

## **Consultation with the Specialist: Who Needs Allergy Testing and How to Get It Done**

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## CONSULTATION WITH THE SPECIALIST

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# Who Needs Allergy Testing and How to Get It Done

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**Objectives** After completing this article, readers should be able to:

1. Understand the indications for immunoglobulin E allergy testing in patients who have allergic disorders.
2. Discuss advantages and disadvantages of different allergy tests.
3. Recognize factors that can influence allergy test results.

## Case Studies

### Patient 1

*A 15-year-old girl whom you have been following since birth is rushed to the local emergency department (ED) following dinner at the family's favorite restaurant. During the meal, she developed facial flushing, acute urticaria, vomiting, and diarrhea. In the ED, she is given epinephrine and diphenhydramine, and the symptoms resolve. At a follow-up visit the next day in your office, the girl's mother informs you that her daughter had eaten cashew-crusted tuna with a serving of fresh fruit, including mango, papaya, and kiwi.*

### Patient 2

*A 4-year-old boy is playing outside and is stung by an unidentified insect. He runs inside crying, and his mother cleans the sting site on his hand. Over the next 2 hours, the hand and distal forearm become red, swollen, and pruritic. His mother takes him to a local ED. He is given diphenhydramine and parenteral corticosteroids and is observed for several hours. Several days later, the ED calls the mother to report that a honeybee venom allergy test performed in the ED is positive at a level of 2.3 kU/L.*

## Allergies and Allergy Testing

Immunologic reactions traditionally are classified by using the Gell and Coombs system (Table 1). This simple scheme is useful for learning and thinking about different mechanisms of immunopathology, although a medical condition in an individual patient might involve more than one of the mechanisms. Reactions involving immunoglobulin (Ig)E-mediated immediate hypersensitivity are called type I. Cytotoxic reactions that are Ig-mediated are called type II. Mechanisms involving immune complexes are type III, and type IV reactions are delayed hypersensitivity reactions mediated by T cells. Antigen-specific tests are available clinically for investigation of type I and type IV immunopathology.

The classic allergy testing methods of skin testing and serum-specific IgE measurement merely test for the presence of allergen-specific IgE, the primary mediator of Gell and Coombs type I reactions. Allergen-specific IgE is either detectable (a "positive" allergy test) or not (a "negative" allergy test).

In clinical practice, the role of allergy testing is not always clear because the term "allergy" has multiple meanings for patients, parents, and health-care personnel. A small child might inform school authorities that he is "allergic" to broccoli, meaning

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**Table 1. The Gell and Coombs Classification of Immunologic Mechanisms**

| Class    | Descriptive Term           | Mechanism             | Clinical Example   |
|----------|----------------------------|-----------------------|--------------------|
| Type I   | Immediate hypersensitivity | IgE                   | Anaphylaxis        |
| Type II  | Cytotoxic                  | Cell-bound IgG or IgM | Hemolytic anemia   |
| Type III | Immune complex             | IgG or IgM            | Vasculitis         |
| Type IV  | Delayed hypersensitivity   | T lymphocytes         | Contact dermatitis |

Ig=immunoglobulin  
 Adapted from Coombs PR, Gell PG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR, ed. *Clinical Aspects of Immunology*. Oxford, England: Oxford University Press; 1968:575–596.

that he doesn't like the taste. To a lay person, "allergy" might indicate some sort of adverse reaction, such as bloating and abdominal pain due to lactose intolerance but inappropriately called "milk allergy." In either case, IgE allergy testing would not be helpful. Even in medical circles, the term "allergies" might be synonymous with "seasonal allergic rhinitis." The European Academy of Allergology and Clinical Immunology (EAACI) defines allergy as "a hypersensitivity reaction initiated by immunologic mechanisms." This broad definition might encompass any of the Gell and Coombs mechanisms. The EAACI defines hypersensitivity as a state that causes objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by healthy individuals. Such definitions are precise and academically useful, but not practical. Thus, a discussion of allergy testing requires precise definitions.

