

The diagnosis of food allergy

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ABSTRACT

Background: Food allergy is increasingly common; however, there is a discrepancy between the large number of people who believe they or their children are affected and the actual number with true food allergies. It is therefore imperative that physicians evaluating patients with possible adverse reactions to foods understand the current modalities used to diagnose food allergies.

Methods: Simple tests including skin-prick testing (SPT) and serum food-specific IgE testing are the most commonly used diagnostic tests to evaluate for IgE-mediated food reactions. However, these tests have pitfalls and their usefulness must be appreciated to avoid over- and underdiagnosis.

Results: A firm diagnosis is imperative because a misdiagnosis could lead to life-threatening reactions and overdiagnosis will lead to unnecessary elimination diets with nutritional and social implications. Physician-supervised oral food challenges (OFC) remain the gold standard for food allergy diagnosis; however, a careful medical history and simple tests can often provide a reliable diagnosis.

Conclusion: In this review, we examine the usefulness and pitfalls of SPT used by allergists and serum food-specific IgE levels that are available to all practitioners. We also review the OFC as a diagnostic modality in food allergy. Finally, we describe emerging tests, such as the basophil activation test, atopy patch testing, and component-resolved diagnostics, that may be of benefit in the future.

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Food allergy is common and appears to be increasing. Reports of prevalence vary according to the definitions used in various studies, study populations, and other factors. It is clear that more individuals consider themselves to have a food allergy than are actually allergic. For self-reported food allergy, the prevalence can range from 3 to 35%, whereas if one uses an objective test such as a medically supervised feeding, an oral food challenge (OFC), the rate ranges from 1 to 10.8%.¹ The most recent report by the Center for Disease Control and Prevention estimates the prevalence of food allergy to be 3.9% in children <18 years of age in the United States, representing an increase of 18% from 1997 to 2007.² With this high and, apparently, increasing prevalence, and the discordance between persons avoiding foods for presumed allergy, compared with verified allergy, it becomes imperative for physicians seeing patients with adverse reactions to food to understand appropriate diagnostic strategies for food allergy and to understand how to interpret the results of laboratory tests.

CLINICAL HISTORY

Before implementing any laboratory diagnostic test, the clinician must decide on the likelihood, based on the clinical history, that the patient's presenting symptoms are caused by food allergy. It is therefore essential that the clinician have a basic understanding of the pathophysiology of food allergies and an understanding of how the common diagnostic tests will aid in the diagnosis. "Food allergy" is a term that refers to those adverse reactions to foods that are immunologically mediated. This most commonly is the result of an IgE-mediated immediate-type hypersensitivity reaction, which leads to the "typical" food allergy symptoms, such as hives, angioedema, vomiting, bronchospasm, etc. There are other syndromes that are immune-mediated reactions to foods that are not exclusively IgE mediated (e.g., food protein-induced enterocolitis syndrome and eosinophilic esophagitis). These food allergies are often referred to as "non-IgE mediated" or "mixed IgE/non-IgE mediated," which is an important distinction when proceeding toward diagnostic testing because standard tests for food-specific IgE may not be relevant.

There are also nonimmune adverse reactions to foods (e.g., lactose intolerance and scombroid food poisoning) that do not qualify as food allergies but may sometimes present in a clinically similar manner to food allergies; these adverse reactions will not be detected by the common diagnostic tests that will be discussed in this study. Typical findings of common food-induced reactions are given in Table 1. The history should determine the food in question, the amount ingested, the timing of symptoms after ingestion, ancillary factors that may be necessary to elicit symptoms (e.g., exercise), whether the patient has ingested the food previously without any reactions (reducing the chance there is an association), and the length of time since the last reaction. These details will permit the clinician to estimate the likelihood of the symptoms being an IgE-mediated reaction, to identify potential culprit foods, and to therefore provide an initial guide to decide on additional testing.³ In summary, testing for food allergy should be reserved for specific indications where IgE mediated allergy is a likely cause. Additionally, testing of specific foods should be performed only to the culprit foods suspected and should not be done to an indiscriminate "panel" of food allergens. Table 2 displays some clinical conditions and whether food allergy testing is warranted.

