

Unproven Diagnostic Tests for Food Allergy



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KEYWORDS

- Food allergy • Diagnosis • Atopy patch test • IgG testing • Provocation
- Electrodermal • Cytotoxic • Kinesiology

KEY POINTS

- Atopy patch testing for food allergies is debatable, and may have an adjunct role in atopic dermatitis and eosinophilic esophagitis.
- Skin prick testing, serum immunoglobulin E (IgE) testing, and oral food challenges remain the currently accepted tests for immediate (anaphylactic) type food allergies.
- Serum IgG testing, provocation/neutralization, electrodermal testing, cytotoxic testing, and applied kinesiology are unproven and currently unaccepted methods to diagnose food allergy.

INTRODUCTION

Although the self-reported prevalence of food allergy is as high as 10% in Westernized countries such as the United States, the prevalence of actual diagnosed food allergy is lower.¹ This discordance often drives patients (and parents of patients) with suspected food allergy to pursue a variety of diagnostic procedures in search of answers and advice. Currently, the gold standard for the diagnosis of food allergy is the oral food challenge (OFC), whereas serum immunoglobulin E (IgE) and skin prick testing (SPT) serve as accepted readily available markers of sensitization to help predict clinical reactivity and obviate challenges. Unfortunately, serum and SPT are only useful for the diagnosis and management of IgE-mediated food allergies, and they have little or no role in diagnosing other food hypersensitivity disorders or intolerances, and the oral challenge can be time consuming, fear inducing, and possibly not readily available to many patients. Thus, many patients may seek alternative diagnostic methods for their (or their child's) suspected food allergy. In fact, based on one report, nearly 1 in 5 patients with self-reported food allergy has undergone unproven

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diagnostic testing.² This testing, if not proven, clearly has the possibility of leading to incorrect diagnoses, unnecessary elimination diets, and altering the quality of life for patients and families. Therefore, it is critical for providers (and arguably patients) to understand the methodology and research behind both proven and unproven techniques in order to counsel patients appropriately. This article briefly reviews proven techniques of food allergy testing for IgE-mediated allergies and focuses on debatable or unproven techniques.

PROVEN TECHNIQUES FOR TESTING IMMUNOGLOBULIN E-MEDITATED FOOD ALLERGY

The following testing modalities are recommended in current guidelines and practice parameters of various organizations and countries and are universally accepted by expert consensus panels on the diagnosis of food allergy (specifically IgE-mediated food allergy).^{3–5}

Skin Prick Testing

A positive SPT response indicates the presence of IgE specific to the antigen in question and represents an observable physiologic response to that allergen. Although SPTs for foods have high sensitivity, they have low specificity and should therefore be correlated with the patient's history to determine clinical relevance.⁶

Food-Specific Serum Immunoglobulin E

Food-specific serum IgE (sIgE) testing is also accepted as an appropriate first-line test for food allergy and is often used in conjunction with SPT. Similarly to SPT, it also has low specificity and should be interpreted in light of the patient's history.

As an aside, it is worth mentioning that sIgE panels to a large number of foods appear to be increasingly popular, especially among primary care providers.⁷ Panel testing has led to an increased cost per patient, overdiagnosis of food allergy, and unnecessary elimination diets in addition to an emotional and financial burden for patients and their families.⁸ Although these tests are widely available and easy to perform, the use of food allergen sIgE panels is discouraged.

Oral Food Challenges

The double-blind, placebo-controlled food challenge (DBPCFB) is widely accepted as the gold standard for diagnosis food allergy, and there are available reports and guidelines to aid clinicians in performing these appropriately.^{9,10} However, DBPCFB is both labor and time intensive, so the open OFC is more often used in the clinical setting; however, one must be aware that the open OFC can be affected by both patient and observer bias.

OTHER FOOD ALLERGY DIAGNOSTIC MODALITIES

Many of the diagnostic techniques discussed in this section either have not been studied in rigorous trials or have conflicting data regarding their utility.