## Understanding Allergy Testing

Certain diseases may be associated with IgE-mediated sensitization to allergens. The classic "diseases of immediate hypersensitivity" include atopic dermatitis, asthma, and chronic rhinosinusitis. These three

components of the "atopic march" tend to occur together in individuals and in families. IgE also can play a role in some cases of anaphylaxis and urticaria, in certain gastrointestinal disorders, and in a few other well-characterized conditions. In each of these disorders, there is an "allergic" and a "nonallergic" form. IgE allergy testing reveals clinically relevant allergen-specific IgE sensitization in some individuals and no evidence of specific IgE in others. Clinical history alone does not allow discernment between the allergic and nonallergic forms of the conditions, although the history can identify potential triggers warranting investigation. Even in a symptomatic individual, a positive test result does not necessarily have cause-and-effect clinical relevance.

The presence of allergen-specific IgE-mediated sensitization is not a disease state. IgE is a tissue-bound immunoglobulin class. It normally is present in the serum in nanogram amounts, in an equilibrium with that bound to mast cells, basophils, and other cells. In an otherwise healthy person, selective IgE deficiency (an undetectable total IgE concentration) is very rare. Thus, skin testing or specific IgE immunoassay can identify IgE-mediated allergen sensitization in about 15% of healthy,

"wheeze-free, sneeze-free" individuals tested. Under these circumstances, the test result is not false-positive. Rather, the test result is not clinically relevant at the time. In long-term follow-up, such individuals are at greater risk of developing disease symptoms than are individuals who have negative test results.

For some other conditions (such as celiac disease) that are associated with exogenous substances (such as wheat gluten), "allergy" is blamed, but the mechanism does not involve IgE. In such situations, allergy testing is not indicated.

Patch testing is the time-honored method for identifying antigens in patients who have contact dermatitis and certain other conditions that involve Gell and Coombs type IV mechanisms. Contact dermatitis sometimes is called "contact allergy," and the antigens that trigger contact dermatitis sometimes are called "allergens." Patch testing traditionally has been the purview of dermatologists, but an increasing number of allergist-immunologists have training in contact dermatitis and patch testing.

In other situations, there are so-called "allergy tests" for mechanisms other than IgE-mediated immediate hypersensitivity. These tests are either "unproved" (should only be used in the context of a peer-reviewed clinical investigation) or "disproved" (should not be used at all).

Failure to recognize the previously noted concepts has resulted in a complex modern mythology surrounding allergy and allergy testing. In some cases, there are expectations that allergy testing should identify sensitization to smoke and perfumes (respiratory irritants) for a person who has chronic rhinitis or asthma or that IgE allergy testing can identify sensitization to contact antigens such

as nickel or poison ivy for a patient who has rashes. Sometimes, legitimate IgE allergy testing is ordered inappropriately for diseases that have not been shown to be caused by IgE-related mechanisms, such as behavior disorders or multiple sclerosis.

The fundamental purpose for allergy testing is to determine whether a patient presenting to a clinician for evaluation and management of a “disease of immediate hypersensitivity” has demonstrable allergen-specific IgE. Allergy testing also is used in prescribing specific allergen avoidance and immunotherapy (“allergy shots”) and in epidemiologic studies of IgE-mediated sensitization. Allergy testing conducted outside the context of a careful clinical evaluation can produce misleading results.

## Who to Test and Why?

The decision to obtain allergy testing comes after the clinician has performed a history and physical examination and considered the differential diagnosis. If there is a clinical scenario consistent with an IgE-mediated disease (Table 2) and if symptoms have been severe or persistent, allergy testing may be indicated, not to diagnose disease, but to assess for trigger factors. Indiscriminate testing can provide misleading results, particularly when testing is ordered without a clinical history or for clinical situations in which testing is not indicated. For example, it is inappropriate to rely on allergy testing to diagnose new-onset asthma in a wheezing toddler. A few coincidentally positive allergy test results might delay the diagnosis of foreign body aspiration. Allergy testing only identifies allergen-specific sensitization; it does not diagnose asthma. Thus, although allergy testing is indicated as part of the evaluation of asthma, it is not useful in the *differential diagnosis*

