Allergy Testing in Children: Which Test When?

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Allergy testing can aid the diagnosis of allergic disorders; however, it is not diagnostic. With skin testing, in particular, a positive result does not necessarily indicate clinical allergy, and a negative result does not always exclude clinical relevance.

ABSTRACT: For the child with persistent or worsening allergy symptoms of more than 2 months' duration, a screening radioallergosorbent test may be initiated after a careful history and physical examination. In the workup, be alert for allergic "shiners" and other signs of allergic disorders (eg, a bulging chest wall is suggestive of chronic asthma). Skin testing, performed on the skin of the back, is the most commonly used allergy test. In patients younger than 2 years with atopic dermatitis (eczema), a test for food allergy frequently identifies an offending food. It is prudent to test for indoor allergens in children younger than 5 years and to delay testing for outdoor allergens until 6 years or older. Consider an allergy test in children with a history of drug, latex, or insect sting allergy regardless of age. Further testing (eg, with an oral food challenge) can be done at the clinician's discretion. Because such tests are time-consuming and require assistance, referring the patient to an allergy specialist is recommended.

Allergy testing can aid the diagnosis of allergic disorders; however, it is not diagnostic. With skin testing, in particular, a positive result does not necessarily indicate clinical allergy, and a negative result does not always exclude clinical relevance. Allergy test results serve only as confirmation of the accuracy of the patient's history and physical examination findings and should be used with discretion. In the best-case scenario, allergy test results can offer a means for advising the patient and parents to avoid offending allergens that can be potentially life-threatening. They can also provide a basis for immunotherapy in cases of drug allergy (rapid desensitization) or respiratory allergy (long-term allergy desensitization).

In this article, I provide a step-by-step guide for the evaluation of children with allergy symptoms. The focus is on the types of allergy tests available and their advantages and limitations, which tests to perform for each age-group, and when referral to an allergy specialist is appropriate.

ALLERGY DEVELOPMENT

The development of allergy involves the formation of the IgE antibody: the higher the IgE antibody level, the greater the manifestation of allergy symptoms. IgE formation depends on complex genetic and environmental influences,\(^1\) which are only now being elucidated. The presence of IgE alone does not necessarily lead to allergic reactions.

Allergy develops in 2 steps: sensitization, in which IgE attaches to mast cells that reside under the surface of tissues of the respiratory tract, GI tract, and skin; and re-exposure of the sensitized person to the allergen (or allergic factors). When enough allergens bind to the IgE that is already present on the mast cells, the mast cells become activated and release mediator granules into the surrounding tissues. An allergy is the response of the tissue to these mediators. The most common mediators—histamine, plateletactivating factor, leukotrienes, and prostaglandin D— increase vascular permeability, dilate vessels, contract smooth muscle, cause bronchospasm, and summon inflammatory cells. Most IgE-mediated reactions occur within minutes to a few hours after exposure (although the manifestations of non–IgE-mediated reactions— mostly GI— may be delayed for several hours or even days).

Allergic disorders are classified as follows, depending on the primary target organ: allergic asthma, allergic rhinitis, allergic conjunctivitis, urticaria, angioedema, atopic dermatitis (eczema), food allergy, insect sting allergy, drug allergy, and latex allergy. The most severe allergic disorder, anaphylaxis, can simultaneously involve the respiratory, cardiovascular, and GI systems and may be caused by allergies to food, drugs, insect stings, or latex. Fatalities have been reported with all of these disorders.

TYPES OF ALLERGY TESTING

Because of the role of IgE in the evolution of allergy symptoms, the most convenient assay used in clinical practice is the measurement of IgE.\(^2\) The next most commonly used tool is the oral food
challenge,\textsuperscript{11,12} in which suspected food allergens are introduced in a graded fashion to determine whether allergy symptoms can be reproduced. The third most common test is the measurement of the serum tryptase level to determine whether the patient has had an anaphylactic reaction.\textsuperscript{13,14}

IgE TESTING

IgE can be measured in 2 ways: by the total serum IgE level or by the amount of functional IgE antibody to a particular allergen. The total serum IgE level helps the clinician determine whether a patient has atopy, but it does not indicate what allergen is causing the reaction. Thus, the functional IgE antibody level, measured in vitro (radioallergosorbent test [RAST]) or in vivo (skin testing), is used to identify the causative allergen.

Total serum IgE. In most laboratories, the total serum IgE level is expressed in international units per milliliter (1 IU is roughly equal to 2 ng). When the amount exceeds the normal range, as determined by the laboratory, the patient is considered to be allergic (have sensitivity to certain allergens). When the clinical manifestation correlates with the value of total serum IgE, the patient is considered to have atopy. IgE, like other immunoglobulins, tends to become more elevated as a person ages. Thus, to determine the real value of total serum IgE, always consider the reference point for the specific age of the patient.\textsuperscript{2}

![Table 1 - Prediction that a child will outgrow food allergy from measurement of IgE levels](image)

RAST. Although the radioimmunoassay test is no longer used, the measurement of functional IgE antibody in the blood is still referred to as RAST. This test is most often performed in special reference laboratories. Some commercial kits are available for use in the clinical office setting; however, it is advisable that only trained laboratory staff conduct RASTs. Also, the necessary test equipment requires a routine calibration even if used only sporadically.

