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How to diagnose IgE-mediated food allergy

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ABSTRACT

Immunoglobulin E (IgE)-mediated food allergy is an immune response, typically to a food protein. Accurate diagnosis reduces unnecessary dietary restrictions and economic and psychological burden on patients and caregivers but relies on a rigorous clinical history, specific IgE diagnostic tests and, where needed, oral food challenge. Increased awareness is needed around which patients to test for IgE-mediated food allergy, as well as terms commonly associated with IgE-mediated food allergy testing, in order to optimise patient diagnosis and management. Herein, we describe approaches to diagnosis of IgE-mediated food allergy, appropriate interpretation of results and risks of overtesting.

INTRODUCTION

Adverse food reactions can be broadly classified into immune-mediated and non-immune-mediated reactions, with classical food allergy being immune mediated.[1] Immunoglobulin E (IgE)-mediated food allergy is an immune response occurring on exposure to a food protein.[2] Symptoms can include urticaria, angioedema, vomiting, abdominal pain, diarrhoea, acute rhinoconjunctivitis, wheezing, coughing, stridor, hypotension and cardiovascular collapse.[2] Although prevalence data are generally complicated by self-reporting (which tends towards over-reporting), prevalence of IgE-mediated food allergy in children aged <5 years is estimated to be ≤10% in Western countries.[3] Over the past decade, most countries have reported increases in prevalence of IgE-mediated food allergy, with no Western countries reporting a decrease.[3]

Currently, the widely accepted process of diagnosing IgE-mediated food allergy consists of an accurate and thorough history supported by confirmatory testing.[4] These confirmatory tests can have poor specificity, present an increased risk of severe allergic reactions and can be time-intensive and resource-intensive procedures.[4] Newer methods may be more accurate, but they also carry downsides, such as decreased sensitivity.[5 6] Additionally, biomarkers that predict diagnosis, identify allergen thresholds, monitor disease severity/resolution and more accurately inform treatment decisions are lacking.

For healthcare providers (HCPs) to use tests appropriately and provide informed clinical guidance, increased awareness is needed around which patient to test for IgE-mediated food allergy, along with an understanding of specificity, sensitivity, positive predictive value (PPV) and negative predictive value of these tests. Overuse of IgE-mediated food allergy testing likely produces overdiagnosis, leading to unnecessary dietary restriction and psychosocial and economic burden. Here, we summarise approaches to diagnosis of IgE-mediated food allergy, appropriate result interpretation and overtesting risks.

CURRENT TESTING GUIDELINES FOR IGE-MEDIATED FOOD ALLERGY

Determining the need for allergy testing and identifying the most accurate testing methods are critical in making relevant diagnoses, as well as limiting overtesting and overdiagnosis. Guidelines in the USA and Europe recommend specific IgE tests in patients with relevant medical history focusing on foods suspected of causing allergic reactions.[2 4 7] Specific IgE test results alone are not considered diagnostic of IgE-mediated food allergy (ie, they indicate sensitisation and must be considered with clinical history).[4] If clinical history and IgE tests are not highly predictive, an oral food challenge (OFC) is recommended.[4 7] Characteristics of recommended food-specific IgE tests and OFCs are detailed in table 1.[2 4 8]

IMPORTANCE OF MEDICAL HISTORY

Guidelines agree that obtaining a medical history is the most important step in the diagnosis of IgE-mediated food allergy.[2 7 9]

Table 1 Characteristics of food allergen tests[2 4 8]

Test	Aid in identification of food allergens	Diagnosis of IgE-mediated food allergy	Sensitivity	Specificity	PPV	NPV
Skin prick test	Yes	Yes*	High	Low	Mid	High
Allergen-specific IgE in serum	Yes	Yes*	High	Low	Mid	High
Component resolved	Yes	Yes*	Mid	High	High	Mid
Basophil activation test	Yes	Yes*	High	High	High	High
Oral food challenge	Yes	Yes	High	High	High	High

*May inform diagnosis but not considered gold standard.

IgE, immunoglobulin E; NPV, negative predictive value; PPV, positive predictive value.