## Table 2. Diseases of Immunoglobulin E-mediated Sensitization

### Classic “atopic” diseases

- Asthma
- Chronic eosinophilic rhinosinusitis, chronic otitis media
- Atopic dermatitis

### Other conditions (some cases)

- Allergic conjunctivitis
- Eosinophilic gastroenteritis
- Anaphylaxis (including insect stings, food, drugs)
- Urticaria–angioedema
- Other types of adverse drug reactions
- Other types of adverse food reactions

sis of asthma. For a child who has moderate persistent asthma, allergy testing could uncover inhalant allergy that, when treated, can improve the clinical course of the asthma.

Interpreting results of testing always takes into account the clinical scenario. A positive test result does not diagnose disease (such as asthma), and a negative test result does not refute disease. The physician who has interviewed and examined the patient must determine the clinical relevance of each test result (whether positive or negative). For example, the positive test for honeybee venom in the patient described in Case 2, who experienced a large, local reaction to a sting from an unidentified insect, has entirely different clinical significance than would the same result in another individual who has had systemic anaphylaxis following a bee sting.

One aspect of the mythology of allergy testing is the belief that infants and very small children cannot

have clinically relevant allergy and cannot undergo allergy testing. Although IgE-mediated sensitization is uncommon in infants, it does occur in both ingested (food allergy) and inhalant (dust mite or animal dander) varieties, with disease expressed in the airways, the skin, or the gastrointestinal system. Pollen allergy is less common in infants and very young children because generally repeated exposure in multiple seasons is required to develop an IgE response. If an infant has a disease that can be associated with IgE-mediated allergic sensitization, allergy testing can be performed.

## Who Should Order Allergy Testing?

Allergy testing is fundamentally a subspecialty procedure because of the level of complexity in medical decision making (Table 3). The American Board of Allergy and Immunology, a conjoint board of the American Board of Pediatrics and the American Board of Internal Medicine, certifies individuals in allergy-immunology upon completion of an examination following a 2- to 3-year fellowship in an accredited training program. Candidates for the examination also must be certified in pediatrics or internal medicine. In practice, most allergists see patients of all ages because allergy often is a “family affair.”

Conceptually, any physician who has time to take a detailed history and the diligence to learn practical aspects of the matters listed in Table 3 could incorporate IgE allergy testing into routine practice. However, the cost of stocking extracts and keeping office personnel trained makes skin testing impractical in most general pediatric offices. Specific IgE immunoassay is an alternative, but not all laboratories report consistent results. That being said, when assistance is

## Table 3. Ordering and Interpreting Allergy Tests

### Cognitive aspects

- General and specific knowledge of aerobiology
- Specific local botanical knowledge
- Correlation between seasonal symptoms and aeroallergen prevalence
- Foods, food allergens, food chemistry
- Fungal, indoor, and other allergens
- Crossreactivity
- Testing methods; how to evaluate laboratory performance

### Practical aspects

- Deciding whether testing is indicated
- Selecting test items from a panel of several hundred available tests
- Interpreting test results, whether positive or negative
- Acting on test results appropriately

not needed with the differential diagnosis and the allergens that need to be tested are clinically clear, the most practical approach is to send blood to a laboratory that uses a reliable method of measuring allergen-specific IgE.

## Nuts and Bolts of Allergy Testing

### Allergen Selection

Hundreds of allergen extracts are available for testing; selecting items for testing a given individual is part of the art of medicine. Development of allergic sensitization is a function of genetic factors, exposure, and time. Because sensitization to seasonal inhalants such as pollens generally requires exposure over multiple seasons, children younger than 3 to 4

years of age are more likely to be sensitized to perennial allergens such as foods and indoor inhalants. Appropriate testing also requires knowledge about local environmental flora so the tests ordered are clinically relevant. Testing to pollens of trees, grasses, and weeds that do not grow in the area where the patient lives will not help explain the patient's symptoms. Testing with a preset "panel" of allergens is not appropriate in infants and young children.

