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Testing for Food Reactions: The Good, the Bad, and the Ugly

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An increasing number of commercial tests for food allergies are marketed to consumers and healthcare practitioners with tenuous claims. The aim of this article is to provide an evidence-based review of the tests and procedures that currently are used for patients with suspected food allergy. A systematic review of the literature evaluating the validity of tests and procedures used in food reactions was performed using conventional search engines (eg, PubMed, Ovid) as well as consumer sites (eg, Google, Bing). The National Library of Medicine Medical Subject Headings (MeSH) term *food hypersensitivity* was used along with *food allergy testing*, *food sensitivity testing*, *food intolerance testing*, and *adverse food reactions*. Of the results obtained, testing for immunoglobulin E (IgE)–mediated food allergy was best represented in PubMed. IgE-based testing continues to be the gold standard for suspected food allergies. Among modalities used by many conventional and alternative practitioners, immunoglobulin G (IgG)–based testing showed promise, with clinically meaningful results. It has been proven useful as a guide for elimination diets, with clinical impact for a variety of diseases. Mediator release testing and antigen leukocyte cellular antibody testing were only represented on consumer sites. Further investigation into the validity and the clinical application of these tests and procedures is required. Disclosing the basis for food reactions continues to present a diagnostic challenge, and testing for food allergies in the context of an appropriate clinical history is paramount to making the correct diagnosis. (*Nutr Clin Pract*. 2010;25:192-198)

Keywords: food sensitivity; food hypersensitivity; allergy and immunology; immunoglobulin E; immunoglobulin G; skin tests

More than 50 million Americans suffer from allergies yearly. Allergy, ranking as the sixth leading cause of chronic disease in the United States, was responsible for a staggering $18 billion U.S. healthcare expenditures in 2001.[1] Of those with allergies, up to 25% of adults report symptoms that may be related to foods. However, testing for food reactions can be challenging for both the patient and the clinician. Many healthcare practitioners have not received formal training in allergy and immunology and, as a result, may not be familiar with the proper application and interpretation of available test results.

In the context of the clinical history, both serum antibodies and allergy skin testing can be of considerable assistance in identifying (or excluding) the particular allergens that may be causing the patient's symptoms. Numerous tests are available on the market and are being used by conventional and alternative practitioners to assess for food reactions. There are 2 main categories of tests available: allergy skin tests (skin prick testing) and measurements of allergen-specific antibodies from blood. We review the various tests along with the published evidence for food reactions for the clinician.

Food Allergies

A food allergy is typically defined as an adverse immune response to the proteins in a food. This may occur as the result of a humoral response (immunoglobulin E [IgE] antibody), a cellular response (ie, T cells), or both. IgE-mediated food allergies affect between 1% and 2% of individuals in the U.S. and United Kingdom; specifically, these allergies are seen in 1% of adults and 6%–8% of children.[2] The prevalence of food allergies in American children seems to be on the rise, now affecting 3 million children, according to the Centers for Disease Control and Prevention.[2] Certain foods are more common allergens among specific age groups. Accounting for the majority of immediate food allergies in young children

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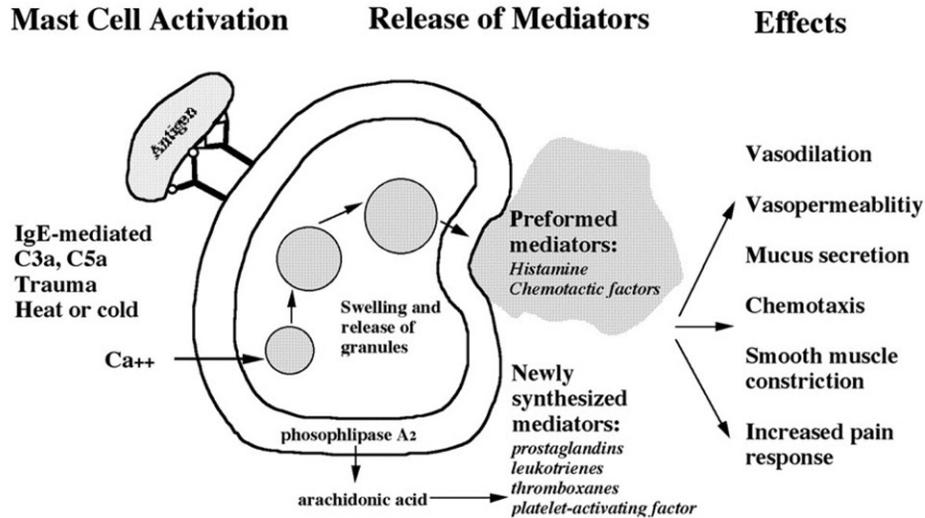
Mast Cell Activation   Release of Mediators   Effects

