Testing For Allergy

Mary V. Lasley and Gail G. Shapiro

Pediatrics in Review 2000;21;39
DOI: 10.1542/pir.21-2-39

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Mary V. Lasley, MD* and Gail G. Shapiro, MD†

OBJECTIVES

After completing this article, the reader should be able to:

1. **List the indications for immediate-type skin testing.**
2. **Delineate the populations in which pollen allergy and food allergies are more common.**
3. **List the most common medicines that can alter the results of allergy skin testing.**
4. **Explain the commonalities and differences between radioallergosorbent testing and skin testing.**
5. **Delineate situations in which in vitro testing is indicated.**

Why Should We "Skin Test" Patients?

Many children in the United States are affected by atopic disease. It has been estimated that 4% to 6% of children have food allergies, 8% to 10% have asthma, and 15% to 25% have allergic rhinitis. Additionally, large numbers of children who suffer from allergic rhinitis have coexisting otitis media and sinusitis. Further, there is a widespread impression that the incidence of allergic diseases has increased in the past 15 to 20 years, most notably in industrialized countries. The purpose of allergy testing is to help identify potential allergen(s) that are contributing to the allergic disease process. By identifying the allergen, the patient and his or her family can avoid exposures, and the clinician can manage the disease appropriately. Allergy testing can be performed for a variety of foods, aeroallergens, latex, venom, and some medications.

History of Skin Testing

Skin testing methods were described initially more than a century ago. In 1873, Charles Blackley performed the first allergy skin tests on patients by scratching the surface of their skin, applying pollen to the scratch, and observing the interaction. In 1908, Mantoux described the intradermal test, which subsequently was used for allergy testing. In the early 1920s, Lewis and Grant described the prick test. The principles of allergy testing described in earlier years remain in practice today, albeit with modifications that include standardized devices and allergen extracts.

How Does Skin Testing Work?

Skin testing is a major method for identifying allergen-specific immunoglobulin E (IgE). Allergen is introduced into the skin and diffuses through it to interact with IgE that is bound to mast cells. Cross-linking of IgE antibodies results in release of histamine and other chemical mediators. The released histamine prompts the development of a central wheal and an erythematous flare. The wheal and erythema are assessed 15 to 20 minutes after the allergen has been placed. To interpret skin test results properly, a positive histamine and negative saline control are placed for comparison. In certain patients, a late-phase reaction occurs 4 or more hours after skin testing. This results from influx of inflammatory cells due to mast cell mediator release. Although this edematous reaction is seen most often in cases of positive immediate reactivity (within 15 to 20 min), its assessment and importance are not clear at this time.

In Vivo Testing

PERCUTANEOUS

Currently, skin testing techniques are divided into two general categories: percutaneous and intradermal tests. Percutaneous tests are used most widely. Percutaneous refers to allergen applied "through" the skin surface. A small quantity of allergen is introduced by either a prick or puncture method. Many commercial devices are available for puncture testing, including hypodermic needles, metal lancets, bifurcated scarifier, Morrow-Brown needles, and multitest devices. Percutaneous tests can be performed on the volar surface of the arm or upper back; the latter site is more reactive. These tests generally are considered safe, cost-effective, and specific. The immediate availability of results is an added benefit (Table 1). Percutaneous tests rarely induce irritant reactions, and they appear to correlate better than intradermal tests with clinical histories and double-blind provocative challenges with allergen. Percutaneous tests typically are evaluated 15 to 20 minutes after being placed. A number of scoring systems for evaluating reactivity exists. A wheal that has at least 3 mm in diameter of induration with surrounding erythema as compared with the control (diluent) site represents a positive reaction.