### Types of Allergy Testing

In practice, the various types of legitimate IgE allergy testing can be classified as skin testing (in vivo) or specific IgE immunoassay (in vitro). The latter method was once called the radioallergosorbent test (RAST). Radioactive isotopes no longer are used, making the term RAST obsolete. Other methods for detecting allergen-specific IgE are primarily for research.

**SKIN TESTING.** Skin testing is the time-honored technique for detecting specific IgE sensitization. In skilled hands, it is fast, accurate, and precise. It provides immediate results and is more sensitive and less expensive than specific IgE immunoassays. There are epicutaneous and intradermal methods, each of which has advantages and disadvantages.

When performed properly, the epicutaneous methods are not particularly painful and, thus, are tolerated better by children. Two techniques called "prick" or "puncture" are in wide use. In general, a small drop of extract is placed on the skin, and a testing device is used to disrupt the superficial epidermal layers, allowing a small amount of the extract to enter. The wheal and flare of a positive test result, which occurs within a few minutes of test application, is obvious to patient and parents. The epi-

cutaneous tests have sufficient sensitivity for the detection of allergy in children when potent extracts are used. The primary disadvantages of prick or puncture testing are that the numerous devices for testing have different performance characteristics and successful testing requires trained, experienced personnel.

Intradermal (ID) test methods are substantially more tedious and painful than the epicutaneous methods. In ID testing, extract is drawn into a syringe fitted with a small needle and injected into the superficial dermis, forming a small bleb. In children, ID testing usually is performed when low-potency extracts (such as venoms or drugs) are tested. ID testing is the gold standard for venoms and drugs. If clinical suspicion of sensitization for a particular allergen is high, but an epicutaneous test result is negative, some clinicians retest with an ID test using a dilute extract. This approach to testing increases sensitivity. However, the extract concentrations used for ID testing can produce irritant reactions in some individuals. ID testing also has a greater risk of provoking a systemic anaphylactic reaction than does epicutaneous testing.

**CONFOUNDING FACTORS IN SKIN TESTING.** In dermographism, physical trauma to the skin leads to a wheal and flare reaction, producing a false-positive test result. Certain epicutaneous methods can produce reliable results in dermographic individuals. Irritant false-positive responses are rare in epicutaneous testing, but in ID testing, concentrated extracts (stronger than 1:1,000 w/v) can yield false-positive irritant responses.

A larger variety of factors can produce false-negative results. Recent use of histamine-1 receptor antihistamines or related compounds (such as selective serotonin reuptake inhibi-

tors, tricyclic antidepressants, and phenothiazine) can be detected by history and by use of positive control substances such as histamine. Histamine-2 receptor antihistamines affect skin testing minimally; current recommendations suggest withholding them on the day of testing. The acute use of oral or topical steroids does not affect skin tests substantially, but use for more than 1 week could inhibit mast cell degranulation and might affect test results.

Medications commonly used in allergic diseases that do not affect skin tests significantly include beta-agonists, antileukotrienes, inhaled or intranasal steroids, and cromolyn. Patients should not be told to stop these before skin testing.

forearms), and poor extract quality. Certain food extracts tend to degrade quickly, and for some such as apple, testing with fresh fruit is preferable to testing with an extract.

#### SPECIFIC IgE IMMUNOASSAYS.

Modern methods for detecting allergen-specific IgE in the serum are immunoassays that report quantitative results related to the World Health Organization IgE standards. A typical test report may state that short ragweed was positive at a level of 3.2 kU/L. Some methods also report semiquantitative class results that are not particularly useful. As in the case of skin testing, the available assays differ in their performance characteristics, as do the laboratories

sults. Also, properly performed epicutaneous skin testing is less painful than phlebotomy, making it usually preferable to blood testing. In less than optimal conditions, such as the necessity for sending blood to a laboratory whose test performance is unknown or performing skin testing with an unqualified tester, allergy testing should be deferred.