Medical history will determine the pretest probability that the patient has an IgE-mediated reaction and will help ascertain whether testing is warranted by asking about symptoms, food of concern and other factors that may be involved, including exercise or medications.[4] Physical examination can identify possible comorbidities (eg, atopic dermatitis) that would make IgE-mediated allergy more likely.[4] Patients who have a history consistent with IgE-mediated food allergy are typically assessed further by skin prick test (SPT), measurement of serum antigen-specific IgE (sIgE) levels or both.[4]

Conversely, patients with a history that is not suggestive of IgE-mediated food allergy should not undergo further testing,[2] as these tests do not screen for intolerances or other immune reactions to foods.[4] Unless history is suggestive, caution is necessary when testing food triggers that are not common allergens, as 95% of all reactions are caused by eight allergens, including soy, wheat, milk and egg (prevalent in younger children and often outgrown), as well as peanut, tree nuts, fish and crustacean shellfish (not commonly outgrown).[2 4 9]

Box 1 Testing methods that are *not* recommended for IgE-mediated food allergy diagnosis[4 13]

Increased risk of systemic reactions
- Intradermal tests.

Insufficient evidence
- ALCAT.
- Atopy patch testing.
- Applied kinesiology.
- Electrodermal testing.
- Lymphocyte proliferation assays.
- Total serum IgE.
- Hair analysis.
- Provocation-neutralisation testing.
- Cytotoxic testing.

Responses are due to normal immunological memory rather than allergy
- IgG tests.

ALCAT, antigen leucocyte antibody test; IgE, immunoglobulin E; IgG, immunoglobulin G.

SKIN PRICK TEST

In the SPT, the food antigen in question (typically an extract) is placed on the volar surface of the arm or the back with a lancet or skin-testing device that introduces the antigen into the epidermis. If the patient has developed an IgE antibody to that antigen, a weal and flare reaction will occur within approximately 15 min. This response is compared with a negative control (eg, saline) and a positive control (eg, histamine).[2 4] How to perform an SPT and interpret the results was recently described by Ferris *et al*.[10]

SIGE TESTS

sIgE tests detect circulating IgE antibodies to suspected allergens, but the predictive value of sIgE levels varies across patient populations and may be associated with a patient's age, ethnicity, geographical location and concomitant allergic diseases (such as atopic dermatitis).[4] False-positive results can occur with sIgE tests because of a high degree of non-specific binding in the test or high total IgE levels in some patients.[8] Also, sIgE results from different laboratories are not directly comparable, as slightly different forms of antigens may be used and produce variable outcomes.[1]

CONFIRMATORY TESTING WITH THE OFC

If patient history is discordant with either the SPT or sIgE result, an OFC can confirm or definitively rule out allergy.[7] During this procedure, patients are given escalating doses—or a single dose if risk is considered low—of the food in question and monitored for reactions under the direct supervision of an HCP.[4 11] Although OFC is considered the gold standard for confirming an IgE-mediated food allergy, it is not mandatory if the patient has an unequivocal and convincing medical history of clinical reactivity and positive SPT or sIgE tests for a known allergen.[4] If no symptoms are present during an OFC, after ensuring an age-appropriate portion of the allergenic food has been eaten, then IgE-mediated food allergy can be

