Testing for Food Allergens

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Author
Elizabeth P. Weinzierl, MD, PhD, FCAP, Department of Pathology, Children's Healthcare of Atlanta, Atlanta, GA

Editors
Richard Brown, MD, FCAP,* Abdulrahman Saadalla, MBBCh, FCAP, Barbara Blond, MBA, Thomas Long, MPH
Diana Desai, MD, FCAP
*Senior Editor, Department of Pathology, Memorial Hermann Health System, Houston, TX.

SYNOPSIS AND RELEVANCE

Food allergies are increasing in prevalence, and laboratory based food allergen testing can be a helpful tool in such clinical diagnoses. This module will:

1. Discuss appropriate test ordering, based on clinical history, of specific IgE based food allergen testing
2. Describe potential interventions to reduce the overuse of serum specific IgE (sIgE) based food allergen testing

OBJECTIVES

1. Understand the clinical utility and sensitivity and specificity of specific IgE-based serum tests.
2. Encourage limitation of IgE-based food allergen testing to targeted testing based on clinical history
3. Discourage use of unproven lab-based testing such as IgG-based testing in the evaluation of food allergens

BACKGROUND

Food allergies are a subset of adverse food reactions that are increasingly common, potentially fatal, and have a major impact on the lives of patients and their families.[1,2,3] More than 170 foods have been associated with food allergies, although the most common of these are milk, egg, peanut, tree nuts, crustacean shellfish, fish, wheat, soybeans, and sesame.[3,4,5,6] These allergic reactions are caused by the release of inflammatory mediators from degranulating mast cells and basophils. For degranulation to occur, cells have to be initially sensitized by the binding of allergen specific IgE (sIgE) to the high affinity receptors (FcεRI) on cell surfaces. Following re-exposure to allergens, allergens bind to sIgE and hence crosslink the FcεRI to induce degranulation. Symptoms are rapid in onset, typically occurring within minutes to a few hours of ingestion. Although some reactions can be mild and manifest themselves in a single system, such as urticaria in the case of cutaneous manifestations, reactions can also be severe and involve multiple systems, and in the case of anaphylaxis, can lead to life-threatening hypotension, cardiovascular collapse, and death.[5,7] Guided by patient's clinical history, testing for food allergy initially starts with skin prick testing (SPT) and the detection of allergen specific-IgE in serum.[8] If SPT and allergen sIgE results are inconclusive, oral food challenges (OFC), which is the gold standard for the diagnosis of food allergy, can be performed to determine if patients are sensitized-tolerant or sensitized allergic to suspected allergens. As OFC can be associated with severe and potentially fatal reactions, there is increased utilization and reliance on basophil activation tests (BAT) as third-line tests.[3,8,9,10]

Skin prick testing is performed in a provider's office and involves pricking or scratching the skin with a very small amount of allergen extracts or components. Histamine and saline are typically used as positive and negative controls, respectively. The test is considered positive if a wheal is formed, although the size of the wheal does not necessarily correlate with severity of the allergy.[11] The advantage of SPT is that the results are generally immediate (within 15-30 minutes), and are potentially more sensitive, albeit less specific, than serum sIgE tests.[1,5,11] However, the patient has to be free of antihistamines or other allergy medications in the days leading up to the test, which can be problematic in patients with severe allergies, and there is also a small risk of systemic allergic reaction. Allergen sIgE testing, on the other hand, requires a blood draw but does not require the patient to discontinue anti-allergic medications.[11] Compared with SPT, results are not immediate, as they need to be processed and tested in a clinical lab. A generalized approach to food allergy evaluation is shown in **Figure 1**.

Figure 1. Generalized approach to food allergy evaluation

Testing for serum allergen sIgE is performed using immunoassays of various methodologies. Examples include enzyme-linked immunosorbent essays (ELISAs), fluorescent enzyme immunoassays (FEIA), chemiluminescent assays, and immunoblots. Commercial FEIA platforms are widely used by clinical laboratories.[5] In these assays, allergens are bound to activated cellulose foam allergosorbent material. If allergen sIgE is present in patient serum, it will bind to the allergen antigens. After washing steps, enzyme-conjugated anti-human IgE secondary antibodies are added and incubated. A substrate (development solution) is then added resulting in the generation of fluorescence proportional to the quantity of bound allergen sIgE. Measured fluorescence signals are interpolated to a calibration curve to obtain sIgE concentration (**Figure 2**).