There is no age limitation for performing percutaneous tests. However, most clinicians rarely test children younger than 6 months of age, and skin testing in these infants would be limited to a few select foods, such as milk, soy, and egg or household inhalants, based on the infant's clinical history. Skin test reactivity may be lessened in very young children, making positive (histamine) and negative (saline) controls essential. The number of skin tests that can be performed in younger children is limited by their smaller body surface. Younger children are more likely to be sensitized to allergens encountered in early life, such as foods and household inhalants (house dust mites, pet dander, cockroach, and mold). Children older than 4 years tend to demonstrate pollen allergies in addition to those mentioned previously. When symptoms or exposures change, skin

**Clinical Assistant Professor.*

†Clinical Professor, University of Washington Medical Center, Northwest Asthma & Allergy Center, Seattle, WA.

TABLE 1. Relative Advantages of Percutaneous (Prick) and Intradermal Testing

VARIABLE	PERCUTANEOUS TEST	INTRADERMAL TEST
Simplicity	+++	++
Speed	++++	++
Interpretation of positive and negative reactions	++++	++
Discomfort	+	+++
False-positive reactions	Rare	Possible
False-negative reactions	Possible	Rare
Reproducibility	+++	++++
Sensitivity	+++	++++
Specificity	++++	+++
Detection of IgE antibodies	Yes	Yes
Safety	++++	++
Testing of infants	Yes	Difficult

Modified from Demoly P, Michel F-B, Bousquet J. In vivo methods for study of allergy skin tests, techniques, and interpretation. In: Middleton E, Jr, Reed CE, Ellis EF, et al, eds.* Allergy Principles and Practice. *5th ed. St. Louis, Mo: Mosby-Year Book; 1998: 432.

testing may need to be repeated. Examples include an allergic child whose test results at a young age indicated sensitivities to foods or indoor allergens, who now develops seasonal symptoms or a change in symptoms after acquiring a new pet or relocating to a different geographic area.

Disadvantages of percutaneous testing include dependence on consistent technique, allergen extract quality, skin reactivity, discomfort, and the risk of anaphylaxis. Also, although these tests are specific, they may lack sensitivity for detecting clinically significant allergies. The amount of antigen introduced depends on the prick/puncture size and the testing device. Loss of extract potency occurs over time and can be costly if the clinician performs these tests infrequently. Recent United States Food and Drug Administration regulation of allergenic extracts may help to improve the quality of skin testing reagents. Previous use of medications that suppress skin testing also may give false-negative results. A review of fatalities from skin testing over a 40-year period reported six fatalities associated with skin testing, although none of these individuals had undergone prick testing alone. Systemic reactions have been observed with percutaneous testing.

INTRADERMAL

Intradermal tests are used commonly when a significant allergic history is obtained and results of the percutaneous tests are negative or equivocal. The intradermal test involves injecting a specific allergen "within" the dermal layer of the skin of the upper arm. When using a 26- to 30-gauge sterile disposable needle, approximately 0.02 mL of allergen is injected to make a small bleb that is 2 to 3 mm in size, similar to the performance of a Mantoux tuberculin test. Allergen extracts for prick testing generally are diluted to 1:10 to 1:100, but intradermal testing is performed with allergen extracts that have a dilution of 1:1,000. Nevertheless, the intradermal test introduces more allergen than the percutaneous test. The site is observed for 15 to 20 minutes for wheal and erythema. A positive reaction is considered to be a wheal that is at least 5 mm in diameter compared with the negative (diluent) control. These tests are considered 100 to 1,000 times more sensitive than prick tests and are associated with fewer false-negative reactions (Table 1). It is important to use appropriate concentrations of allergen when performing intradermal testing because frequent false-positive results can be obtained at high, irritating concentrations of certain allergens. The use of multiple intradermal concentrations of allergens more potent than a 1:1,000 concentration (end point titrations) is discouraged for this reason and because of the questionable value of the semiquantitative data on final outcome. Due to the low but real risk for anaphylaxis, intradermal allergy testing should be performed only in a facility in which personnel are trained and equipped to manage these severe reactions.

Who Should Be Skin Tested?

Skin testing can be performed for any patient who has a suspected IgE-mediated reaction, but certain situations require clinical judgment. Patients who have dermatographism will react to the trauma of the scratch with a false-positive result. Patients who have a history of dermatographism should have positive (histamine) and negative (diluent) controls placed prior to any attempt at allergy skin testing to determine if valid results can be expected. Patients who have severe eczema may have such extensive involvement that skin available for testing is inadequate. Such patients can be treated aggressively and tested when their skin has improved or may be served better by in vitro testing.

