

Appropriate Allergy Testing and Interpretation

by Jay M. Portnoy, MD

Given the improved sensitivity and specificity of *in vitro* tests, appropriate allergy testing can be performed by a trained provider in a primary care setting, ideally in collaboration with an allergy specialist.

Abstract

In vitro tests for specific IgE allow primary care providers to do allergy testing, which can be helpful for allergic patients. Diagnostic testing for allergies is used to determine whether symptoms are caused by IgE antibodies and exposure to an allergen. The presence of IgE in the absence of symptoms does not indicate clinical allergy. Nonselective use of large panels of allergens can lead to false positives and misinterpretation of the results, particularly in food allergy.

Introduction

A 13-year-old girl is seen in a medical office with symptoms consistent with allergic rhinitis including sneezing, itchy runny nose, and itchy watery eyes. You want to determine whether she has allergies or not. What is the best approach for doing this?

This is a common question in the primary care setting. While allergy testing ideally is performed by physicians who are trained in allergy/immunology, a growing number of primary care providers find it helpful to perform allergy testing in their offices. This is because there are too many patients with allergic conditions such as rhinitis, asthma and food allergy for allergy specialists to see all of them. The need for testing has

increased as a result of the 2007 NHLBI guidelines recommendation that allergy testing be performed in all patients with persistent asthma.¹ In one survey of allergic patients with asthma, approximately 70% of those who might need allergy testing were followed exclusively by primary care providers.²

There are many reasons to identify allergens to which a patient is sensitive beyond the need to establish an accurate diagnosis. These include targeted avoidance of relevant exposure(s) which has been shown to improve outcomes more effectively than untargeted avoidance,³ determination of a seasonal pattern so that treatment can be initiated in a timely manner and selection of individuals for allergen immunotherapy. In addition, a correct diagnosis increases the likelihood that appropriate treatment such as non-sedating H1 histamine antagonists will be provided to allergic patients and not to non-allergic patients who are unlikely to benefit from this treatment.⁴

Definition of Allergy

The terms "allergy" and "atopy" refer to the presence of clinical symptoms that occur following an interaction between allergen-specific IgE and exposure to an allergen.⁵ Though specific IgE is necessary for a reaction to be called "allergic," other mechanisms can cause similar



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symptoms making it necessary to test for the antibodies when making a diagnosis.

Common allergy-related conditions include allergic rhinitis, conjunctivitis, asthma, urticaria and some gastrointestinal manifestations. While atopic dermatitis may be associated with specific IgE, other immunologic mechanisms often are involved suggesting that this disorder is not purely an allergic disease. When a patient has symptoms consistent with one or more of these conditions, it is helpful to determine whether specific IgE is present and if so, whether it is associated with development of symptoms after the patient is exposed to the relevant allergen. This information can be used to make a diagnosis and to guide treatment.

Allergy tests are used to determine whether a patient's symptoms are due to the allergen-specific IgE antibodies.⁶ This is necessary because many symptoms can also be caused by other factors such as viral infections and irritants. The most important diagnostic test is the clinical history.⁷ A patient is unlikely to have allergies if they do not have symptoms after exposure to the suspected allergen. The history should focus on whether there is a relationship between exposure to allergens and development of symptoms.

When obtaining a history, it is important to be familiar with the common types of aeroallergens including when and where they are likely to be present in the environment as well as specific situations that increase the likelihood of exposure. This includes determination of whether there is a seasonal pattern to the symptoms, since many allergens, such as pollens and outdoor molds, are present in the environment at specific times of the year. The pattern of exposure for common outdoor aeroallergens is shown in Table 1.⁸ Perennial allergens such as furry animal dander, cockroaches, dust mites and indoor molds, are often present year-round and therefore are likely to cause symptoms that are persistent.

