

Vol 129, No 1, January 2012
ISSN: 0031-4005
www.pediatrics.org

Reprinted from...

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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SECTION ON ALLERGY AND IMMUNOLOGY

American Academy of Pediatrics

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CLINICAL REPORT

Allergy Testing in Childhood: Using Allergen-Specific IgE Tests

Scott H. Sicherer, MD, Robert A. Wood, MD, and the SECTION ON ALLERGY AND IMMUNOLOGY

KEY WORDS

allergy, allergy testing, immunoglobulin, IgE, immunotherapy, pediatrics

ABBREVIATIONS

IgE—immunoglobulin E
sIgE—allergen-specific IgE
SPT—skin prick test
IgG—immunoglobulin G

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www.pediatrics.org/cgi/doi/10.1542/peds.2011-2382

doi:10.1542/peds.2011-2382

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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abstract



A variety of triggers can induce common pediatric allergic diseases which include asthma, allergic rhinitis, atopic dermatitis, food allergy, and anaphylaxis. Allergy testing serves to confirm an allergic trigger suspected on the basis of history. Tests for allergen-specific immunoglobulin E (IgE) are performed by in vitro assays or skin tests. The tests are excellent for identifying a sensitized state in which allergen-specific IgE is present, and may identify triggers to be eliminated and help guide immunotherapy treatment. However, a positive test result does not always equate with clinical allergy. Newer enzymatic assays based on anti-IgE antibodies have supplanted the radioallergosorbent test (RAST). This clinical report focuses on allergen-specific IgE testing, emphasizing that the medical history and knowledge of disease characteristics are crucial for rational test selection and interpretation. *Pediatrics* 2012;129:193–197

INTRODUCTION

Allergic diseases (allergic rhinitis [hay fever], asthma, atopic dermatitis, and allergic or anaphylactic reactions to foods, drugs, insect venom, or other allergens) often warrant identification of specific allergic triggers for treatment. Most allergic responses are mediated by immunoglobulin E (IgE) antibodies specific for the trigger allergen, which can be detected with in vitro tests or skin testing. This clinical report focuses on using in vitro allergen-specific IgE (sIgE) testing, which is widely available to pediatricians. A full description of the use of tests for diagnosis and management of allergic disease is beyond the scope of this report, but is described in recent guidelines and practice parameters.^{1–9}

TESTS AVAILABLE FOR DETECTING sIgE

A number of enzymatic assays that are based on anti-IgE antibodies have supplanted the radioallergosorbent test.¹⁰ Commercial laboratories that are federally licensed under the Clinical Laboratory Improvement Act of 1988 often use automated systems capable of detecting and quantifying sIgE. Laboratory reports may indicate a number of readouts (eg, classes, counts, or units), but quantification of results in units reflecting concentrations of sIgE is becoming more common (eg, kU_A/L). Although the 3 commercial detection systems approved by the Food and Drug Administration have excellent performance characteristics (analytical sensitivity, 0.1 kU_A/L), the

individual systems appear to detect different populations of IgE antibody or do not measure IgE antibodies with comparable efficiencies. Thus, a result for an allergen in 1 of the 3 test systems may not be equivalent to the same allergen tested in a different system.

The skin prick test (SPT), typically used by allergy specialists, is another means of detecting sIgE antibodies.¹¹ A number of devices are available for introducing allergen into the surface of the skin with minimal discomfort; a resulting wheal-and-flare response can be measured in 10 to 20 minutes. Saline and histamine controls are placed for comparison. Intradermal skin testing is performed in special circumstances when increased sensitivity is required (eg, after negative SPT for vaccines, venom, penicillin, and some inhalant allergens, such as *Alternaria* organisms and perhaps other outdoor molds).

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties.^{11,12} Advantages of the SPT include immediate results visible to the patient/family and low cost compared with serum sIgE tests. Disadvantages include the need to withhold medications with antihistamine properties and having rash-free skin available for testing. Advantages of the serologic tests include availability and lack of interference from antihistamines or extensive dermatitis. Disadvantages include the need to obtain blood samples, delayed results, and cost. Some discrepancies exist, however; one test or the other may be more sensitive to detect specific allergens, probably because different proteins or IgE binding sites are represented.^{2,3,7,9,11,13}

TEST SELECTION AND INTERPRETATION

Tests might be selected to identify triggers from a number of potential common allergens, for confirming a

specific trigger when there is suspicion of one, or in less common circumstances, screening for atopy. A positive serum sIgE or skin test denotes a sensitized state. However, detection of sensitization to an allergen is not equivalent to a clinical diagnosis. In fact, many children with positive tests have no clinical illness when exposed to the allergen.^{2,3,7,9,11,13} This limitation highlights the need for the clinician to use a detailed medical history and have knowledge of the features of the specific illness when selecting and interpreting tests. For example, there is no need to test for an allergen that is clearly tolerated (eg, egg in a child who eats egg without symptoms) or when exposure is not relevant (eg, testing a pollen to which the child is not geographically exposed). Knowledge of local aerobiology is, therefore, essential. Testing large panels of allergens without consideration of the history, geographic relevance, and disease characteristics may result in many clinically irrelevant positive results, which, if overinterpreted, may lead to costly and socially, emotionally, and/or nutritionally detrimental actions of unnecessary allergen avoidance. Similarly, caution is advised when testing is negative despite a convincing history. Testing for sIgE would also generally not be useful when the disorder has no pathophysiological basis for a relationship to sIgE (eg, behavioral disorders; allergic disorders not related to sIgE, such as allergic contact dermatitis).