Some medications can suppress skin tests, but a withholding period may allow successful evaluation. Most commonly, antihistamines inhibit the wheal and flare reaction to histamine (Table 2). Generally, if antihistamines are withheld for 48 to 72 hours, skin testing can be performed easily. Older first-generation

TABLE 2. Inhibitory Effect of Various Treatments on IgE-mediated Skin Tests

DRUGS		SUPPRESSION		
GENERIC NAME	TRADE NAME	DEGREE	DURATION	CLINICAL SIGNIFICANCE
First-generation Anti-H_1 Histamines				
Chlorpheniramine	Chlor-trimetron®	++	1 to 3 days	Yes
Clemastine	Tavist®	+++	1 to 10 days	Yes
Cyproheptadine	Periactin®	0 to +	1 to 8 days	Yes
Diphenhydramine	Benadryl®	0 to +	1 to 3 days	Yes
Hydroxyzine	Atarax®	+++	1 to 10 days	Yes
Second-generation Anti-H_1 Histamines				
Astemizole	Hismanal®	++++	30 to 60 days	Yes
Azelastine	Astelin®	++++	3 to 10 days	Yes
Cetirizine	Zyrtec®	++++	3 to 10 days	Yes
Loratadine	Claritin®	++++	3 to 10 days	Yes
Terfenadine	Seldane®	++++	3 to 10 days	Yes
Anti-H_2 Histamines				
Cimetidine	Tagamet®	0 to +		No
Ranitidine	Zantac®	+		No
Corticosteroids				
Systemic, short-term		0		No
Systemic, long-term		Possible		Yes
Inhaled		0		No
Topical skin		0 to ++		Yes
Antiasthma Medications				
Beta-2 agonists, inhaled		0 to +		No
Cromolyn	Intal®	0		No
Nedocromil	Tilade®	0		No
Theophylline		0 to +		No
Tricyclic Antidepressants				
Doxepin	Sinequan®	++	3 to 11 days	Yes
Imipramines		++++	>10 days	Yes
Phenothiazines		++		Yes

Modified from Demoly P, Michel F-B, Bousquet J. In vivo methods for study of allergy skin tests, techniques, and interpretation. In: Middleton E Jr, Reed CE, Ellis EF, et al, eds.* Allergy Principles and Practice. *5th ed. St. Louis, Mo: Mosby-Year Book; 1998:434.

antihistamines may interfere with skin test reactivity for up to 24 hours. Newer second-generation antihistamines have longer half-lives and can block the reaction for 3 to 10 days, except for astemizole, which may produce interference for 30 to 60 days. Some other drugs, such as tricyclic antidepressants, have potent antihistaminic effects and may interfere with performance of skin tests. H_2 antagonists (eg, cimetidine, ranitidine) have a limited inhibitory effect, and stopping these medications on the day of skin testing probably is sufficient. Asthma medications, including inhaled corticosteroids, cromolyn, nedocromil, beta-2 agonists, theophylline, and a short burst of oral corticosteroids, do not suppress skin testing results. Therefore, these medications do not need to be stopped. High-dose, long-term oral steroids and potent topical steroids applied to the skin test site for a period of 1 week or longer may suppress skin test results.

TABLE 3. Determination of Specific IgE by Skin Testing and RAST*

VARIABLE	SKIN TEST	RAST
Risk of allergic reaction	Yes	No
Sensitive	Very	Less
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermatographism	Yes	No
Broad selection of antigens	Yes	No
Immediate results	Yes	No
Expensive	No	Yes
Semiquantitative	No	Yes
Lability of allergens	Yes	No

RAST = Radioallergosorbent test as an example of other in vitro tests.
Modified from Sly RM. Allergic disorders. In: Behrman RE, Kliegman RM, Arvin AM, eds.* Nelson Textbook of Pediatrics. *15th ed. Philadelphia, Penn: WB Saunders Co; 1996:617.