Figure 1.   Type I hypersensitivity. Immediate hypersensitivity is mediated by immunoglobulin E (IgE). The primary cellular component in this hypersensitivity is the mast cell (as shown in this figure) or basophil. The mechanism of reaction involves preferential production of IgE, in response to certain antigens (allergens). IgE has very high affinity for its receptor on mast cells. A subsequent exposure to the same allergen cross-links the cell-bound IgE and triggers the release of various pharmacologically active substances. Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased calcium influx, which is a crucial process; ionophores, which increase cytoplasmic calcium, also promote degranulation, whereas agents that deplete cytoplasmic calcium suppress degranulation. Both preformed mediators (histamine, chemotactic factors) and newly synthesized mediators (prostaglandins, leukotrienes, thromboxanes, and platelet-activating factor) are relapsed in response to antigen cross-linking on mast cells. The end results are vasodilation (redness), vasopermeability (edema), mucus secretion, chemotaxis, smooth muscle constriction (bronchoconstriction), and increased pain response.

are cow's milk, hen's eggs, peanuts, tree nuts, and sesame seeds, with kiwi allergy becoming more prevalent in this group.[3] Among adults, shellfish, fish, peanuts, and tree nuts are the most common causes of food allergies.[4]

Type I Hypersensitivity and IgE Testing

Type I hypersensitivity reactions are potentially life-threatening because they are immediate, systemic, and intense. Mast cells release vasoactive mediators systemically once the triggering antigen cross-links its surface IgE antibody (Figure 1, Table 1).

In addition to the more common presentations of anaphylaxis and urticaria, Type I reactions occurring after food ingestion may include rhinorrhea, asthma, diarrhea, and vomiting. These adverse reactions are often associated with a positive skin prick test and with measurable serum IgE antibodies to the relative food.[5]

Skin Prick Testing

The principle behind the skin prick testing method is that sensitized tissue mast cells display IgE antibodies on their cell membranes. When specific antigens or nonspecific

Table 1.   Most Common Immunoglobulin E–Mediated Food Allergens[3]

Chicken	Peanuts and tree nuts
Corn	Soy
Dairy	Wheat
Egg	

antigens such as lectins cross-link with the Fc receptor for IgE, the mast cell releases histamine and other inflammatory mediators. This reaction results in a wheal and flare of the skin marked by redness and swelling. Skin testing is minimally invasive and when performed correctly has good reproducibility. It is also preferred because the test results are available within minutes of the test application while the patient is under direct observation by the clinician. Skin testing is easily quantifiable and can allow the evaluation of multiple allergens in 1 session. Skin prick testing does carry the risk of inducing anaphylaxis and false positives and can be influenced by medications commonly used by allergy patients, such as antihistamines.

For IgE-mediated disorders, skin prick tests provide a rapid method of detecting sensitization. A positive skin prick test result may be considered confirmatory in the setting of a clear and recent history of a food-induced

Table 2. Pitfalls in Food Challenge Testing

Time	The process is time-consuming, for both patient and clinician.
Risk	The process carries the risk of producing a severe reaction.
Reproducibility	Reproducibility can be affected by multiple variables in the process of presentation, ingestion, and absorption of food.
Specificity	Coincidental factors are highly likely to affect outcomes.
Sensitivity	False negatives are possible.
Discrimination	False positives commonly occur due to the range of implicated substances and possible clinical responses; a standardized form of testing is difficult to construct.

allergic reaction to the tested food. In contrast, a negative test result makes an IgE-mediated allergy to a suspected allergen less likely. However, a negative skin prick test does not exclude a food reaction, and if symptoms warrant further investigation, the clinician should continue to pursue identification of culprit antigens by testing as outlined below.

