin and its metabolites are small molecules (haptens) that must react with body proteins through covalent bonds before they induce an immunologic response. Conjugation of the penicillin to the protein following cleavage of the β -lactam ring (penicilloyl group) has provided a skin test reagent that shows a positive correlation with clinical allergic sensitivity in more than 75% of all penicillin-allergic individuals.⁸⁶ For this reason, the penicilloyl group has been termed the *major determinant*. Penicillin also is metabolized in small quantities by other pathways to products that are referred to as the *minor determinants*. The minor determinants consist of crystalline penicillin and its hydrolysis product, sodium penicilloate, and other simple chemical products of penicillin degradation including sodium α -benzylpenicilloylamine.⁴¹ Though most of these metabolites develop following administration of penicillin, some may be found in intravenous preparations mixed and stored for over 4 hours at room temperature.^{46, 47}

In 1969, Levine and Zolov³⁸ showed that skin testing for penicillin allergy can be used to accurately determine whether a history-positive patient will tolerate penicillin if both the major and minor determinants are used in testing. This work has been corroborated in several other studies,^{25, 77} but despite this conclusive data, the minor determinants have not been approved for routine clinical use. Although the antibody against penicilloyl (the major determinant) is most common, skin tests to both major and minor determinants of penicillin are necessary, as approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant.³² Evaluation by specific IgE immunoassays such as the RAST does not reliably rule out the presence of specific IgE antibodies to penicillin, as it has not been used successfully to assay for all of the minor determinants.³⁵

Skin tests should be performed with penicillin polylysine (PPL) and a minor determinant mixture (MDM): benzylpenicillin, penicilloate, penicilloate. The major determinant reagent, PrePen R (Schwartz Pharma, Milwaukee, WI) may be obtained commercially, but minor determinant mixture is only available at certain medical centers. Penicillin G is an acceptable substitute if an MDM is unavailable, recognizing that there is

a slight risk of a false-negative skin test because it does not contain all relevant antigenic determinants. There is no published evidence supporting the widely held belief that the aging of solutions of penicillin G increases its suitability as a skin testing reagent.¹

Skin testing of patients should be performed with placement of histamine and saline controls. Antihistamines taken within 48 hours and adrenergic drugs within 4 hours may attenuate skin test results and should be avoided. Corticosteroid therapy at less than 60 mg of prednisone or the equivalent per day does not affect skin test results. The penicillin skin test should be read at 10-minute intervals. Providing no local or systemic reactions develop, skin testing is continued at 15-minute intervals, using increasing concentrations of test materials as outlined in Table 1.

Only a small number of patients (1%) who have negative skin tests develop accelerated urticarial reactions, usually several days after beginning penicillin therapy. Anaphylaxis has not been reported in skin-test negative patients.⁸⁵ In contrast, in a patient with a positive history and positive skin tests to the major or minor determinants of penicillin, there is at least a 50% chance of an immediate hypersensitivity reaction if penicillin is given again. With negative histories of penicillin allergy, the rate of positive skin tests is 7% or less, and it is unknown whether these patients are at an increased risk of allergic reaction to penicillin. Skin testing for penicillin-specific IgE does not predict reactions occurring more than 24 hours after administration of the drug. These reactions include late-onset cutaneous reactions, non-IgE-mediated immune complex syndromes, and bullous, mucocutaneous responses.³²

Patients with a past history of penicillin allergy and a positive skin test to either major or minor determinants are at increased risk for an immediate or accelerated reaction to penicillin. In this case, the patient should receive an alternative antibiotic. If alternative antibiotics are not available or indicated, penicillin desensitization should be performed.

Table 1. PENICILLIN PROVOCATIVE TEST DOSING

Skin Test Reagents	Route	Drug Test (concentration)	Skin Test (volume)
Benzylpenicilloyl-polylysine (Pre-Pen; 6×10^{-5} M)	Epicutaneous (prick)	Full strength	1 drop
	Intradermal	Full strength	0.02 mL
Penicillin-G (fresh to 1 week old)	Epicutaneous (prick)	10,000 U/mL	1 drop
	Intradermal	10,000 U/mL	0.02 mL
	Serial (optional)	10, 100, 1000 U/mL	0.02 mL
Penicillin minor determinant mixture* (10-2M)	Epicutaneous (prick)	Full strength	1 drop
	Intradermal	Full strength	0.02 mL
	Serial (optional)	10, 100, 1000 U/mL	0.02 mL

*Reagents available at some medical centers.

Data from De Swartz RD, Patterson R: Drug allergy. In Patterson R, Grammer LC, Greenberger PA (eds): Allergic Diseases, ed 5. Philadelphia, Lippincott-Raven Publishers, 1997, p 317.