In Vitro Testing

In vitro testing is indicated for patients who have severe cutaneous disease, cannot discontinue medications that interfere with skin testing, or have experienced severe anaphylaxis. The discovery of IgE in 1967 has played a large role in the scientific advancement of allergic disease. Subsequently, in vitro tests were developed to measure levels of antigen-specific IgE. Radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) are used commonly. Although good correlation exists for high titers of antigen-specific IgE as identified by in vitro tests and skin tests, in vitro testing generally is not as sensitive as skin testing in defining clinically pertinent allergens (Table 3). For highly atopic patients who have elevated total IgE, a nonspecific binding occurs that results in lessened specificity. Additional disadvantages of in vitro testing are increased cost, delays in providing results, and laboratory reliability. Selection of a reliable laboratory is fundamental. Most RAST tests are semiquantitative and reported in arbitrary units on scales ranging from 0 to 4 or 0 to 6. Assessment of threshold values for clinical significance is difficult to interpret. It is inappropriate to send specimens for extensive RAST testing without paying careful attention to the clinical history and the relevant antigens.

RAST testing involves a sandwich method in which specific antigen is attached to a solid-phase paper disc (allergosorbent) (Figure). The solid-phase disc is incubated with the patient's serum, which contains IgE antibody. Unbound antibody is removed, and radiolabeled anti-IgE antibody added. A gamma scintillation counter measures the amount of radioactivity as a reflection of the amount of specific IgE in the patient's serum. Results are compared with standard reference sera.

Another version of the RAST measures IgG or IgG4 (rather than IgE) for specific food allergens. Because there is no correlation between positive IgG or IgG4 RAST results and clinical disease, these tests serve no purpose, and their use for evaluating purported food allergy should be discouraged.

The principles of ELISA are identical to those of RAST except that an enzymatic marker is used rather than a radioactive marker. The solid-phase component consists of polystyrene plates, tubes, or beads that provide a binding site for the specific antigen. The patient's serum, containing the antibody, is added to the antigen-coated solid-phase. The presence of bound antibody is detected by using a second antibody that is enzyme-labeled. On binding, a colored reaction product is produced, which can be measured spectrophotometrically.

Are All Tests Appropriate for All Patients?

One of the most important aspects of allergy testing is to correlate the test with the clinical history. For children who have seasonal symptoms, testing is performed for the pollens that are found in the highest concentrations at the time of the

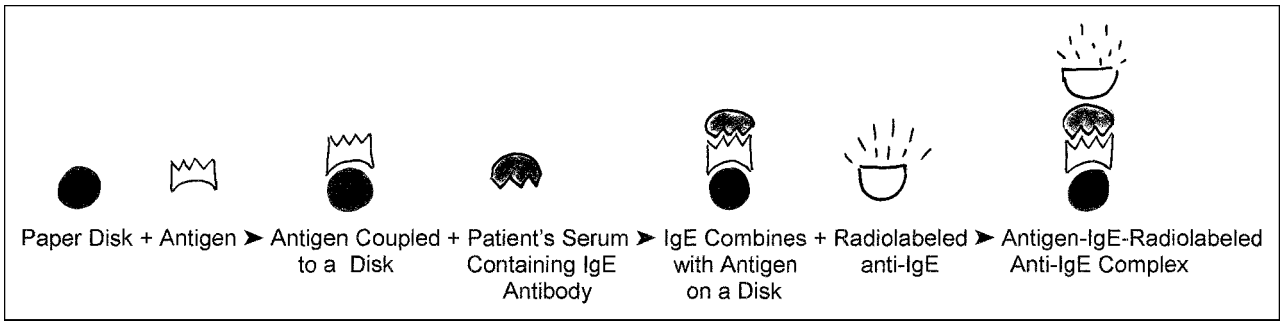

FIGURE. The principle of the radioallergosorbent test (RAST).

year when the child is symptomatic. For example, trees usually pollinate in early spring, grasses in late spring to summer, and weeds from summer through fall. The regional flora determines pollen exposure. Most flora causing significant allergic reactions are wind-pollinated, and their pollen can travel many miles. For children who have perennial symptoms, the likely allergens include dust mites, pet dander, cockroach spores, and mold spores.