Specific IgE immunoassays are indicated in several situations in allergy-immunology practice: 1) the inability to stop an antihistaminelike medication; 2) the inability to stop a medication (such as a beta blocker) that is a relative contraindication to skin testing; 3) a clinical history suggestive of great risk of a systemic reaction to skin testing; 4) lack of an adequate amount of healthy skin, as in severe atopic dermatitis; and 5) testing with some substances that are not available commercially for skin testing (eg, natural rubber latex), which necessitates the use of specific IgE measurement.

**QUANTITATIVE TESTING.** The fundamental question to be answered by immunoassay is whether allergen-specific IgE antibody is detectable. In carefully defined patient populations, high levels of allergen-specific IgE antibody are more likely to be associated with clinical symptoms than are low levels. The levels that provide 95% positive predictive value vary with allergen, patient age, and disease. This correlation has been investigated carefully in children who have atopic dermatitis, in whom the finding of high levels of food-specific IgE antibody obviates the need for traditional food challenges.

#### ALLERGY TESTING FOR FOODS.

The general principles of allergy testing already described apply to patients who are suspected of having food allergy. The folklore and myths

**In allergy practice, skin testing is more sensitive and less expensive than immunoassay and provides immediately available results.**

Although the skin of infants and small children is less reactive than that of children and adults, skin testing usually is possible when clinically indicated.

A potential cause of false-negative results is failure to introduce an adequate amount of allergen into the epidermis. In allergy practices that conduct periodic proficiency assessments of testing personnel, improper skin testing technique should not be a common cause of false-negative results. Other factors that could influence skin test results include certain chronic diseases (renal failure, neuropathies, and malignancies) associated with decreased skin reactivity, body location for skin test placement (the back is more reactive than the

that test. Perusal of the results of the quarterly proficiency testing survey conducted by the College of American Pathologists documents these differential performance characteristics and demonstrates that individual laboratories vary in their ability to report consistent results with the same assay method.

When serum IgE immunoassays and epicutaneous skin testing are performed under optimal conditions, the results generally agree. The sensitivity of immunoassay compared with skin testing is between 80% and 100%, depending on the allergens studied and the test methods used. In allergy practice, skin testing is more sensitive and less expensive and provides immediately available re-

associated with IgE and various types of “adverse food reactions” warrant special attention because “food allergy” is not a diagnosis. The clinical approach is as stated previously, including obtaining a history, performing a physical examination, and formulating a differential diagnosis. If a disease associated with food allergy, such as atopic dermatitis or eosinophilic gastroenteritis, is diagnosed, food allergy testing can be undertaken to identify specific triggers. However, particularly in atopic dermatitis, food-specific IgE may be present in patients who have no clinical symptoms from food ingestion, and inappropriate dietary restrictions can affect normal growth and development. Thus, the gold standard for assessing the relevance of a positive or negative allergy test result for patients who are suspected of having adverse food reactions remains a double-blind, placebo-controlled food challenge (DBPCFC), which is safest to perform in a medical setting and generally is not performed if the adverse reaction has been severe anaphylaxis. Because DBPCFCs are labor-intensive, open challenges are used more commonly in office settings.

**OTHER TESTS USED IN CLINICAL ALLERGY.** Allergen nasal provocation testing and allergen bronchial challenge are counterparts to the DBPCFC used in food allergy. The patient inhales large amounts of allergen into the nose or the lungs in an attempt to establish relevance of a positive allergy test result. Both of these tests primarily are research tools.

## Discussion

### Patient 1

*Because the episode happened during a meal, a cause-and-effect relationship between the foods she ate and the subsequent reaction can be postulated. The fundamental question, however, relates to the nature of the reaction. The reported symptoms have some features of anaphylaxis, and the time course is consistent with that of IgE-mediated allergy. Thus, allergy testing is indicated. However, a telephone call to the restaurant to get specific details of the ingredients used revealed that some other customers who ate tuna that night had similar, but less severe, symptoms. This additional information suggests that the reaction may have been scombroid fish poisoning and lessens the likelihood of (although it does not exclude) anaphylaxis. In such a situation, skin prick testing to tuna, cashews, mango, papaya, and kiwi might be useful to reassure the patient, parents, and physician. All of this patient's skin test results were negative with good controls, and she subsequently tolerated open oral challenges to each of the foods in question. The diagnosis was probable scombroid fish poisoning.*