RAST has several advantages over allergy skin tests:

- Less uncomfortable for the patient.
- Safer, with no risk of an anaphylactic reaction.
- Easier to perform in patients with extensive skin lesions, such as in a severe case of atopic dermatitis or eczema (which is a common problem in children).
- Results are unaffected by the patient's medications.
- Qualitative results, ie, the quantity of IgE, may be used to predict outcome, as in the case of food allergy (Table 1).

Drawbacks of RAST compared with an allergy skin test include the following:

- Test results are delayed.
- Multiple tests may require a large volume of blood, which can be challenging in younger children.
- Careful interpretation of results in relation to the patient and patient's family is essential.
- High cost.
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Variability among laboratories and methods.
• Fewer allergens are tested.
• Results are less impressive to patients and parents.

Allergy skin test. A direct challenge of antigen(s) on the skin is the most widely used allergy test in clinical practice. The prick technique, usually applied to the skin of the back, is used most often in children (Figure). Devices that reduce trauma to the patient are available. With such devices, at least 40 antigens can be easily applied on the back, even in children younger than 3 years. The response to allergens is always compared with that to histamine and normal saline. The former serves as a positive control to rule out interference from antihistamine. The latter serves as a negative control to rule out sensitive skin, such as that seen in children with mastocytosis. The positive reaction is read as a 3-mm or more response to the size of induration of the negative control.

Advantages of allergy skin testing over RAST include the following:
• Rapid results—15 minutes after the application of the test.
• Many allergens can be applied.
• In-office procedure that is easy to perform.
• Low cost.
• Results provide visual confirmation of reaction.

Drawbacks to the allergy skin test include the following:
• Affected by the use of antihistamines; patients must discontinue antihistamine use before the test (3 days for short-acting H1 or H2 antihistamines, 7 days for long-acting, nonsedating antihistamines).
• False-positive results are more common.
• Potential for severe anaphylactic reactions.
• Patients with active and extensive skin lesions, such as eczema or atopic dermatitis, are not ideal candidates.
• Requires trained personnel.

Intradermal allergy testing is no longer considered useful in providing new information. Limitations of functional IgE testing. There are several important factors to consider when deciding whether an allergy test will be useful.

Patient age. Allergic sensitization takes time to develop. With the limited sensitivity of both the RAST and skin test, IgE values may not be meaningful because the levels may be low. This is especially true in children.

Number of allergens available. Clinicians must rely on companies to provide the skin test reagents or RAST currently available—every substance cannot realistically be tested.

Limited drug allergy testing. RAST is available for IgE antibodies to penicilloyl V or G, the major determinant of the penicillin molecule. The only meaningful skin test available is for penicillin G (for minor determinants). The accuracy of skin tests for other drugs remains conjectural. Limited testing for latex protein allergy. Currently, the only test available for latex allergen is RAST; skin test reagents for latex have not been approved by the FDA.

Anaphylaxis. During the anergic phase that follows an episode of anaphylaxis, IgE tests may yield falsenegative results. Thus, an IgE workup should be delayed a month in patients who have had
anaphylaxis.

**What test for what age.** A few rules can help determine the choice of allergy test. For a patient younger than 2 years with noticeable atopic dermatitis (eczema), a skin test for food allergy is an ideal choice. In nearly 70% of these patients, an offending food will be identified. Consider an allergy test in children with a history of drug, latex, or insect sting allergy regardless of age. Because the IgE in blood or on mast cells is lower in children, neither RAST nor skin tests for airborne allergens may produce meaningful results until a child is 5 years old. However, in children 5 years and younger, it is prudent to test for indoor allergens, such as house dust mites, molds, animal dander, feathers, and cockroaches. In school-aged children (6 years and older), it is helpful to test for outdoor allergens, such as grass, tree, and weed pollens.

For children with urticaria or angioedema, allergy testing is left to the discretion of the clinician, because often the search for an allergic cause is not fruitful. A summary of skin test reagents for different ages is provided in Table 2.

Parents are always concerned about the volume of blood needed for in vitro allergy testing; thus, the skin test remains an attractive choice in younger children.

**ORAL FOOD CHALLENGE**

With the number of children with food allergy increasing worldwide, it has become more of a challenge to distinguish food allergy from other food-induced reactions. Reactions to food include both true food allergy (IgE-mediated, non-IgE-mediated, or a combined reaction in which both IgE- and non-IgE-mediated mechanisms are involved) and food intolerance (metabolic, pharmacological, or idiosyncratic). The known non-IgE-mediated food allergies include food protein–induced enteropathy; food protein–induced enterocolitis; food protein–induced proctitis; celiac disease; and allergic eosinophilic esophagitis, gastritis, and gastroenteritis.