Patch Testing

Atopy patch testing (APT) is a diagnostic procedure for delayed hypersensitivity reactions and is commonly used in the diagnosis of contact dermatitis. It has been studied in various forms of food allergy, but it must be noted that the methods and interpretation of results have yet to be standardized for foods and APT may be especially difficult to interpret in patients with underlying atopic dermatitis (AD), where irritant reactions

could be interpreted as false positive results. In addition, given that APT is directed at a specific hypersensitivity reaction, the utility of the test for food allergy will greatly depend on the population studied and what type of “food allergy” for which the patients are undergoing testing.

“Mixed” allergy

Some researchers have examined the utility of APT as a diagnostic marker for food allergy with varying clinical presentation. For example, Caglayan-Sozmen and colleagues¹¹ examined the diagnostic utility of APT and SPT in comparison with OFC in children with suspected egg or milk allergy with varying clinical presentations (including eczema, urticaria, anaphylaxis, proctocolitis, and so forth). The results showed that APT had a low sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both milk and egg, and, thus, the investigators concluded that there was insufficient evidence to support the use of APT in predicting the outcome of OFC to these foods. Another study of children with varying presentations of suspected food allergy to milk, egg, wheat, or soy also showed that APT alone was of little diagnostic utility.¹² When examining these studies, however, one must realize that by enrolling children with varying clinical presentations, some may have had IgE-mediated disease and some cell-mediated diseases; thus, the ability of APT to perform for a specific condition is difficult to interpret from these studies.

Although the above studies suggest that APT was not useful in evaluating patient groups with a wide range of presentations, it may be more useful in patients with more specific complaints suspected to be secondary to a non-IgE-mediated reaction to foods. For example, in one study of diagnostic tests in patients with food-related gastrointestinal symptoms (excluding eosinophilic esophagitis [EoE]), the combination of SPT/APT was shown to have a high sensitivity and NPV.¹³ Another study also found the SPT/APT combination had a high sensitivity; however, this study found that the combination had a low NPV, and thus it did not decrease the need for OFC in these patients.¹⁴

Patch testing has also been studied in food protein-induced enterocolitis syndrome (FPIES), another non-IgE-mediated food hypersensitivity. FPIES presents a diagnostic dilemma because there is no useful diagnostic tool short of an OFC, which carries risk of severe reactions, with up to half of patients requiring fluid resuscitation after a positive challenge.¹⁵ One study found that APT had high NPV (100%) and PPV (75%) and thus could be a helpful tool in determining the need for OFC.¹⁶ However, a similar study found that APT had NPV of only 55% and PPV 40%, perhaps because of different methods of interpreting APT results between the 2 studies.¹⁵ Clearly, more research needs to be done in the non-IgE-mediated food hypersensitivity patient population (and a better understanding of the pathophysiology of the disease being tested is needed) before a clear recommendation can be made.

Atopic dermatitis

Patients with AD represent a particularly interesting subset of food allergy patients, given that their manifestations can represent an overlap of IgE-mediated and cell-mediated reactions to foods.¹⁷ Therefore, one could reason that these patients warrant food allergy testing beyond SPT and/or sIgE in order to optimize treatment. Various studies have examined the use of APT in subjects with AD and suggest that it may be helpful in this patient population as an adjunct test along with sIgE or SPT.^{18–22}

One of the earlier studies done on food APT in patients with AD evaluated children 2 to 36 months of age with both SPT and APT for milk before an OFC. Although SPT could predict acute-onset reactions, APT was often positive (89%) in subjects with

delayed-onset reaction (worsening of AD). The investigators concluded that using both SPT and APT together can enhance the accuracy of diagnosis of milk allergy in AD patients.¹⁸ A similarly designed study evaluating SPT and APT for milk, egg, wheat, and soy also found that using both tests together was helpful in predicting a positive OFC. Furthermore, these investigators suggested that using APT as a predictor for positive delayed-onset OFC may help prevent unnecessary elimination diets based on history alone.¹⁹ More recently, one group compared APT and SPT when examining AD flares over time. The results suggested that APT and SPT performed nearly identically when examining all tests/foods, and the investigators also suggested that when both tests are positive, all patients had a positive OFC.²² Similar results have been found in studies that combine APT with sIgE testing, suggesting that APT plus sIgE can help predict AD flares due to foods and may help obviate OFC.^{20,21}

As always, there are limitations to the previously mentioned studies. First, they were all done in pediatric AD patients. Second, there is yet to be a standardized protocol for completing and interpreting APT for foods. Third, one must be able to tease out when the studies are specifically looking at the utility of the test for AD flares (delayed reactions), or if they examine the utility of APT in immediate reactions as well, as the pathophysiology of these are quite different.