ELIMINATION DIETS

It stands to reason that elimination of foods from a patient's diet with resolution of chronic symptoms would support a diagnosis of food-induced symptoms. There are many pitfalls, however, with this approach. Difficulties include the ability to accurately maintain an elimination diet over time, patient or observer bias, and nutritional concerns.⁴ In addition, one should also appreciate that with chronic disorders such as atopic dermatitis, the symptoms often wax and wane leading to false associations with food triggers.^{5,6} Because of these pitfalls, one should not rely solely on an elimination diet to diagnose food allergy.

SKIN-PRICK TESTS

Skin-prick tests (SPT), typically done with commercial extracts at 1:10 or 1:20 w/v on the back or volar surface of the forearm, are a quick, inexpensive, and sensitive means to detect the presence of IgE antibodies to the food under consideration. Although SPT have been used for >100 years to diagnose allergic disease, their limitations in diagnosing food allergy when compared with the "gold standard," OFC, were first delineated by Charles May in 1976.⁷ Since that time, many studies have evaluated the diagnostic value of SPT to predict clinical reactivity using OFC as a comparator. What is clear from these studies is that a negative SPT essentially confirms the absence of

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Table 1 Differential diagnosis in food allergy

Disorder	Symptoms	Symptom Course	Diagnostic Pearls
IgE-mediated food allergy	Sneezing, oral pruritis, urticaria, angioedema, facial erythema, vomiting, wheezing, and hypotension	Minutes to 2 hr	Positive SPT, positive serum IgE
Oral allergy syndrome	Oral pruritis, tingling, and lip angioedema (to raw fruits and vegetables)	Immediate	Positive SPT to pollens; symptoms may vary with pollen season
Lactose intolerance	Abdominal pain, bloating, nausea, and diarrhea	Minutes to hours	Symptoms improve with lactose-free milk or lactase supplementation
Scombrototoxicism	Flushing, dizziness, headache, urticaria, nausea, and tachycardia	Minutes	After fish ingestion due to conversion of histidine to histamine
Eosinophilic esophagitis	Dysphagia, abdominal pain, vomiting, and food impaction	Chronic	Biopsy required for diagnosis; responds to elemental diet and swallowed steroids
Eosinophilic gastroenteritis	Abdominal pain, emesis, poor appetite, and failure to thrive	Chronic	Biopsy required for diagnosis
Allergic proctocolitis	Bloody stools in an infant	Chronic	Milk typical culprit; seen in breast-fed infants; usually resolves by age 1 yr
Food protein-induced enterocolitis syndrome	Emesis, diarrhea, poor feeding, and failure to thrive	Symptoms start ~2 hr after feeding	SPT negative; usually resolves by age 2–3 yr; can have severe dehydration and hypotension
Celiac disease	Abdominal pain, bloating, diarrhea, and failure to thrive	Chronic	Full resolution with gluten elimination; tissue transglutaminase antibodies usually positive; biopsy required for diagnosis

SPT = skin-prick test.

Table 2 Examples of indications and nonindications for food allergy testing

Clinical Presentation	Recommendation on Testing
Acute urticaria	Dependent on clinical history and relation to ingestion or contact of certain food; without any relationship, food allergy testing is not warranted
Allergic rhinitis and or asthma	Isolated airway allergy is not an indication for food allergy testing
Chronic idiopathic urticaria	No indication for food allergy testing
Headaches attributed to food	No indication for food allergy testing
Chronic fatigue symptoms	No indication for food allergy testing
Generalized diarrhea, bloating, and constipation	No indication for food allergy testing
Infant with and older sibling who has food allergies	This decision is generally physician and family dependent
Atopic dermatitis	Dependent on age, severity, and response to treatment; typically, food allergy testing is done for younger infants with moderate to severe dermatitis; physician must consider the ramifications and treatment strategies if testing is positive, before initiating testing

IgE-mediated food allergy, with negative predictive accuracy of >90%.⁸ A positive test, by convention described as a mean wheal diameter of 3 mm greater than the saline control, however, does not confirm the diagnosis; rather this result simply confirms sensitization to the tested allergen. That is, a positive test does not equate with clinical reactivity to the tested food. One must therefore use the SPT in combination with the clinical history, and often other diagnostic tests, to arrive at a diagnosis. The test provides more information when it is evaluated according to the size of the wheal, rather than simply as being positive or negative. Numerous studies have tried to determine a correlation between test sizes and probability of true allergy by comparing results against a physician supervised OFC.^{9–16} Notable from these studies is that with increasing SPT size, there is increasing likelihood of clinical allergy to the tested food. For example, Sporik and colleagues defined mean wheal diameters in a pediatric population for milk, eggs, and peanuts, above which all of their young subjects reacted to the ingested food: cow's milk, >8 mm; eggs,

>7 mm; and peanuts, >8 mm.¹² Most studies discussed used single application testing devices, which may give different wheal sizes than multiapplicator devices.