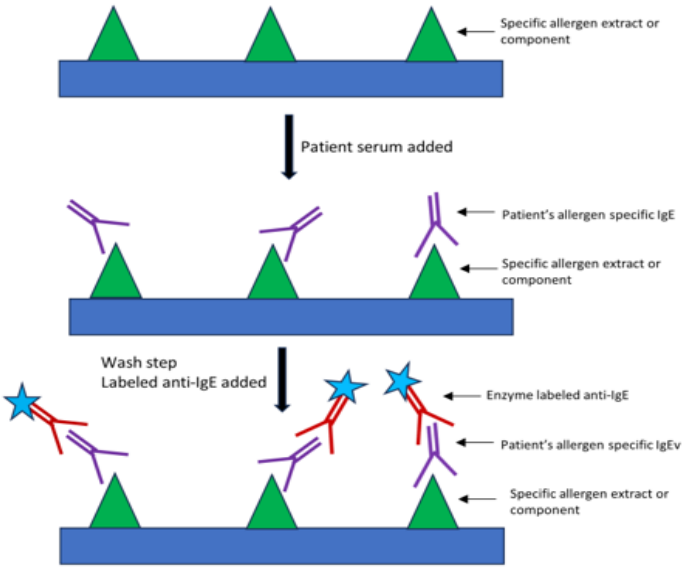

Figure 2. Traditional solid phase specific allergen assay for detecting serum sIgE

Serum sIgE based food allergen testing has high sensitivity and negative predictive value but somewhat low specificity.[8,13,14] It is important to understand that several factors translate the presence of sIgE to allergic responses, including properties of the IgE antibodies (avidity, affinity, ratio specific to total IgE), interindividual variability in cell surface expression of the high-affinity FcεRI receptors and downstream intracellular signaling pathways.[15] A positive sIgE result (ie, sensitization) therefore does not necessarily indicate that the patient has a clinical food allergy. The level of positivity also does not correlate with severity of reactions. This emphasizes that serum sIgE based testing should be only performed in patients with clinical history suggestive of IgE-mediated food allergy.

Food allergen screening panels are a feature of many laboratory test menus. Panels can be designed for screening to include common food allergens, or by groups and categories of allergens (eg, tree nuts, meats, and fish). A major disadvantage of such panels is that they can lead to over testing, misinterpretation of results and unnecessary dietary restrictions, especially in patients with intolerance symptoms due to non-IgE mediated reactions.[2,16] As previously stated, testing for sIgE should be guided by clinical history. Panels however can be appropriate in some situations; for instance, in the case of a confirmed shrimp allergy, a larger panel including other shellfish may be helpful due to cross-reactivity.[1]

Component-resolved diagnostics (CRD) refers to the utilization of purified native or recombinant major allergenic proteins to detect serum specific-IgE against the individual allergenic molecules.[17] Components are more standardized than whole allergen extracts used for serology and SPT. Since components are present in higher concentrations in assay allergosorbent materials than in whole allergen extracts, they significantly improve the analytical sensitivity and specificity for sIgE detection **(Figure 3).**[18] Testing for individual components can also allow working up cross reactions between different foods and can be helpful in risk stratification of patients (eg, eligibility for OFC and immunotherapy; **Figure 3**). As an example, detection of high sIgE concentrations to the storage protein Ara h2 provides high diagnostic accuracy in patients with suspected peanut allergy. An expanding menu of components are now available for clinical validation and testing.[10,14,18] CRD can be offered as standalone assays or in panels in combination or reflexive to detectable sIgE to whole allergen extracts.

Figure 3. Component resolved diagnostics in allergy diagnosis

Alpha-Gal syndrome (AGS) is allergy to red meat that nowadays is increasingly diagnosed by clinicians. This is partially driven by the availability of component testing for sIgE to the culprit allergen, alpha-Gal (galactose-alpha-1,3-galactose) glycans. Alpha-Gal is present in mammalian red meat (eg, pork, beef and lamb) and derived products, including gelatins in food and vaccines. It is now established that Lone star ticks (*Amblyomma americanum*) play the central role in AGS pathogenesis. Patients can develop AGS symptoms 1-3 months after exposure to tick bites. It is understood that tick saliva contains alpha-Gal, which in addition to the local and systemic inflammation effects induced by tick bites, can promote sIgE response to alpha-Gal. sIgE to alpha-gal then sensitizes effector cells

(basophils and mast cells) and on re-exposure to alpha-gal present in consumed red meat, can lead to severe allergy symptoms. Interestingly, detection rates and positivity for serum alpha-Gal sIgE is higher in the Midwest and Southeastern regions of the country, matching the known geographic distribution of Lone star ticks. In a key publication that established our understanding of AGS, unusual clusters of hypersensitivity cases to Cetuximab (anti-EGFR monoclonal therapeutic) reported in Southeast US states were attributed to the presence of alpha-Gal-specific IgE in treated patients and the presence of alpha-Gal moieties on the Fab portion of the antibody molecules.[19] One difference to note between AGS and typical food allergies is the delayed onset of symptoms (2-6 hours) after ingestion of red meat. This has been explained by the time needed for the digestion of glycolipids rich in alpha-Gal moeiteis.[10,14]

There is no scientifically proven role for IgG-based testing in the diagnosis of food allergies.[12] The American (AAAAI), Canadian (CSACI), and European (EAACI) allergy and immunology societies have put out statements or communications against specific IgG testing for the diagnosis of food allergies.[20,21,22]

INSIGHTS

1. Serum sIgE testing for food allergies is extensively available but should be limited to targeted testing based on clinical history.
2. IgG-based food allergen testing is of no known value to the diagnosis of food allergies.
3. Component-resolved testing to specific food proteins can be useful in some situations.

INTERVENTIONS

Food allergen laboratory testing should be used in conjunction with clinical history in the diagnosis of food allergies, although such tests suffer from relatively poor positive predictive value. To optimize use of food allergen testing, the following approaches are recommended.