While the history can accurately determine whether a patient has symptoms after exposure to certain allergens, there are some limitations to how accurately it can identify others. In one study, 145 children had a history and physical

examination performed by two different board certified allergists. When their clinical diagnosis along with skin prick tests and specific IgE measurements of seven common inhalants were compared, skin tests and specific IgE measurements correlated well, but neither correlated well with the histories. This was because the clinical assessments were positive for allergies in 23% of patients who did not have IgE-mediated disease suggesting that the allergists overestimated the presence of clinical allergy.⁹ Discrepancies were dependent both on the specific allergen and on the allergist suggesting that allergists use available information from the history differently.

Ideally, the clinical history should provide enough information to form an opinion about whether a patient's symptoms are due to allergies and if so, what they are likely to be allergic to. The purpose of a diagnostic test is to determine whether a patient's symptoms are caused by an allergic disease as opposed to other common causes. Diagnostic testing also can better define the specific triggers when the history alone is unclear.

An ideal test should be capable of identifying patients who have a disease with 100% sensitivity while also

identifying those who do not have the disease with 100% specificity. Unfortunately, there is no perfect test so it is necessary to rely on probabilities rather than on certainty. The performance characteristics of a diagnostic test usually are described relative to a gold standard test that

is as close to perfect as possible. In the case of allergies, the most accurate type of test is a provocation or challenge test in which the patient is exposed to the allergen of interest under conditions that match the natural exposure that is suspected to have caused their symptoms. For rhinitis this can be done either with chamber studies or nasal instillation of allergen, while bronchial provocation can be used in asthma. Oral challenges often are used for food and drug allergies and sting challenges have been used as a gold standard for insect allergy.

The problem with gold standard tests are that they usually are expensive and difficult to perform, they are associated with a risk of anaphylaxis and they can only be performed with one allergen at a time. Were it not for these

Table 1
Seasonal Pattern of Exposure to Common Aeroallergens in the Central United States

Allergen	Where Found	Season
Tree pollen	Outdoors	Feb through April
Grass pollen	Outdoors	May through July
Weed pollen	Outdoors	August through early October
Molds	Outdoors	May – June and Sept – Oct
Molds	Indoors	Perennial
Furry animals	Indoors	Perennial
Dust mite	Indoors	Perennial
Cockroach	Indoors	Perennial

limitations, there would be no reason to do a different test. For these reasons, surrogate tests that are less expensive, safer and more convenient, have been developed that can be used to predict the results of the gold standard allergy tests.

The most useful performance characteristic of a diagnostic test relative to a gold standard test is its likelihood ratio, which for a positive test result is the ratio of the odds that a patient with a positive test has the disease over the odds that a patient with a positive test does not have the disease. A large positive likelihood ratio increases the odds that a patient with a positive test actually has the disease. Conversely, a small negative likelihood ratio can substantially decrease the odds that a patient with a negative test has the disease.¹⁰

There are two types of diagnostic allergy tests that can be used to identify the presence of allergen-specific IgE antibodies: skin tests and *in vitro* tests.

Allergy Skin Tests

Allergy skin tests rely on the presence of allergen-specific IgE antibodies bound to mast cells in the skin. When an introduced allergen interacts with the specific IgE, mast cells are stimulated to release their mediators including histamine.

A percutaneous test involves pricking the skin with a sharp object (usually a plastic device or needle) in the presence of a dilute solution (usually 1:10 to 1:40 w/v) of the allergen of interest. See Figure 1. If specific IgE antibodies bound to mast cells are present, the allergen induces histamine release resulting in formation of a characteristic wheal and flare reaction after 10-15 minutes. The size of the reaction can be measured and compared to a positive control (usually histamine 10mg/mL) and negative control (saline). If the reaction is significantly larger than the negative control, then the reaction is usually considered to be positive. A negative prick skin test is associated with a very low likelihood that the patient is allergic to that allergen. A positive skin test usually corresponds with clinical symptoms after allergen exposure for aeroallergens.

Figure 1

A percutaneous test involves pricking the skin with a sharp object in the presence of a dilute solution of the allergen of interest.