It is important to take the population being studied into account when trying to extrapolate these data to everyday clinical practice, because the predictive values obtained from these studies are dependent on the population being studied. The prior probability of allergy in these populations may be different from that seen in the typical office setting, and therefore the results may not directly apply to all settings. Importantly, studies from different populations show differences in correlation of skin test size to outcomes of food challenges. Additional limitations are also evident. Commercial food extracts for skin testing still need to be standardized, and, therefore, may have varying concentrations of relevant proteins.¹⁷ This may lead to slightly varying skin test results.¹⁰ Given the lability of some food proteins, especially those for fruits, commercial extracts may be inadequate; therefore, fresh foods may need to be used for skin test-

Table 3 Food-specific IgE levels that give 95% likelihood of reaction

Allergen	Serum IgE Level (kIU/L)
Cow's milk (<2 yr old)	≥5 ²⁵
Cow's milk (> 2 yr old)	≥15 ²⁴
Eggs (<1 yr old)	≥10.9 ³⁰
Eggs (>1 yr old)	≥13.2 ³⁰
Peanuts	≥14 ²⁴
Tree nut	≥15 ²⁸

ing.¹⁸ If commercial extracts are not available, some groups have shown usefulness of SPTs with fresh foods to common food allergens.^{19,20} Intradermal testing is currently not recommended because this approach is overly sensitive and carries risks of reaction.^{21,22}

FOOD-SPECIFIC IgE

In vitro, serum-specific IgE measurements have now replaced radioallergosorbent testing as the means of measuring serum IgE levels and are now routinely used in the evaluation of food allergies by both primary care physicians and specialists alike because of the test's ease and availability, although the tests are more costly than SPT. Many studies in the past 30 years have been published with data on serum-specific IgE and their correlation with results of food challenges, which have provided the clinician with IgE levels that can help predict the likelihood of a reaction.^{5,23–32} The overall characteristics and limitations of the data on using food-specific IgE for diagnosing food allergy are quite similar to those for SPT described previously. As with SPT, there is a direct correlation between increasing concentrations of food-specific serum IgE and the probability that an individual will react to an ingested food. Table 3 shows diagnostic values of various foods based on several studies, mainly in children. As derived from these studies, if a patient has a serum food-specific IgE level above the values shown, they are >95% likely to experience an allergic reaction if they ingest the specific food.³ Like with SPT, one must take into account when interpreting these data that "cutoffs" for diagnostic predictions may vary depending on the population studied and that population's prior probability of having a food allergy; therefore, these results may not apply to all populations. If one combines interpretation of the results of SPT to the food-specific IgE levels, the diagnostic accuracy increases in some studies.¹⁵ Although these values can help predict reactivity, they unfortunately have not been shown to accurately predict the severity of the reaction. In addition, like the majority of diagnostic tests in medicine, the serum-specific IgE level is not 100% sensitive or 100% specific. Studies have shown reactions in patients with values under the lowest detectable limit for the test, and as discussed earlier, positive values simply reveal sensitization and do not assure clinical reactivity, giving further evidence that the test should not be used in isolation to diagnose food allergy.

Most of the studies examining the role of serum IgE levels in food allergy use the Pharmacia CAP or ImmunoCAP assay (Pharmacia Diagnostics, Uppsala, Sweden) to quantitate the food-specific, serum IgE. There are, however, other available serum IgE systems, and it is important to note that not all *in vitro* tests for serum-specific IgE measurements yield similar results and results may not be comparable between tests.³³ Additionally, different "units" or measures may be provided, *i.e.*, classes, counts, or units, and these are not interchangeable. Another caution in interpreting both SPT and serum IgE levels is the contribution of protein cross-reactivity between related foods, as well as between pollens and foods. For example, patients with pollen allergies may test positive for multiple foods (*e.g.*, hazelnut, apples, and carrots) despite having little or no symptoms and

patients with peanut sensitivity may also test positive to multiple legumes despite tolerating various beans in their diet.³⁴