### Patient 2

*The honeybee venom allergy test result is positive (the assay's lower limit of detection is less than 0.10 kU/L), and the mother is asking whether her son will need allergy shots, like his uncle. This is an example of an inappropriate use of allergy testing that has resulted in the identification of an individual who has made IgE antibody to honeybee venom, but who has not had a systemic reaction. Such individuals remain at risk for “large local” reactions*

*in the future, but are not at substantially greater risk for anaphylaxis than is the general population. Thus, venom immunotherapy is not indicated, and the test should not have been ordered in the first place.*

## Summary

Allergy testing helps to determine whether IgE is playing a role in the pathogenesis of a disease of immediate hypersensitivity. History alone does not distinguish allergic from nonallergic individuals reliably. In some cases, such as mild intermittent asthma or rhinitis, distinguishing between allergic and nonallergic patients may not be important clinically. However, for patients who have persistent or acute severe symptoms, testing is indicated. Identification of allergens can allow the patient to institute appropriate avoidance measures, especially with allergy to dust mites, foods, and animals. Knowledge of pollen sensitization can predict seasonal exacerbations so therapy can be increased during these times. Finally, allergy testing can be used to initiate allergen-specific immunotherapy, a treatment that has provided substantial, proven benefit to patients for almost 100 years.

## Suggested Reading

- Dykewicz MS. Rhinitis and sinusitis. *J Allergy Clin Immunol.* 2003;111(suppl):S520–S529
- Gruchalla RS. Drug allergy. *J Allergy Clin Immunol.* 2003;111(suppl):S548–S559
- Lemanske RF Jr, Busse WW. Asthma. *J Allergy Clin Immunol.* 2003;111(suppl):S502–S519
- Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2003;111(suppl):S540–S547

## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

10. A 10-year-old boy who has moderate persistent asthma and allergic rhinitis has an appointment for skin testing in a week. He takes daily montelukast and low-dose inhaled fluticasone regularly for his asthma, but he has been taking oral prednisone and inhaled albuterol for the past 2 days because of an exacerbation. He also is taking cetirizine for allergic rhinitis. Which of his medications should be discontinued before he undergoes skin testing?
  - A. Albuterol.
  - B. Cetirizine.
  - C. Fluticasone.
  - D. Montelukast.
  - E. Prednisone.
11. Which of the following patients should undergo immediate-type (type I) skin testing?
  - A. A child who has contact dermatitis over the arms and legs.
  - B. A preschool-age child who has developmental delay of unknown cause.
  - C. A toddler who has gluten sensitivity.
  - D. An adolescent who has asthma and has severe symptoms at the same time each year.
  - E. An infant who has recurrent bronchiolitis.
12. You are seeing an adolescent who has chronic rhinosinusitis, and you feel that he should undergo testing for IgE-mediated sensitization. Which of the following factors in his history would make you *more* likely to order specific IgE immunoassays instead of skin testing?
  - A. He completed a trial of ranitidine for "heartburn" symptoms last week.
  - B. He had an anaphylactic reaction when he was skin tested a few years ago.
  - C. He has been taking intranasal steroids for the past 6 months.
  - D. He has mild atopic dermatitis.
  - E. His rhinitis symptoms are more severe in the winter.
13. Which of the following statements regarding allergy testing is true?
  - A. A double-blind placebo-controlled food challenge should be performed in all children who have a history of an adverse food reaction.
  - B. Children who are suspected of having asthma should undergo allergy testing to confirm the diagnosis of asthma.
  - C. Infants do not develop IgE-mediated sensitization and, therefore, should not undergo allergy testing.
  - D. Skin testing is less expensive and less painful than blood testing for specific IgE immunoassays.
  - E. Specific IgE immunoassays are more sensitive than skin testing in detecting IgE-mediated sensitization.

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