Food Challenge Testing

The double-blind, placebo-controlled food challenge is performed when an incremental dose of food allergen vs placebo is given at 20-minute intervals while the patient is observed for objective signs of food allergy. Patients who tolerate the final dose of this challenge then undergo an open (unblinded) challenge in which a regular-sized portion of the food is eaten in order to establish tolerance.[6] Until recently, double-blind, placebo-controlled food challenge testing had been the gold standard for IgE-mediated food allergies. However, there have been many pitfalls to this testing, such as the risk of severe reactions and the difficulty of designing standardized testing procedures (Table 2).

ELISA IgE food allergies (sensitivity) testing. ELISA (enzyme-linked immunosorbent assay) is a quantitative/semiquantitative in vitro analysis designed to detect and quantify IgE antibodies reactive to various food proteins. ELISA has been reported to be more sensitive than skin prick testing in the identification of IgE-mediated food allergies.[7] Quantification of food-specific IgE is a valuable tool that will aid in the diagnosis of symptomatic food allergy and might decrease the need for double-blind, placebo-controlled food challenges.

Commercial laboratory allergy tests for s-IgE. The first test evaluating IgE used radioisotopically labeled anti-IgE and

was subsequently called the radioallergosorbent test (RAST). RAST was essentially a qualitative test, but with minor exceptions, is now obsolete. However, the term *RAST* subsequently became an all-inclusive term applied to all varieties of these tests. To date, there are mainly 3 methods used: Turbo RAST (Agilent Technologies Santa Clara, CA), Immulite (Siemens Medical Solutions Diagnostics, Tarrytown, NY), and ImmunoCAP (Phadia, Uppsala, Sweden). ImmunoCAP is the assay that has been most extensively studied.

Unfortunately, recent publications have confirmed that the results of one method are not generally comparable with those of another.[8,9] Thus, clinicians ordering these tests should be aware of the assay their laboratory is using. The difference in the performance patterns of the various laboratory tests was demonstrated in a study that compared the 3 most commonly used systems in the United States: Turbo RAST, Immulite, and ImmunoCAP.[10] The study found poor concordance of the qualitative testing among the 3 different assay systems, with the Turbo RAST being the most variable. Significant discrepancies were also found with the quantitative evaluations. Overall, Immulite was reported to overestimate whereas Turbo RAST underestimated s-IgE when compared with ImmunoCAP.[10] Thus, clinicians cannot compare test results among these 3 different methods in assessing changes in patients' IgE reactivity to a given food.

Summary of laboratory testing for IgE-mediated food allergy. Advantages of testing for food-specific IgE antibodies using serum intrinsically include availability in a primary care office setting, and good sensitivity (approximately 70%–90%) and specificity (approximately 50%–80%). Skin prick tests with commercial extracts or, in some cases, fresh extracts of the suspected food are primarily available to the allergist (Table 3). In some cases, the skin test may be more sensitive than the serum tests,[10-12] and additional advantages include lower cost and immediate results. However, the in vitro assays can be used in some situations where skin tests are not appropriate, such as in patients who have an extensive rash or who are using antihistamines.

Food allergy test results (blood or skin) should always be interpreted in the context of the patient's clinical presentation, age, relevant allergen exposures (cross-reactivity between aerosolized and food allergens), and the performance characteristics (ie, sensitivity, specificity, reproducibility) of the allergy tests themselves. Conventional allergy tests yield information on sensitization that is not always equivalent to clinical allergy (ie, sensitivity). Therefore, interpretation in the context of clinical history is important. Additionally, the clinical history should guide what food allergens are selected for testing. The practical value of allergy skin or blood tests rests in their ability to give accurate and consistent results when used as a confirmatory tool. Different allergy laboratory

Table 3. Diagnosis of Food Allergies With the Specific IgE and Skin-Prick Tests[3]

Food	95% PPV of Specific IgE, kU/L	95% PPV of Skin Wheal, mm
Egg	6	7
Milk	32	8
Peanuts	15	8
Tree nuts	15	8
Fish	20	7