Few studies have correlated clinical outcomes to test results.^{2,3,4,11} Studies have generally supported the notion that increasingly strong tests correlate with increasing likelihood of clinical reactivity.^{2,3,11} Patients should not be told they are allergic based solely on either a skin test or the identification of sIgE. The test characteristics underscore the need to select and interpret tests with consideration of the medical history,

which increases diagnostic value by applying previous probability.⁴

A physician interested in screening for atopy (eg, distinguishing recurrent viral infections from allergic rhinitis) might select a small panel of common triggers. Another means to screen for atopy is to use a multiallergen test that contains several common allergens in one test (eg, one test that includes several perennial allergens, such as dust mite, dog dander, and mold). Availability and composition of these tests varies by manufacturer. A positive result will not identify IgE to a specific antigen but can, at less cost than performing many individual tests, identify a child whose symptoms may relate to exposure to a specific allergen and warrant further specific testing or referral. The multiallergen test had excellent predictive value for identifying atopic children compared with SPTs and an allergist's diagnosis.^{14,15}

ISSUES SPECIFIC TO RESPIRATORY ALLERGY^{1,6,11}

The disorders that respiratory allergy comprises are allergic asthma and seasonal or perennial allergic rhinitis. National asthma guidelines¹ suggest that patients with persistent asthma be evaluated for the role of allergens as contributing factors, with an emphasis on testing for perennial indoor allergens (eg, dust mite, animal dander, cockroach, mold) that might otherwise not be identified as contributing to disease and also suggest testing seasonal or perennial allergens for selected patients with any level of asthma severity as a basis for education about the role of allergens for avoidance and for immunotherapy.

The clinician may be interested in identifying specific indoor (eg, dust mite, animal dander, molds, mice, and cockroach) or outdoor (eg, pollens, molds) triggers. Rational selection and interpretation of specific tests

requires consideration of the environmental exposures (housing, pets, and geographic floristic patterns), medical history (nature of symptoms, timing in relation to exposures), and disease characteristics (eg, pollen allergy is uncommon in infancy; patients are unlikely to have acute symptoms from dust mite exposure; food allergens do not typically cause chronic respiratory disease). Provocation tests can confirm environmental allergy but are not often undertaken for clinical purposes.

ISSUES SPECIFIC TO FOOD ALLERGY^{2,3,4,11}

Food allergy may be suspected when specific symptoms (eg, urticaria, angioedema, cough, wheeze, vomit, and anaphylaxis) occur minutes to hours after the ingestion of a food, and in children diagnosed with certain disorders, such as moderate to severe atopic dermatitis, eosinophilic esophagitis, and other allergic gastrointestinal tract disorders. Testing for sIgE to foods might be considered to identify or confirm triggers, to assist in diagnosis of chronic disorders, or to monitor for allergy resolution. However, they are not considered diagnostic in and of themselves. SPT and serum sIgE provide similar sensitivity and specificity.¹² It is common to have positive test results for tolerated foods; therefore, indiscriminate testing (ie, panels that include foods that are already tolerated) is not advised. Additional means to assist in diagnosis include the medical history and results of medically supervised oral food challenges. Elimination diets, if initiated, should not be maintained in the absence of a convincing previous history of a reaction or a medically supervised oral food challenge. A comprehensive description of the diagnostic and management process is reviewed in recent guidelines.²⁻⁴ Key observations include:

- Screening panels of food allergens without previous consideration of the history is not recommended, because sensitization without clinical allergy is common. For example, ~8% have positive test results for peanut, but ~1% are clinically allergic.¹⁶
- A negative SPT or serum sIgE test result does not entirely exclude a diagnosis of a food allergy. One test may be positive when the other is negative. SPT using fresh food extracts may increase sensitivity, especially for fruits. Caution is needed when tests are negative when a specific food allergy history is convincing; a medically supervised oral food challenge may be needed.
- Cross-reactivity among proteins may result in a much higher degree of positive sIgE test results among related foods than clinical reactions (eg, >50% of patients with peanut allergy test positive to other legumes, but <5% have clinical symptoms of allergy from ingestion of legumes). Cross-reactivity among homologous proteins of aeroallergens and food allergens may result in positive tests to foods, often without clinical allergy (eg, birch pollen with hazelnut, peanut, soy; grass pollen with wheat, peanut; dust mite with shrimp).
- Strong positive test results correlate with increasing probability of clinical allergy, and particularly high values may indicate a high degree (>95%) of likely allergy; however, there are few studies correlating outcomes to test results, and results vary by age, disease, and other factors.
- sIgE serum concentration or SPT wheal size do not accurately predict the severity of allergic reactions, but do reflect the likelihood of an allergic reaction of variable intensity.
- Testing for total IgE does not identify specific allergies. Atopic individuals often have elevated total IgE, but there is no current evidence to support the interpretation of sIgE in relation to total IgE.
- Tests measuring immunoglobulin G (IgG) antibodies for diagnosis are not recommended.
- Intradermal tests are not recommended, because they are too sensitive and carry risk of a severe allergic reaction.
- Food protein-induced enterocolitis and proctocolitis (eg, cell-mediated food allergic disorders) are not associated with positive IgE tests.

ISSUES SPECIFIC TO OTHER ALLERGIES (DRUG ALLERGY, INSECT VENOM, VACCINES, LATEX)⁷⁻⁹

The general caveats regarding sensitization and clinical allergy described previously also apply to allergy tests for substances that may cause acute allergic reactions or anaphylaxis, such as medications, insect venom, vaccines, and latex. The medical history is essential in decision making regarding testing and interpretation, including understanding whether the symptoms are likely to be IgE mediated.

Tests for drug allergy (eg, acute allergic reactions) are generally not standardized, and the sensitivity of serum tests appears poor.⁸ IgE tests are not relevant for many drug reactions (maculopapular rashes, Stevens-Johnson syndrome). SPT and intradermal tests for penicillin allergy using recently available reagents have potential utility for IgE-mediated allergies.⁸

Allergy testing for venom allergy should be considered when symptoms of anaphylaxis occur after a sting. When anaphylactic allergy to venom is confirmed by skin testing, immunotherapy

is indicated and highly effective.^{7,9,11} Isolated, localized swelling at a sting site does not identify a risk of anaphylaxis, and testing is not warranted. Generalized urticaria without other symptoms of anaphylaxis in children 16 years and younger usually does not warrant testing, because more severe reactions appear to be unlikely; however, systemic anaphylaxis in any age group and generalized urticaria in adolescents older than 16 years warrant testing. SPT and intradermal testing are considered the standard means of diagnosis, although serum IgE tests for venom or venom components may be performed when skin tests are negative and the history is suggestive. SPT and intradermal tests can be performed for vaccines suspected of triggering allergic reactions, although care is needed to choose the proper dilution to prevent irritant reactions.^{7,17,18} Skin tests are not available for latex; serum tests are available, but the diagnostic utility is not well characterized.^{7,11}

TESTS UNDER DEVELOPMENT AND UNPROVEN TESTS

Tests are under development that detect IgE binding to specific proteins in foods (component-resolved diagnosis), with a potential to more accurately identify people likely to react or with more severe allergies; however, further validation of these tests is needed.^{2,3,11} Additional tests requiring more validation include basophil activation and atopy patch tests with foods.^{2,3,11} These tests are currently primarily research tools, although specific uses have been identified.^{8,11}

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A number of tests have no evidence to support their use and are not recommended, including: lymphocyte stimulation, facial thermography, gastric juice analysis, hair analysis, applied kinesiology, provocation-neutralization, allergen-specific IgG/IgG4, cytotoxic assay, electrodermal test (VEGA), and mediator release assay.^{2,3,11}

SUMMARY

1. Treatment decisions for infants and children with allergy should be made on the basis of history and, when appropriate, identified through directed serum sIgE or SPT testing. Newer in vitro sIgE tests have supplanted radioallergosorbent tests.
2. Allergy tests for sIgE must be selected and interpreted in the context of a clinical presentation; test relevance may vary according to the patient's age, allergen exposure, and performance characteristics of the test.
3. Positive sIgE test results indicate sensitization, but are not equivalent to clinical allergy. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.
4. Tests for sIgE may be influenced by cross-reactive proteins that may or may not have clinical relevance to disease.
5. Increasingly higher levels of sIgE (higher concentrations on serum tests or SPT wheal size) generally correlate with an increased risk of clinical allergy.
6. sIgE test results typically do not reflect the severity of allergies.

7. Use of a multiallergen serum test can be helpful for screening for atopic disease if there is a clinical suspicion. If positive, allergen-specific testing may be considered.
8. Tests for allergen-specific IgG antibodies are not helpful for diagnosing allergies.
9. Because test limitations often warrant additional evaluation to confirm the role of specific allergens, consultation with a board-certified allergist-immunologist should be considered.

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ACKNOWLEDGMENTS

Comments on this clinical report were solicited from committees, sections, and councils of the AAP; 3 responded. The Specific IgE Task Force Committee of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology also reviewed this clinical report.

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