Cross-Allergenicity Between Carbapenems, Monobactams, and Penicillin

Carbapenem (e.g., imipenem) has been shown to be cross-reactive with penicillins.⁶⁹ The monobactam aztreonam does not seem to cross-react with penicillins,² but anecdotal episodes of anaphylaxis have been reported.⁵ Skin testing should be performed by epicutaneous (such as prick) and intradermal (if the prick test is negative in 15 minutes) methods, using concentrations of aztreonam 3 mg/mL and imipenem 1 mg/mL.¹⁸ Intradermal testing can be performed with serial 10-fold dilutions if desired; however, testing for these agents has not been validated, and negative tests do not rule out a possible reaction.

Cephalosporins

Penicillins and cephalosporins have a common β -lactam ring structure, and moderate immunologic cross-reactivity has been demonstrated in vitro.^{15, 27} First- and second-generation cephalosporins are responsible for most of the in vitro cross-reactions with penicillins.⁷ Since 1980, reaction rates in penicillin history-positive, skin test-positive patients who were given a cephalosporin have decreased to 2%.⁷⁵ It is important to emphasize that the majority of the 2% reactors were cases of anaphylaxis, some of which were fatal.⁵⁷ Penicillin skin test-positive patients should undergo a formal cephalosporin desensitization regimen before receiving this class of antibiotic.

A positive skin test to a cephalosporin, when carefully performed, may predict clinical sensitivity; however, such skin testing is not standardized and the negative predictive value is unknown. The cephalosporin desired for treatment should be used for the skin test reagent. Epicutaneous (e.g., prick) testing should be performed at 3-mg/mL concentration along with placement of controls according to standard procedure. If the prick test reaction is negative at 15 minutes, a 0.02-mL intradermal test should be placed at 3-mg/mL concentration. If the patient has a history of previous clinical reaction documented as anaphylactic or life threatening, testing should start at 0.3 mg/mL or lower. A positive skin test to a cephalosporin implies the presence of drug-specific IgE antibodies, and the patient should receive an alternate antibiotic or undergo desensitization.

Insulin

Clinical immunologic reactions to insulin are relatively uncommon despite over six million individuals requiring insulin for diabetes in the United States. Human insulin consists of two polypeptide chains, α and β chains, connected by two interchain disulfide bonds. There is species variation in the amino acid sequence, which may account for the fact

that human recombinant DNA (rDNA) insulin is less allergenic than porcine insulin, which is generally less allergenic than bovine insulin.

The incidence of allergic reactions to insulin as reported by Patterson and colleagues⁵⁴ has declined over the last several decades. The increasing use of rDNA insulin and the availability of purified commercial preparations are likely contributing factors to this decline. Current preparations contain less than 50 parts per million impurities, whereas those used in the 1970s contained as much as 1000 parts per million.⁷⁶ Human rDNA insulin does not contain these contaminants.

The vast majority of patients who receive insulin, regardless of the preparation used, develop antibodies to insulin molecules.⁷² The majority of these antibodies are from the IgG class, although other immunoglobulin classes have been detected. Systemic allergic reactions to insulin are IgE mediated.

Most commonly, these patients have a history of hiatus in insulin therapy and report large local reactions when insulin is reinstituted. Systemic reactions occur most commonly within 12 days, usually between the fifth and eighth days following reinstituting insulin therapy.

Immediate-type insulin reactions occur within 30 minutes of the injection and are characterized by urticaria, angioedema, hypotension, and bronchospasm. Patients with this history have positive immediate hypersensitivity skin tests to insulin, and a negative skin test rules out insulin allergy. A positive test does not establish a diagnosis of insulin allergy, as approximately half of patients on insulin have positive skin tests to insulin. Skin testing has a limited predictive value in the clinical management of insulin allergy. Once the diagnosis of insulin allergy is confirmed, it should be ascertained whether insulin is necessary. If possible, another type of insulin should be prescribed to which the patient is not allergic or to which the patient is desensitized.

Local Anesthetics

Allergic reactions to local anesthetics are rare.⁴ The significance of the problem lies in the fact that patients who have had an apparent adverse reaction to a local anesthetic often are denied the benefits of local or regional anesthesia. Patients who require a procedure that normally could be performed under local anesthesia often are subjected to the increased risks of general anesthesia.

In the majority of these instances, the patient is not allergic to local anesthetics. Reactions to local anesthetics that are reported are often the result of toxic or vasovagal reactions, epinephrine side effects, or are psychomotor in nature.¹⁷

Local anesthetics, based on their structure, can be divided into two groups. The first group includes benzoic acid esters, such as benzocaine, procaine, tetracaine, and piperacaine. The antigenicity of this group of drugs has been established by patch testing. These drugs cross-react

with one another to a significant extent. The second group is composed mostly of amides that may or may not be chemically related. Among them are lidocaine, mepivacaine, prilocaine, and dibucaine. The antigenicity of the amide group has not been established clearly, and apparent adverse reactions often are avoided by the use of preservative-free preparations. It is believed that if these drugs are immunogenic, they do not cross-react to any great extent.