IgE, immunoglobulin E; PPV, positive predictive value.
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Table 4. Symptom Characteristics of Immunoglobulin (Ig)E vs IgG (Mixed Immunological)

	IgE	IgG
Onset	Rapid (minutes)	Delayed (hours)
Duration	Brief (hours)	Prolonged (days)
Mechanism	Mast cell	Circulating complexes (macrophage overload)
Quantity of food	Tiny	Dose dependent
Food	Any (rare)	Common foods
Patient awareness	Always	Variable
Persistence	Lifelong in some, disappears in others	Months after eliminations

methods may not yield comparable results (ie, the level of specific IgE antibodies to milk from the ImmunoCAP is not comparable with the level measured by the Immulite system), even if they are reported in the same units or classes. Treatment decisions for allergic patients should be based on the appropriate diagnosis and the identification of causative food allergens.

Delayed Food Hypersensitivities, Immune Complexes, and IgG Testing

Repeated exposure to an antigen can eventually produce allergic-like responses or hypersensitivities. These reactions are usually delayed, with symptoms not being evident for hours—or even days—after the initial exposure. IgG antibodies drive these "delayed" reactions (Table 4).

Delayed food hypersensitivities, also known as food sensitivities, trigger an immune response by producing IgG antibodies. Unlike IgE reactions, IgG antibodies do not directly trigger degranulation of mast cells. IgG antibodies are elaborated approximately 1 month following antigen recognition. Thus, the presence of specific IgG antibodies generally corresponds to a "maturation" of the antibody response. The IgG immunoglobulin class has an exceptionally long half-life in circulation (serum half-lives of IgG ranging from 22 to 96 days) and constitutes about 75% of the total serum immunoglobulin pool. IgG also plays an important role in antibody dependent cell-mediated cytotoxicity (ADCC) and is also associated with type II hypersensitivity (cytotoxic hypersensitivity involved in antibody-mediated reactions such as Goodpasture's syndrome) and type III hypersensitivity (immune complex hypersensitivity with serum sickness being an example of this).[13,14]

The symptoms associated with delayed food allergy are a consequence of the absorption of food antigens; this results in the production of IgG antibodies systemically and causes diverse symptoms (Table 5). IgG antibodies are classified into 4 subcategories: IgG_1, IgG_2,

Table 5. Delayed Food Allergy Symptoms[25-27]

Target Organ	Symptom
Systemic	Fever
	Fatigue
	Sweating
	Chills
	Weakness
	Reduced exertional tolerance
Digestive tract	Abdominal pain
	Bloating
	Nausea
	Vomiting
	Diarrhea
Lungs	Food-induced bronchitis and asthma
Joints, muscles, connective tissue	Food-allergic arthritis
	Pain
	Stiffness
	Swelling
Skin	Itching
	Rashes
	Hives
	Thickening
	Redness
	Swelling
	Scaling (as in eczema or psoriasis)
Brain	Disorganized or disturbed thinking and feeling
	Memory disturbances
	Behavioral problems

IgG_3, and IgG_4. IgG_1 and IgG_4 subtypes are associated with immune responses to foods. The IgG antibodies may do more than just trigger a cascade of mediators producing the "allergic" response to food. Rather, the

Table 6. Results of Studies of Immunoglobulin G (IgG) Antibody-Elimination Diets for Irritable Bowel Syndrome (IBS)