The specificity is lower for food allergens because it is common for a skin test to a food to be positive in patients who can eat the food without a reaction.¹¹

Intracutaneous tests involve injecting 0.05mL of a dilute extract (1:100 or 1:1000 w/v) into the skin, usually of the patient's arm. This type of test is more sensitive than a prick test so it is used when it is important to avoid a false negative result such as in drug or stinging insect allergy.

There is evidence that intracutaneous tests may be too sensitive and non specific, leading to false positive reactions for some allergens.¹² In addition, intracutaneous tests are painful, which is an issue particularly in small children. There also is an increased risk that an intracutaneous test could induce a systemic reaction in exquisitely sensitive patients, particularly if done with food. For that reason, intracutaneous tests for foods are not recommended.⁶ Many allergists do not routinely perform intracutaneous tests unless they are specifically indicated.

The advantage of skin tests is that they are rapid, sensitive and specific, safe and relatively inexpensive per test. The disadvantages of skin tests are that there is a small risk of a systemic reaction, they are associated with some discomfort and the reaction is inhibited if the patient has taken antihistamines prior to the test. For that reason, patients should be advised to avoid taking H-1 antihistamines for at least seven days prior to undergoing skin tests. Patients who are unable to discontinue their antihistamines, who have widespread skin disease that precludes testing or patients who exhibit dermatographism are not candidates for skin testing.⁶

Though skin testing is convenient, cost-effective and accurate, there is some variation in how it is performed, interpreted and documented even by trained allergists. In addition, skin test results can vary with the season (more sensitive in October for seasonal allergens and in February for perennial allergens), the location where they are applied (back is more sensitive than the arm), the device used to do the pricking (bifurcated needle is more consistent than dermapik), the source of extract (standardized vs

unstandardized) and even the time of day when it is performed (AM is more sensitive than PM). Therefore, allergy skin tests should be performed by physicians who have been trained to perform and interpret them.^{13 14 15} Ideally, healthcare professionals who perform and interpret skin tests should undergo proficiency testing at least one or two times per year.

In Vitro Tests

In vitro tests rely on the ability of specific IgE antibodies in a patient's serum to bind to allergens that are attached to a solid phase. These IgE antibodies are subsequently detected using an enzyme-conjugated anti-IgE which causes a substrate either to turn a color or to become fluorescent. The color change or fluorescence can then be measured and, when compared to appropriate control reactions, reported as units or nanograms per mL. These enzyme immunoassays are both sensitive and specific, though there are differences depending on the specific technology that is used. Though the original Radio-Immunsorbant Assay is no longer available, *in vitro* tests are still commonly referred to as a RAST. Technically, they should not be referred to as RASTs. Newer technologies have made *in vitro* tests comparable to skin tests both in sensitivity and specificity.

Current clinically available allergen-specific IgE assays licensed in the United States include Phadia, Siemens, and Hycor. The assays have comparable sensitivities, precision, and reproducibility with coefficients of variation generally <15%. Unfortunately, the 3 IgE antibody assays may give different results when used to measure the same samples.¹⁶ Consequently, results from the 3 assays are not interchangeable so it is important to know the brand of IgE test when interpreting the results. In addition, decision values from one assay cannot be used to interpret results from a different assay.¹⁷

For the primary care provider, *in vitro* tests have the advantage that they are readily available, they require a single venipuncture, the office staff do not need to be trained to perform them, there is no risk to the patient since directed exposure to the allergen is avoided, and the tests are not affected if the patient has taken an antihistamine. The disadvantages are that they are more expensive than skin tests on a per test basis and there is a delay in getting the results.

Selecting Allergens for testing

Regardless of whether a skin test or *in vitro* test is used, it is important to select allergens to be tested for based on the patient's history and the need to identify which

allergens are relevant for that patient. In the primary care setting, *in vitro* tests are the most common allergy test used. Many laboratories offer panels of allergens from which the physician can select. These are provided as a convenience, particularly if the physician is not familiar with the individual allergens and wants to order a panel that represents aeroallergens common to a particular region. Even so, it is not necessary to select a panel if measurement of IgE to selected allergens would be more appropriate for a particular patient.