ATOPY PATCH TESTS

Atopy patch tests (APT) have been studied as an adjunct diagnostic test to SPT in food allergy. The test involves placing a porridge or extract of the food on the skin for 24–48 hours under occlusion and evaluating the area for erythema and eczematous reactions 24–72 hours after removal. Their role appears to be most helpful to identify late reactions in atopic dermatitis and non-IgE mediated, food-induced gastrointestinal symptoms, such as those seen in eosinophilic esophagitis and food protein-induced enterocolitis syndrome.^{35–38} Although there may be a role for the use of APT in select clinical settings, more research is needed in this field. Some studies of using the APT as an adjunct to diagnosing food allergies in atopic dermatitis have shown relatively poor additional predictive value.^{37,39} Because of a lack of standardization, difficulty in test interpretation, and limited studies, the most recent practice parameters in the United States do not advocate its use in routine practice at this time.²¹

OTHER DIAGNOSTIC TESTS AND UNPROVEN TESTS

Basophil activation assays or basophil activation tests, which currently use flow cytometry to detect up-regulation of certain cell surface markers such as CD63 to identify basophil activation, allow for *in vitro* measurement of a functional response with only small amounts of whole blood. Use of this newer method with flow cytometry as a diagnostic tool for IgE-mediated food allergy was first published in 1999.⁴⁰ Although this assay shows promise in multiple IgE-mediated diseases, including food allergy, there are only a few studies, to date, validating this method and it is therefore not currently used in clinical practice.⁴¹

Food-specific IgG and IgG4 antibody levels do not have a role in the diagnosis of food allergy. They are both likely to be positive in food-allergic individuals and normal controls simply because of exposure and, in fact, IgG4 levels have been shown to be a marker of immunologic tolerance in oral immunotherapy trials to date.^{21,42,43}

With recent advances in molecular biology and biochemistry, researchers have been able to identify and clone or purify specific allergenic proteins in foods. With this ability to differentiate exact components of the whole food, so-called component-resolved diagnostics can allow for determination of IgE binding to various proteins within the food in question, which may, in turn, inform diagnostics and prognostics. For example, detection of binding to labile proteins may be associated with mild reactions or tolerance whereas binding to proteins that are stable to digestion may correspond to more severe reactions. Another approach evaluates where on proteins the IgE binds; this epitope binding analysis may also inform diagnostics. For example, those patients whose IgE binds a higher number of sequential or linear epitopes may in fact have more severe reactions and persistent food allergy, versus those whose IgE binds higher numbers of conformational epitopes (those epitopes only present in the protein's folded state that may be sensitive to digestion).^{44–46} These assays are only for use in investigational studies and are not available for commercial use at this time.

ORAL FOOD CHALLENGES

The double-blind, placebo-controlled food challenge (DBPCFC) is considered to be the "gold standard" for the diagnosis of food allergy. The first case report documenting the use of the OFC for diagnosis of food allergy was published in 1971, and the first trial in children was reported in 1976 and in adults in 1982.^{47–48} Since that time, the DBPCFC has been used as the standard to which all other IgE allergy diagnostic studies are compared. There are published guidelines on performing OFC.^{49–51} First, suspected foods are eliminated from the

patient's diet for 2–8 weeks (including suspected food from mother's diet in breast-fed infants). The test feeding is then performed under physician supervision when the patient is asymptomatic and on no medication that could mask symptoms, *e.g.*, antihistamines. This may be done in the hospital setting with i.v. access if there is any history of systemic reaction or if there is high suspicion of reaction, but is typically performed in an outpatient, office setting. The suspected food or placebo is given to the patient starting with a low dose (lower than any dose that would be suspected to cause a reaction), which is then gradually increased, until a cumulative dose at least equal to the usually eaten quantity is reached. It is ideal to have a third party prepare the foods and placebo, and randomize the feeding so that the food is masked and has similar odor, taste, color, and texture to the placebo vehicle. Examples of vehicles include applesauce, ground meat patties, oatmeal, and mashed potatoes.⁵¹ There are published studies to help mask foods for blinded food challenges, because many patients have an *a priori* fear of ingesting suspected allergens and this could lead to subjective symptoms despite no evidence of immunologic reaction.⁵² Challenges may be done in 1 day, with one session in the morning, and another in the afternoon, thus allowing separation of the placebo and active challenges, although they can be separated by days. Patients should be monitored throughout the challenge, with cessation of the challenge with any reaction. Depending on the population studied, food challenges are negative in up to 2/3 of suspected food-allergic patients, and thus can quite often provide both the patient or the parent and the physician with visual proof of tolerance. There are, however, documented false negative food challenges in up to 3% of cases; therefore, all double-blind food challenges should be followed with open feeding of the food in its natural form.^{53,54} Possible reasons for false negative results include inadequate dosing, unknown or undocumented use of medications that can mask symptoms, and the requirement for an eliciting factor to bring out symptoms (such as exercise being required for symptoms to be elicited with food-associated, exercise-induced anaphylaxis).