Author	No. of Subjects	Trial	Results
Atkinson et al[19]	150 IBS	True diet vs sham 3 mo	True diet resulted in a 10% greater reduction in symptom score than the sham diet ($P = .024$), with this value increasing to 26% in fully compliant patients ($P < .001$).
Zar et al[17]	52 IBS-D, 32 IBS-C, 24 IBS alternating, 43 controls	IgG_4 and IgE antibodies	IBS had significantly higher IgG_4 titers to wheat ($P < .001$), beef ($P < .001$), pork ($P < .001$), and lamb ($P = .009$) compared with controls. These differences were maintained across all 3 subgroups. Testing for IgE food antibodies was not helpful for IBS, except in a small subgroup of patients with diarrhea predominant-disease and atopy.
Drisko et al[18]	15 IBS, refractory to medical therapy	Elimination-rotational diet, 6 mo	Baseline abnormalities were identified on serum IgG food and mold panels in 100% of the study subjects ($P < .005$); significant improvements in stool frequency, pain, IBS-QOL.
Yang et al[22]	55 IBS-D, 32 IBS-C, 18 controls	8-wk elimination diet	The positive rate of serum food-specific IgG antibodies was 63.5% in patients with IBS-D and 43.8% in IBS-C; improved IBS symptom relief.
Zuo et al[23]	37 IBS, 20 controls	IgG_4 antibodies	IBS patients had significantly higher titers of IgG antibody to crab ($P = .000$), egg ($P = .000$), shrimp ($P = .000$), soybean ($P = .017$), and wheat ($P = .004$) than controls. Serum IgG antibody titers to some common foods were increased in IBS patients compared with controls.

IBS-C; constipation-predominant IBS; IBS-D; diarrhea-predominant IBS; IgE, immunoglobulin-E; QOL, quality of life.

IgG antibodies themselves may be pathogenic. For example, IgG antibodies have been shown experimentally to increase the permeability of the wall of the small intestine.[15] This, in turn, might lead to food allergy. Moreover, developmental immaturity of components of the gut barrier leading to hyperpermeability might account for the increased prevalence of food allergy in infancy.[16] Diminished intestinal barrier function is believed to portend enhanced food antigen circulation systemically and sensitize immunocytes.

Testing for IgG4. There is no standardized methodology for IgG testing. Different laboratory methods may not yield comparable results, even if they are reported in the same units or classes. A number of tests may be useful in identifying foods to which a patient is reactive, but no one test is likely to identify all reactive foods.[17]

Using IgG_1 or IgG_4 laboratory results. Laboratories use ELISA testing to quantify reactions for specific foods. IgG laboratory test results must be taken in clinical context. If more than 3 items in any food family are positive, it is recommended that all foods in that family be eliminated for 4–6 months.[18]

IgG is a protective response by the body to a foreign antigen. Because there are false positives (and possibly false negatives), there will often be foods that test high but do not provoke any clinical symptoms. On the other hand,
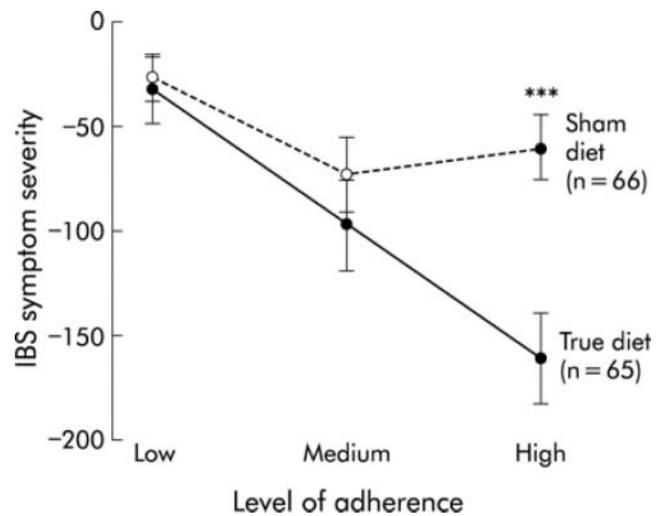

Figure 2. Reduction in the irritable bowel syndrome (IBS) symptom severity index improves with higher levels of adherence. Mean change in symptom severity scores at 12 weeks according to degree of adherence. Difference between the groups with high adherence: 101 (95% confidence interval, 54–147); ***P < .001. Reproduced from Atkinson W et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial. ***Gut***. 2004;53:1459-1464 with permission from BMJ Publishing Group Ltd.

a patient who has not eaten gluten-containing grains for months may display negative results to gluten-containing grains because this reaction is not being provoked.