1. IgG-based food allergen testing is of unproven use and should be eliminated from test menus intended for allergy diagnoses.
2. Although serum sIgE food screening panels may be appropriate in some situations, these should be used in a limited fashion. An EMR alert or pop-up could be considered in such cases, with a recommendation for targeted testing based on clinical history.
3. Serum sIgE-based whole food allergen tests should be offered individually in the test menus.
4. Component-resolved testing can be helpful in the diagnosis of some food allergens, such as peanuts, and can be utilized as an initial diagnostic test or as a reflex from a positive whole food allergen sIgE test.

INTERVENTION ANALYSIS

Collect data on current allergen panel ordering before and after a soft stop is added for recommended targeted testing. If access to this data is limited, this information may be manually collected over a period of time determined by how frequently these tests are ordered. It is easiest to use the same time period for before and after the intervention to do the assessment, for example, 3 months for pre-intervention and 3 months post-intervention. A factor must be applied if different time periods are used.

APPENDIX A: CALCULATING THE INTERVENTION IMPACT

Collect data, preferably using the same measurement period of time before and after implementing interventions (eg, 3 months). Correct the volume accordingly if different time periods are used for pre-intervention and post-intervention studies.

Pre-Intervention

Prior to taking any interventions steps: Determine the number of food allergen panels ordered. It is acceptable to choose specific food allergen panels, or all offered food allergen panels. (A1)

Post-Intervention

After the interventions steps are taken:

1. Determine the number of food allergen panels ordered. Collect data on the same panels as analyzed in the pre-intervention column. (B1)
2. Calculate the percent change in the pre-intervention and post-intervention test volumes to find the impact of the change(s) instituted by your laboratory. (C1)

Description	Pre-Intervention	Post-Intervention	Pre - Post Volume Change %
Determine the number of food allergy panels ordered (or specific food allergen panels)	A1	B1	B1 – A1/B1 X100%= C1

QUESTION AND ANSWERS

QUESTION 1 OBJECTIVE

Understand the clinical utility and sensitivity and specificity of specific IgE-based serum tests.

QUESTION 1

Positive results stemming from a specific IgE-based serum food test indicate the following:

A. The patient has an allergy to that food
B. The patient is sensitized to that food
C. The patient should stop eating that food and retest in 6 months
D. The results should be confirmed by a skin prick test

The correct answer is B. The patient's immune system is sensitized to that allergen, resulting in a positive IgE test.
A is incorrect. Although the patient may have a clinical allergy to that food, an allergy should not be diagnosed by a positive serum sIgE alone, but must incorporate clinical history.
C is incorrect. There is no evidence that removal of a food from a patient's diet will result in a clinically meaningful change in his/her serum sIgE test
D is incorrect. Although skin prick testing can be useful in some situations, it also suffers from low positive predictive value and must be interpreted in the setting of clinical history.

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QUESTION 2 OBJECTIVE

Encourage limitation of IgE-based food allergen testing to targeted testing based on clinical history

QUESTION 2

A young child develops hives and vomiting shortly after drinking a glass of cow's milk. The child avoids cow's milk and is seen in several weeks by his/her pediatrician. The pediatrician appropriately orders the following test to confirm that the child has a food allergy to cow's milk:

A. A general serum sIgE food screening panel, which includes cow's milk
B. Serum sIgG cow's milk test
C. Serum sIgE cow's milk test
D. Cow's milk IgE-based component test

The correct answer is C. The patient has evidence of an anaphylactic reaction, and cow's milk is a relatively common food allergy in infants and young children. The most specific test should be ordered.

A is incorrect. Although such a panel could have successfully confirmed the patient's milk allergy, there is no need, in this clear clinical setting, of testing for other allergens concomitantly.

B is incorrect. There is no value of IgG-based testing in the setting of the diagnosis of food allergy.
D. is incorrect. Component testing can be used in some cases as a supplement to whole food allergen testing. However, the whole food should be initially tested first, although component testing can be appropriate as a reflex algorithm to a positive test.

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QUESTION 3 OBJECTIVE

Discourage use of unproven lab-based testing such as IgG-based testing in the evaluation of food allergens.

QUESTION 3

A 3-year-old girl has diarrhea after eating an almond-based dessert. An IgG test for almonds comes back positive. The most appropriate next step or interpretation is as follows:

A. The patient has a food allergy to almond
B. A full IgE panel for nuts should be performed.
C. If there is concern for an almond allergy, an IgE test for almond should be performed.
D. The patient should avoid all almonds in the future.

C is correct. Food-specific immunoglobulin G (IgG) testing is not a recognized diagnostic tool for food allergy, and an IgE test for almond should be performed if there is concern for food allergy to almond.
A is incorrect. A positive IgG test in this setting only indicates immunologic sensitization by the food allergen in question, but not a food allergy
B is incorrect. There is no indication to perform allergy testing to all nuts in this clinical scenario.
D is incorrect. There is no proof that the patient's symptoms were caused by a food allergy to almond. Further follow up is warranted before almonds are restricted permanently from her diet.

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