In general, patients with respiratory diseases such as rhinitis and asthma should have IgE measurements for aeroallergens which are more likely to be associated with their symptoms. Food-specific IgE tests should be reserved for individuals who have symptoms after eating a particular food. When there is a suspicion that symptoms are related to a food, but it is not clear which food among several is responsible, measurement of IgE to a limited panel of foods may be helpful.

Nonselective testing with large panels of allergens should be avoided, since it increases the risk that a number of clinically irrelevant false positive results will occur. This is because a positive IgE indicates that the patient is sensitized (ie: has specific IgE) but not necessarily that the patient has clinical allergy (i.e. has symptoms on exposure to the allergen). In other words, many patients have positive tests to allergens to which they do not react when they are exposed.

If the history is consistent with allergy but unclear about the specific allergen, it is reasonable to screen for atopy using a small panel of common aeroallergens (for respiratory conditions) or foods (for atopic dermatitis). These panels should contain representative allergens that are present where the patient lives. For example, a screening panel may include perennial allergens such as dog, cat, dust mite, cockroach, several molds (eg: *Alternaria*, *Cladosporium*, *Aspergillus*, *Penicillium*), and pollens (eg: ragweed, Timothy grass, Oak, Elm and Maple). Pollen mixtures can be used to screen for a variety of sensitivities. If a mixture is positive, then the individual components can be enumerated.

Allergens that do not cause symptoms after exposure (such as a food that the patient regularly eats without any symptoms) should not be selected for IgE testing. Unfortunately, reliance on large panels of specific IgE tests can result in over interpretation of positive results. This is a particular problem with food allergy where unnecessary avoidance of foods can lead to restricted diets and in some cases, to malnutrition.

Interpretation of Results

The size of a skin test or the concentration of specific IgE corresponds to the probability that a patient will develop symptoms after exposure to the allergen. These measurements do not correspond to the likely severity of the reaction. In general, the size of a skin test corresponds with the concentration of specific IgE antibody that is present in serum. Skin test in children with food allergy with wheal sizes 13mm greater than the negative control for hen's egg and 12.5mm for cow's milk were associated with a 95% probability that the patient would react to the food in one study.¹⁸ Similar results have been found for other foods.¹⁹ In the same way, food-specific IgE concentrations have been identified that can predict a reaction to egg ($>7\text{kU/L}$), milk ($>15\text{kU/L}$), peanut ($>14\text{kU/L}$), and fish ($>20\text{kU/L}$) with greater than 95% certainty.^{11, 20} Clearly, an IgE value >0.35 to an allergen does not necessarily mean that the patient is sensitized to that allergen. Since the critical values vary with each allergen, results of specific IgE tests should be interpreted carefully and always in the context of the patient's clinical symptoms.

Certain clinical conditions such as behavior problems, autism, chronic urticaria and contact dermatitis, have no relationship to IgE, so an allergy test should not be done. In addition, there is no reason to measure specific IgG antibodies to foods since such antibodies normally are present to foods that the patient regularly eats and have no association with any disease.⁶

Conclusion

Allergy testing can determine whether a patient has allergic sensitization and, when combined with an appropriate history, whether they have clinical allergy. Tests are done to make a diagnosis, target environmental control, predict seasons and guide prescription of allergen immunotherapy when indicated. The 2007 NHBLI asthma guidelines recommendation that all patients with persistent asthma undergo allergy testing means that the need for allergy testing is growing.

Given the improved sensitivity and specificity of *in vitro* tests, allergy testing can easily be performed in the primary care setting. Since 70% of patients who need allergy testing are seen at the primary care level, there is a need for primary care providers to do some allergy testing in selected patients. While selection of tests and interpretation of results can be tricky, with proper training it should be possible for primary care providers to include some allergy testing into the routine care of allergic patients, ideally in

collaboration with an allergy specialist.

Finally, since food allergy is significantly more challenging both to diagnose and to treat, it is probably best for primary care providers to refer patients with suspected sensitivity to foods to an allergy specialist for co-management.

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Disclosure

None reported.



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