Table 7.   Laboratory Comparison Chart: Delayed Sensitivity Reactions

Type of Testing	Memory Antibodies	Lymphocyte Cell Culture	Automated Cytotoxic Assay	Complement Activation
Labs	Alletess Medical Laboratories, Rockland, MA Genova Diagnostics, Asheville, NC Great Plains Laboratories, Lexana, KS Immuno Laboratories, Fort Lauderdale, FL Metametrix Clinical Laboratory, Duluth, GA Meridian Valley Laboratories, Renton, WA US Biotek Laboratories, Seattle, WA	ELISA/ACT LRA (Lymphocyte Response Assay), Sterling, VA	ALCAT (Antigen Leukocyte Cellular Antibody Test) Cell Science Systems, Deerfield Beach, FL NuTron/NOVO Immogenics, London, UK MRT/LEAP Testing (Mediator Release Testing/Lifestyle Eating and Performance), Riviera Beach, FL	Sage Medical Lab, (complement testing), Ormond Beach, FL
Specific IgG or IgG4 (memory)	√	√		√
Specific IgE (allergy)	√			
Specific IgA (mucosal)		√		
Specific IgM (current)		√		
Type III immune complex		√		√
Type IV cell activation		√		

There is little standardization of non–IgE-mediated laboratory testing for food sensitivities. The laboratories listed above use a variety of methodologies to test for delayed food hypersensitivity reactions. This table gives specifics on what each laboratory is measuring, which varies from specific antibodies (IgA, IgE, IgG, IgG4, IgM), type III immune complexes, and type IV cell activation.

Often there will be entire food families, such as dairy products or legumes, that all test positive. When test results indicate IgG sensitivities to a large number of foods, many alternative practitioners have anecdotally observed an associated increased intestinal permeability rather than frank food intolerances.

IgG food sensitivity testing in irritable bowel syndrome (IBS). Patients with IBS often report some form of dietary intolerance and self-experiment with elimination diets. Studies that support the use of IgG antibody testing and elimination diets for IBS are illustrated in Figure 2 and Table 6, and are summarized briefly.

Atkinson et al[19] were the first to study IgG antibodies in conjunction with elimination diets for IBS. From their findings, Atkinson and colleagues concluded that food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research. Zar et al[17] used the same hypothesis as the previous study by Atkinson's team with data from dietary elimination and food challenge studies. Serum IgG$_4$, but not IgE, antibodies were found to be raised in IBS in response to common foods like wheat, beef, pork, and lamb. Drisko et al[21] conducted an open-label pilot study of 15 patients with IBS by Rome II criteria who had failed standard medical therapy in a tertiary medical clinic. Drisko and colleagues concluded that identifying and addressing food sensitivity in IBS patients who had not responded to medical therapy can result in a sustained clinical response affecting well-being and quality of life. Other investigators (Yang and Li,[22] Zuo et al[23]) corroborated the above studies by demonstrating that serum IgG antibody titers to some common foods are increased in IBS patients compared with controls.

Other laboratory tests on the horizon. A number of popular tests used in the diagnosis of food allergies are available to clinicians, including antigen leukocyte cellular antibody test (ALCAT), applied kinesiology, electroacupuncture tests (the Vega test), and mediator release test (MRT) (Table 7). Proponents of each method claim that it is helpful in the diagnosis of food allergies and treatment of a number of conditions including IBS, migraine headaches, skin rashes, chronic fatigue syndrome, and

other complex disorders.[24] In addition, the tests are often marketed to clinicians and patients to eliminate the tedious efforts that are required by the conventional prescription of an oligoantigenic elimination diet. Although some practitioners have found them helpful, no well-designed controlled trials have validated the use of these tests.

Summary

Testing for true food allergy (IgE mediated) can be performed by using either skin testing or by measuring serum IgE to specific foods. Overall, these tests determine whether sensitivity exists to a given food of interest. The clinical history and physical exam are of utmost importance in determining whether an IgE-mediated food sensitivity is producing an allergic response (food allergy). IgG antibody testing for delayed food sensitivity remains controversial. However, data suggest that eliminating foods identified using IgG antibody food testing in IBS can result in significant symptom improvement. Other emerging in vitro tests (ALCAT, MRT) use applications of food products in vitro to simulate what occurs physiologically in vivo. However, well-designed clinical trials should be published before patients are subjected to expensive testing for delayed hypersensitivities (eg, ALCAT and MRT testing) that offer little evidence of effectiveness.

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