Eosinophilic esophagitis

APT is also beginning to gain popularity in management of food elimination in patients with EoE. It has been shown that elimination diets are successful in producing histologic remission of EoE, seen in approximately 90% of those on elemental diet and 70% of those on 6-food elimination diet (SFED).²³ Clearly, a test-based, guided diet would be ideal; however, to date, there is no single best test to determine this. In the most recent consensus guidelines for EoE in fact, there is no recommendation on how to test for food allergies in EoE or how to use these tests for dietary modifications.²⁴

Most of the reports on APT in patients with EoE have come from a single center.^{25–28} The most recent retrospective report from that center analyzed 941 patients with EoE. All patients underwent SPT and APT to a panel of foods (unless already positive based on SPT). The investigators identified a cohort of 319 patients in whom causative foods had been identified based on diet and biopsy and used this population to calculate NPV and PPV of the SPT, APT, and the combination of the 2. In contrast to AD studies wherein the combination led to a high PPV, the investigators found that the SPT/APT combination in EoE had a high NPV (greater than 96% for all foods tested except milk, egg, and wheat) but a low PPV (42% or lower, with the exception of milk at 82% and egg at 61%). More importantly, they concluded that elimination diets based on SPT/APT results were equally successful (based on histology) as the SFED but accomplished this with elimination of a fewer number of foods.²⁸ One other institution reporting results of SPT/APT-driven diets in a retrospective study also suggested that a diet based on removal of foods that were positive on SPT and/or APT led to similar remission rates as compared with the SFED.²⁹ A third group has shown that the use of a combination of SPT/APT to guide elimination diet in children with EoE can lead to an improvement in symptoms, regardless of disease severity, and allowed for a reduction or discontinuation of pharmacotherapy.³⁰

The utility of APT in EoE may be limited to a pediatric population, however. In one study of SPT/APT in an adult population with EoE, none of the subjects had a positive APT to the foods in the SFED. Those with positive SPT had similar success with SPT-driven elimination diet as those in the SFED group, and the SPT-driven diet group achieved these results with elimination of a fewer number of foods.³¹

Conclusions on patch testing

The current literature clearly has conflicting evidence on the utility of APT in the diagnosis of food allergy. Furthermore, there are no standardized food reagents for APT and significant variability in APT interpretation. Therefore, there is insufficient evidence to suggest that it, especially when used alone, is a useful tool in the diagnosis of food allergy. Although it may have some limited utility in predicting delayed positive reaction to OFC in the setting of AD and/or EoE, future research remains to be done.

Food-Specific Serum Immunoglobulin G

Several studies have demonstrated that production of food-specific IgG is the body's natural response to a regularly ingested food,^{32–37} and recent studies have shown that IgG to cow's milk protein can be detected in 98% of healthy children by 2 years of age.³⁷ In addition, there are no established, standardized reference values for IgG specific for foods.³⁸ Despite these facts, large panel assays are readily available to providers. Most laboratories and clinicians that offer these tests suggest that they are not meant to diagnose immediate, anaphylactic-type food allergies, but rather that they can be used to diagnose other, chronic-food mediated disease, for example, irritable bowel syndrome (IBS), chronic fatigue, migraines, and so forth. Although studies examining the utility of food-specific IgG testing in these various conditions do exist, there are no well-designed trials using DBPCFC, and many of the studies are not controlled studies. Thus, the results must be taken cautiously.

Irritable bowel syndrome

It is clear that symptoms of IBS can be related to food, and dietary therapy for IBS is a treatment option.³⁹ In addition, many patients with IBS strongly believe that food intolerance contributes to their symptoms and report improvement with elimination diets.⁴⁰ Thus, although allergists are not typically trained to diagnose and manage IBS, many patients may seek the care of allergists for diagnosis and management if they think that "food allergies" are causing their symptoms.