Though there are isolated reports of immediate hypersensitivity reactions to local anesthetics in both categories, true IgE-mediated anaphylaxis to local anesthetics is rare. Contact dermatitis commonly occurs with local anesthetics, and it is estimated that type IV reactions account for more than 80% of the allergic responses reported.³ Acute immunologic reactions not mediated by IgE have been reported.⁸¹ In addition, local anesthetic preparations contain vasoconstrictors, sulfites and parabens. Reactions to these substances generally are of a nonimmunologic nature.

The goal in management of a patient with a previous reaction to a local anesthetic is to establish the safety of this type of drug should the drug be required in future procedures. Although it is recognized that the majority of previous reactions to local anesthetics are not IgE mediated, the skin test procedure does serve several purposes. If the skin test is negative, it reassures the physician and the patient that provocative dosage procedures can be performed with relative safety. Should the skin test be positive, it should alert the physician that a more cautious approach to the administration of the drug is warranted. Schatz and colleagues⁷⁰ demonstrated the safety of anesthetic challenge following negative skin test in 257 reported subjects in whom a negative skin test has been followed by uneventful challenge.

The skin testing protocol, at 15-minute intervals, involves epicutaneous tests with 1:100 and full strength preparations, followed by 0.02-mL intradermal injections of 1:10,000, 1:1000 and 1:100 solutions. The provocative incremental challenge is performed after skin testing. Its protocol is shown in Table 2. The challenge must be performed in the presence of a physician with emergency facilities and therapy available.

It is prudent in most instances to challenge a patient with a drug other than the agent to which the patient had a previous reaction. In almost all instances, incremental challenge should be an amide anesthetic. Unless there is a question that the sulfites or vasoconstrictor could be responsible for a reaction, a nonvasoconstrictor preparation should be used for both procedures.

After successful administration of the local anesthetic preparation, a letter should be given to the patient and referring physician stating that he or she can take this particular preparation but that the results do not apply to any other preparation. Notation should be made regarding the trade name of the preparation and the presence or absence of a vasoconstricting agent.

Table 2. PROVOCATIVE INCREMENTAL CHALLENGE PROCEDURE FOR PATIENTS WITH A HISTORY OF LOCAL ANESTHETIC REACTION*

Dose No.	Vol (mL)	Concentration
1	0.1	1:10,000
2	0.1	1:1000
3	0.1	1:100
4	0.1	1:10
5	0.1	Full strength
6	0.5	Full strength
7	1.0	Full strength

*All injections given 15 minutes apart.

Protamine

Protamine sulfate is a polycationic protein of low molecular weight (4500 D) purified commercially from the sperm or matured testes of salmon. It is used intravenously to reverse the anticoagulant effects of heparin after a variety of procedures including hemodialysis and cardiopulmonary bypass. It also is added to insulin preparations (neutral protamine Hagedorn [NPH] insulin) to delay the absorption and thus increase the duration of action of insulin.

Protamine has been associated with immediate generalized reactions mediated by both immune (IgE) and nonimmune mechanisms.⁴⁸ Acute reactions to protamine may include anaphylaxis, bronchospasm, urticaria, hypotension, transient elevations in pulmonary artery pressure, cardiovascular collapse, and death.^{24, 88}

It has been proposed that exposure to protamine insulin may sensitize patients to protamine, leading to higher rates of anaphylactoid reactions on subsequent exposure to protamine sulfate during cardiac catheterization or during cardiac surgery. The risk of such reactions in patients requiring protamine insulin is uncertain, with disparate risk association reported in the literature ranging from no increased risk to greater than 50% increased risk in NPH insulin-dependent diabetics. In more recent, prospective studies of diabetic patients receiving NPH insulin, no significant incidence of clinical reactions has been identified.^{39, 40} Additionally, data have not substantiated a history of fish allergy or previous vasectomy as risk factors for protamine reaction.^{26, 40}

Antibody tests for immunospecific IgE to protamine have not been validated for the clinical significance of protamine antibodies. Serum antiprotamine IgE and IgG have been demonstrated in vitro in patients with clinical reactions.⁸⁷ Epicutaneous (prick) skin testing can be performed using 1- and 10-mg/mL protamine concentrations without causing nonspecific skin responses. Negative cutaneous reactions may help exclude antiprotamine IgE; however, this does not exclude all patients at risk for severe immediate reaction.

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