Unfortunately, the DBPCFC is time-consuming and expensive, requiring ~6–8 hours of in-office or hospital, nurse-observed time for a full challenge. Therefore, the single-blind and open food challenges, which require only half the time, are often used in the clinical setting, when practicality must be taken into account. The single-blind challenge, in which the tested food is masked in a vehicle, is commonly used in patients, such as older children, who may have an established fear of the food, and are therefore more likely to have subjective symptoms on challenge. The open food challenge can be easily done with the natural food in patients with a low likelihood of subjective symptoms.

TYING IT ALL TOGETHER

Case 1

Patient AA is a 3-year-old boy with a history of atopic dermatitis. He was recently diagnosed with peanut allergy after he was found to have hives and angioedema after eating a peanut butter sandwich for the first time in his life. His serum IgE to peanut was 35 kIU/L. The initial laboratory work was sent by his primary care physician and included a serum IgE panel to 16 food allergens. It was noted on this panel that his serum IgE to shrimp was 4 kIU/L. His parents now inquire whether he is allergic to shrimp, because he has been eating shrimp regularly since the age of 1 year, with the most recent ingestion being 1 week ago, and has never had a reaction, but he had been told he is now allergic to shrimp as well.

This case points out two important issues. First, the symptoms, food ingested, and the temporal relationship of ingestion and symptoms are typical for IgE-mediated food allergy, and diagnostic evaluation for the suspected food, in this case peanuts, was appropriate. Sending a battery of tests to multiple foods that the patient is already eating was not appropriate. Now, the clinician is faced with a positive

serum IgE to a food that the patient tolerates and a decision has to be made as to what to do with that food, shrimp in this case. This case points out the importance of using the laboratory test to supplement the clinical history, and not to diagnose disease in isolation. In this case, we would recommend that the patient continue eating shrimp despite a positive IgE, because this finding suggests sensitization without clinical reactivity.

Case 2

Patient BB is a 1-year-old girl who has been referred for vomiting and diarrhea that occurs ~2 hours after meals over the past month. The family suspects soy as a possible causative food, as they transitioned her from a milk-based formula to soy recently. The vomiting caused dehydration and on one occasion she required i.v. fluids in the emergency room. After evaluation by her physician, the family was told that the patient's symptoms were not caused by soy allergy, because serum IgE to both milk and soy were negative. The patient, however, continued to experience severe delayed vomiting and diarrhea when exposed.

This case points out that not all allergic (immune mediated) reactions to food are IgE mediated, and therefore tests are expected to be negative in some situations. The clinical history and understanding of the pathophysiology of the disease must be considered. This patient likely has food protein-induced enterocolitis syndrome, a cell-mediated response where, classically, after ingestion of the culprit food there is a 2-hour delay and then severe vomiting and later diarrhea. Because this is a cell-mediated disorder, undetectable serum milk and soy-specific IgE would be expected.⁵⁵

SUMMARY

With increasing prevalence of food allergies worldwide, the need for accurate diagnosis is of increasing importance. Although DBPCFC remains the most definitive test to diagnose food allergies, they are time-consuming, put the patient at risk of reaction, and are not always cost-effective. Therefore, it is imperative for the clinician to use appropriate and available diagnostic modalities to screen for food allergies and decide on the need to perform an OFC. A combination of a thorough history and testing for food-specific IgE when appropriate will allow the clinician to predict the likelihood of reaction and make appropriate decisions on whether to perform the OFC.

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