Some researchers have postulated that IBS symptoms may be mediated by IgG antibodies and thus could be immune mediated. For example, in perhaps the most widely cited of these articles, Atkinson and colleagues⁴¹ enrolled 150 patients with IBS into a randomized controlled trial of elimination diet based on elevated IgG values or to a sham diet. The subjects who eliminated foods to which they had elevated IgG values had a 10% reduction in symptom score when compared with subjects who consumed a sham diet. In a similar study of patients with both IBS and migraines, IgG-based elimination diet also led to subjective improvement in both disorders.⁴² These findings, however, if accurate and reproducible, do not mean that IgG antibodies are pathogenic in IBS and offer no data to suggest a true hypersensitivity or immune response to the foods in question.

Other suspected allergic conditions

In addition to IBS, other chronic conditions have been studied in relation to food-specific IgG. Dixon⁴³ reported results of IgG-based food elimination diet in 114 patients who were suspected of having a "delayed food allergy" based on any of a wide variety of reported symptoms, such as gastrointestinal discomfort, nasal congestion, headaches, chronic fatigue, and behavioral problems. Participants underwent IgG testing to 10 to 15 foods that they consumed at least twice weekly and subsequently were instructed to eliminate foods that the author considered to have significantly elevated IgG levels. Eighty patients reported dietary compliance for a minimum of 4 months, and 71% of these patients were considered to have a successful outcome (defined as a 75% improvement in original symptoms). This study has been

cited as evidence that IgG testing may be helpful in evaluation of suspected food allergy. There are several limitations to this study that cannot be overlooked, however. First, there was no control group (sham diet or other). Thus, there was likely a very high placebo effect in these patients with subjective symptoms alone. Second, there was no reintroduction or challenge to prove symptoms returned on ingestion. Third, there were no biomarkers checked prediet or postdiet to detect any objective effect. Fourth, there was no strict protocol for these patients, and this was not a prospective study; rather it was a single author's experience and reportedly did not require institutional board review. Thus, when examining these data, it is clear that further, more rigorous studies are needed in this area if any positive conclusions can be drawn.

Immunoglobulin E-mediated allergy

To date, there are no data linking food-specific IgG to immediate-type reactions. In fact, on the contrary, allergen-specific IgG4 is commonly accepted as a marker of tolerance induced by allergen immunotherapy, and many recent studies on food allergy immunotherapy (whether by oral, epicutaneous, or sublingual route) support this concept.^{44–48}

Interestingly, one side effect of food allergy immunotherapy (at least oral immunotherapy) has been EoE.⁴⁹ Although the pathogenesis is not fully understood, there are now various studies suggesting that IgG4 to foods may actually play a role in the pathogenesis and/or the symptomatology of EoE.^{50,51} Clearly, more data are needed in this regard, but it does perhaps provide one small framework in which IgG may be a useful marker in at least one form of food allergy.

Conclusions on serum food specific immunoglobulin G

Based on available data, there clearly is no role for IgG testing for immediate-type food reactions. For delayed “food allergies” or chronic complaints that may be related to foods, there are some studies that have suggested that dietary modification based on IgG testing does lead to symptom improvement; however, one must realize that these studies are likely to be biased because of the placebo effect, and more rigorous studies are clearly needed to support its use.

Provocation and Neutralization

Provocation tests are conducted by exposing a patient to an antigen (sublingually or intradermal) and observing for 10 minutes. Any symptom (dry mouth, headache, anxiety, and so forth) reported by the patient during this observation period is interpreted as a positive test. The provocation test is sometimes followed by a neutralization procedure during which the same antigen is given in a different dose until the reaction is “neutralized.”^{52,53} Test doses are not standardized and often are not used with a negative control. Two randomized, double-blind, placebo-controlled studies showed that a similar percentage of patients reacted to the antigen as they did to placebo.^{54,55} Based on these results, it is reasonable to conclude that provocation/neutralization should not be used as a form of detection/intervention. Furthermore, the use of neutralization can potentially lead to severe adverse reaction in those patients with true IgE-mediated food allergy, with one case showing that it was associated with a near-fatal reaction in a patient who had unrecognized symptoms that were eventually diagnosed as systemic mastocytosis.⁵⁶

Pulse Testing

Sometimes used as an additional objective measure during provocation-neutralization testing, the pulse test is considered positive if the heart rate changes 16 beats per minute after a sublingual or intradermal dose of food (or also during OFC). As best the

authors can tell, the test interestingly has its roots in a book written by Dr Arthur Coca in 1956.⁵⁷ However, outside of this book, which is not a report of research (rather a description of a technique he used in various patients with various complaints), the authors can find no research articles actually examining this technique. Thus, there is no standardized technique, and there are no blinded studies examining its reliability or validity. Although this test seems to still be a popular technique in alternative/complementary medicine, there is little scientific evidence to support its use.