A positive IgE test result for food sensitivity is by itself insufficient to arrive at the diagnosis of food allergy. When the offending food has not been identified despite a thorough history and attempt to document sensitization or when multiple foods are implicated, the oral food challenge is used to determine which of the suspected foods is causing symptoms. When something other than an IgE-mediated sensitivity is suspected, an oral food challenge may be the only accurate means of verifying the diagnosis. Before an oral food challenge, it is appropriate to enforce an elimination diet to see whether the patient's symptoms decrease.

Oral food challenges are categorized into open, single-blind placebo-controlled, and double-blind placebo-controlled. The last of these methods is the one currently recommended. The foods suspected of causing allergy are introduced slowly and steadily, with 30 minutes between each feeding. Pediatric clinicians who attempt an oral food challenge must have access to emergency rescue equipment in case of a reaction. Generally, this test is best performed in an allergy specialist's office or in an inpatient service.

**TRYPTASE MEASUREMENT**

In patients with a suspected anaphylactic reaction, immediate measurement of IgE is unhelpful because of the anergic phase that follows an anaphylactic episode. Serum tryptase peaks 60 to 90 minutes after the onset of symptoms of anaphylaxis and can remain elevated for as long as 5 hours. In contrast, plasma histamine begins to rise within 5 minutes but remains elevated for 30 to 60 minutes. Because of its longer half-life, serum tryptase is used to confirm the anaphylactic reaction of severe allergy. A normal serum tryptase value is less than 10 ng/mL; the higher the value, the higher the sensitivity. Under ideal conditions, the positive predictive value of serum tryptase can be 92.6%; however, the negative predictive value is only 52%.

**DIAGNOSING ALLERGY**

The Algorithm provides a step-by-step guide for the evaluation of a child with allergic symptoms.
Medical history. A detailed medical history can provide significant information for use in establishing or ruling out the diagnosis of allergic disorders. A typical allergy history includes the age at symptom onset, route of possible exposure, relation to food or environmental exposure (e.g., accidental, seasonal, or perennial), nature and course of the reaction, concurrent events (e.g., illness, exercise, drug ingestion), feeding history, and response to administered treatment. Consider the history in the context of a cause-and-effect relationship. Children with a personal or family history of atopic disease are more likely to have allergic conditions than children without such a history.

Physical examination. When evaluating the patient with suspected allergy, it is important to distinguish signs of allergy from other diseases. The presence of allergic shiners, Dennie lines, pale and swollen nasal mucosa, cobblestone appearance of the pharyngeal wall, elevated palate, geographic tongue, gaping mouth, or injected conjunctivae are highly suggestive of allergic rhinitis with conjunctivitis. A bulging chest wall is suggestive of chronic asthma. Eczema or atopic dermatitis in young children is indicative of possible food sensitivity. Abnormal growth may signal a chronic allergic condition (respiratory or GI).

Initial laboratory tests. Depending on the differential diagnosis, preliminary testing may be necessary to rule out systemic conditions.

When to consider an allergy workup. Because of the large number of patients with allergy symptoms, it is unrealistic to refer all of them to allergy specialists. For the child with persistent or worsening allergy symptoms of more than 2 months' duration, the pediatric clinician may initiate screening tests for allergens with RAST after a careful history and physical examination. At the University of Florida, 2 panels of RAST are used for screening purposes. For respiratory diseases, such as allergic rhinitis and asthma, the list of possible offenders includes European house dust mites (Dermatophagoides pteronyssinus); American house dust mites (Dermatophagoides farinae); the fungi Alternaria alternata, Aspergillus fumigatus, Cladosporium herbarum, and Penicillium fumigatus; cat dander; dog dander; and cockroaches. For patients with suspected food allergy, the RAST panel includes cow's milk, egg, peanut, soy, wheat, tree nut, shellfish, and fish.

Diagnosis confirmation. For verification purposes, further testing (e.g., with an oral food challenge) can be done at the clinician's discretion. Because such tests are time-consuming and require assistance, referring the patient to an allergy specialist is recommended. When to Refer to an Allergy Specialist

Consider referral to an allergy specialist in the following settings:

- **Severe disease:** When the child has a history of anaphylactic reactions or history suggestive of severe allergy; RAST should be performed as soon as possible.
- **Persistent disease:** When quality of life is significantly affected despite therapy.
- **Progressive disease:** When clinical symptoms progress from mild to severe or when the disease involves other organs, such as the spread from the upper airway to the lower airway.
• **Complex disease:** When more than 1 allergen is likely to be involved (such as with food allergy, drug sensitivity, insect sting allergy, or airborne allergy).

• **Positive RAST results:** When preliminary RAST results indicate sensitivity to selected allergens.

• **Further testing:** When the child requires an extensive workup or verifying test, such as oral food challenge.

• **Rapid desensitization for drug hypersensitivity reaction:** When sensitivity testing indicates that the treatment of choice is the allergenic antibiotic, and no alternative antibiotic can be used to treat the child.

• **Education or long-term treatment:** When the child requires extensive education or complex, lengthy treatment, such as allergy immunotherapy.

• **Affected growth:** When the child shows no signs of growth, according to the growth chart findings, for 3 to 6 months.

**References:**


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