Aeroallergen testing generally is viewed as correlating well with the patient's symptoms. On the other hand, food testing, whether by skin tests or in vitro techniques, is deemed less reliable. Caution should be used when interpreting food skin tests because only a small fraction of patients who have a positive food skin test will react when a double-blind placebo-controlled food challenge is performed. The avoidance of foods in the diet never should be based on skin test or in vitro test results alone. For children who have a clinical allergic history of food reactions, skin testing can help confirm the suspected food allergen. It also can be helpful in children who have eczema, whose rash may be triggered by ingestion of certain foods. The most common food allergies in children are to milk, wheat, soy, egg, peanut, tree nuts, and fish. Although many children outgrow milk, wheat, soy, and egg allergy, peanuts, tree nuts, and fish typically elicit life-long reactions and can result in severe, life-threatening anaphylaxis. The practice of placing children who supposedly have extensive food allergies on highly restrictive diets should be discouraged, especially when the clinical history does not reveal an allergic response to the food ingestion. It is important to remember that behavioral issues such as poor sleeping, crying, and hyperactivity, are nonIgE reactions. A board-certified allergist often can help families differentiate between allergic (IgE) reactions and food intolerances (nonIgE).

Who is an Allergist?

The board-certified allergist has completed a 2- to 3-year period of concentrated study in the field of allergic and immunologic diseases after having completing a pediatric or internal medicine residency. Board certification entails successful completion of the pediatric or internal medicine boards and the allergy and immunology boards. Like the pediatric board certification, which must be renewed every 7 years, the allergy and immunology board certification must be renewed every 10 years. In making a referral to a board-certified/board-eligible allergist, the primary care physician should assume that an appropriate history and physical examination will be performed to determine which diagnostic tests, including skin tests, are indicated. Most importantly, these tests will be interpreted for the patient and the referring physician. In addition, advice for allergen avoidance and proper medical management should be discussed.

Conclusion

Allergy skin testing represents one of the major tools in the diagnosis of IgE-mediated diseases. When performed properly, it yields important information, but the interpretation of these tests requires correlation with the patient's history and physical examination because the presence of IgE antibodies alone does not equate with disease. Conferring with a board-certified allergist should maximize the care of the affected patient.

SUGGESTED READING

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

1. You are asked to evaluate a 6-year-old child who has a known history of asthma for allergy to trees, grasses, and weeds. He is being treated with inhaled beclomethasone, albuterol, cromolyn sodium, and theophylline for reactive airway disease and diphenhydramine for allergic rhinitis. Which of the following is *most likely* to interfere with allergy skin testing?
   A. Albuterol.
   B. Beclomethasone
   C. Cromolyn sodium.
   D. Diphenhydramine.
   E. Theophylline.

2. Which of the following allergen-specific immunoglobulins is involved in skin testing for allergy?
   A. Immunoglobulin A.
   B. Immunoglobulin D.
   C. Immunoglobulin E.
   D. Immunoglobulin G.
   E. Immunoglobulin M.

3. You are evaluating a 12-year-old girl who has atopic dermatitis and allergy to multiple agents. Which of the following is the *most* important advantage of radioallergosorbent test (RAST) over skin testing for allergy?
   A. Increased specificity in atopic patients.
   B. Lower cost.
   C. Not influenced by antihistamines.
   D. Rapidity of diagnosis.
   E. Testing for greater number of allergens.

4. Which of the following is a *true* statement regarding testing for allergy?
   A. Avoidance of suspected food allergen should be based on skin testing.
   B. Intradermal skin testing carries lower risk of anaphylaxis compared with percutaneous skin testing.
   C. Percutaneous skin testing has high specificity but low sensitivity for clinically significant allergies.
   D. RAST is more reliable than skin testing.
   E. Skin test reactivity is increased in young infants.

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