Electrodermal Testing

Electrodermal testing (ET) is performed by measuring skin conductance in an electrical circuit that contains an aluminum plate in contact with a sealed vial of food extract; a drop in conduction (presumably indicating disruption to the electric field) is interpreted as an allergy.⁵⁸ Perhaps the earliest scientific analysis of this method reported the ability to discriminate allergic versus nonallergic subjects up to 96% of the time using a double-blind study method.⁵⁹ However, since that study, other studies have suggested otherwise. One double-blind, placebo-controlled study on ET to diagnose respiratory allergy showed that the method not only has poor reproducibility but also that it could not reliably differentiate between allergens and negative controls.⁶⁰ Another double-blind, randomized study concluded that ET was unable to differentiate atopic and nonatopic patients.⁶¹ Although it has not been studied specifically for food allergy, the available literature shows that ET is neither valid nor accurate.

Cytotoxic Testing

Cytotoxic testing is based on the hypothesis that when exposed to a noxious substance (in this case, a suspected allergen), leukocyte morphology changes. Initially, microscopy was used to detect these morphologic changes. One study in 1976, using a control population as well as a food-allergic group, concluded that there was no correlation between test results and clinical picture; furthermore, there was a high rate of false positives and inconsistency in interpreting results (even among tests read multiple times by the same investigator).⁶² Another controlled double-blinded study also found no correlation between test results and clinical symptoms.⁶³ More recently, studies were done using flow cytometry to assess morphologic changes in cells after exposure to food antigen and have also found this method to be inconclusive and controversial.^{64,65}

Despite the above, the antigen leukocyte antibody test (ALCAT), a commercial blood test that uses flow cytometry and cell impedance technology, remains easily obtainable by patients and claims to diagnose food sensitivity, with some panels testing more than 200 foods.⁶⁶ Based on an individual's sensitivity results, a diet is designed. The company acknowledges that their product does not test for IgE-mediated food allergy, but does not release information regarding the methodology or reliability/validity of their test. Furthermore, the literature provided by the company to support its use, including reports using double-blind studies, could not be accessed in PubMed or have only been presented in abstract form and have not been published as a peer-reviewed journal article.

Applied Kinesiology Testing

Applied kinesiology (AK) testing is performed by having a patient hold a vial containing an allergen in question while the muscle strength in the opposite arm is measured (by the test performer applying a light pressure to that arm); a positive test is indicated by a decrease in strength of the tested arm.⁶⁷ Several studies regarding the utility of this form of testing have been published by the International College of Applied

Kinesiology; however, a review of the literature published in this field during the 1980s showed that the vast majority of these studies were based on poor research designs and/or poor reporting techniques.⁶⁸ One recent blinded study done to assess the test-retest reliability and validity of kinesiology testing in the diagnosis of venom allergy concluded that “kinesiology as a diagnostic tool is not more useful than random guessing.”⁶⁹ Similarly, another double-blind randomized study to assess the validity of AK testing also concluded that it was an unreliable tool.⁷⁰ Little research has been done on the usefulness of AK testing in the diagnosis of food allergy.

FUTURE CONSIDERATIONS/SUMMARY

The most current expert consensus panels agree that although the DBPCFC remains the gold standard for food allergy diagnosis, sIgE and SPT are acceptable alternatives.^{3,4} Although largely considered unreliable, the other previously discussed unproven methods of food allergy testing are still available and are often appealing to patients. Although APT, and possibly food-specific IgG testing, may be of some benefit when used in conjunction with other proven methods in certain patient populations, more research needs to be done in this area. Experts agree that APT may have limited utility in guiding dietary management of pediatric EoE, but it is still not recommended for routine use in food allergy diagnosis.⁴ The other techniques discussed have largely been discredited or are unproven and are not recommended.

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