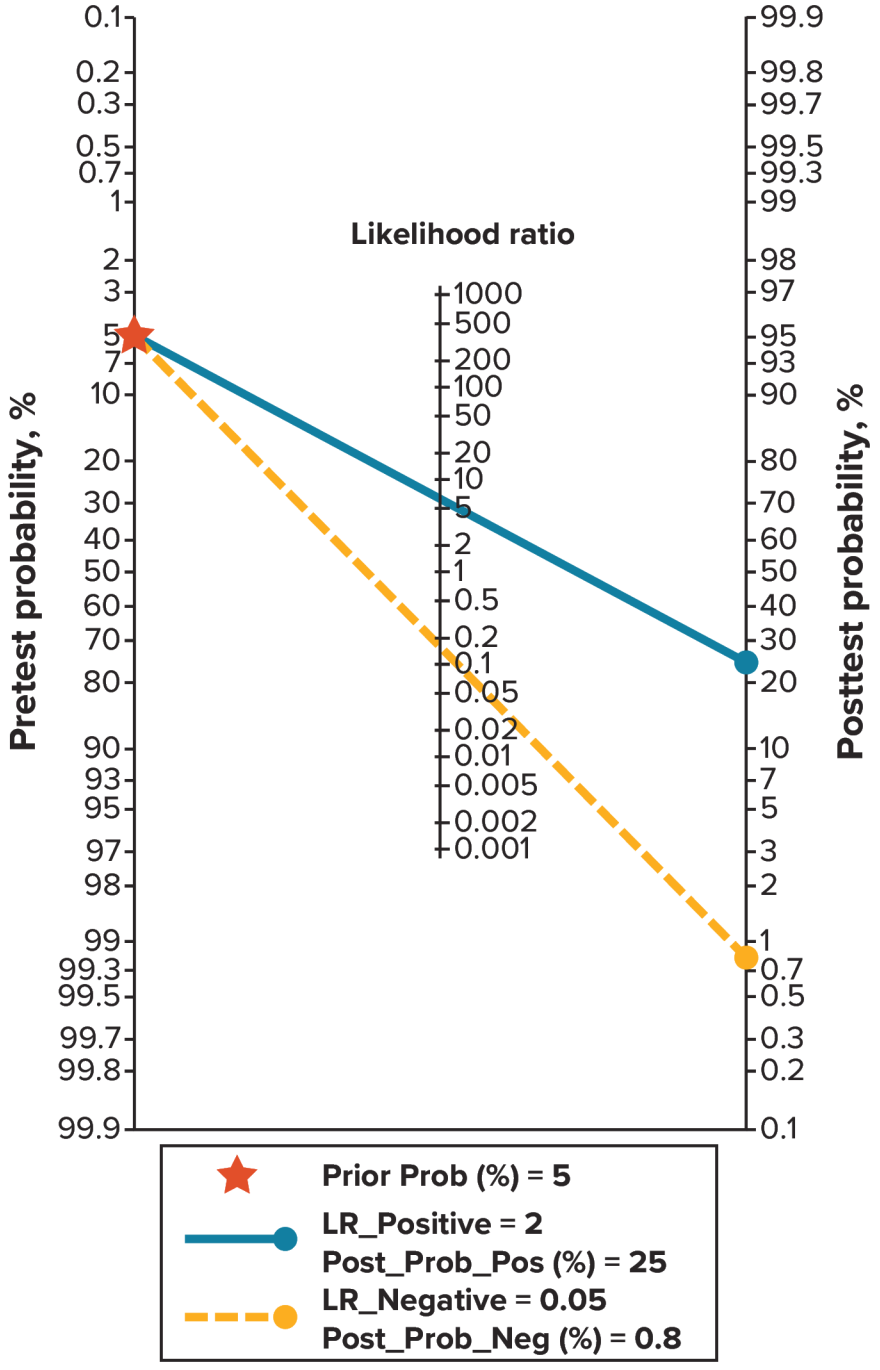

Figure 1 Fagan nomograms incorporate multiple parameters to visualise the probability of an IgE-mediated food allergy. IgE, immunoglobulin E; LR, likelihood ratio; Neg, negative; Pos, positive; Prob, probability.

ruled out for that allergen.[12] The allergen needs to be eaten frequently to ensure tolerance and confidence that it may be eaten in an unsupervised setting.[12] If unequivocal, immediate-onset symptoms develop, then a food allergy diagnosis can be confirmed and the food should be avoided.[4] As food allergies may be outgrown, an OFC may be performed regularly to evaluate development of oral tolerance.[4]

TESTS THAT ARE NOT RECOMMENDED

As summarised in box 1, additional testing technologies are available; however, these are not widely recommended, as they lack specific allergen information, present unnecessary risks or require additional research for clinical use.[4 13] Furthermore, large panel screens are not recommended, as they increase risk of false-positive results, unnecessary food restrictions and additional follow-up testing.[4] Component-resolved diagnostic testing for the Ara h2 component is recommended for peanut allergy[14]; however, US guidelines do not recommend component testing for other foods, and European guidelines only recommend component testing in addition to SPT or sIgE results if additional information is needed.[4 7]

INTERPRETING RESULTS OF IGE-MEDIATED FOOD ALLERGY DIAGNOSTICS

Understanding and communicating differences between IgE-mediated food allergy and sensitisation to the food is crucial for accurate treatment, as 50–90% of declared allergies are not actual allergies.[2 9] While studies have identified sIgE values with a PPV of 95% for an allergic reaction to use as cut-off decision points to reduce the need for OFCs for some antigens,[15] cut-off decision points are derived from specific populations and need validation for each population, limiting clinical utility.[6] Rather than using previously defined cut-off points, pretest probability based on a patient's history and likelihood ratio provided by diagnostic testing should be used together to develop a post-test probability. When using probabilities and likelihood ratios, clinical history is as informative as the specific confirmatory test results, because post-test probabilities account for clinical history as well as diagnostic outcomes.[16] Medical history, SPTs and/or OFCs are still informative, as patients with high total sIgE levels that are also below a 95% PPV may still be at risk of allergic reactions. Additionally, associations between specific allergens, such as egg and peanut, have been identified that need confirmation via testing.[17]

IMPLICATIONS OF OVERTESTING

Overtesting and misuse of at-home diagnostics result in overdiagnosis of IgE-mediated food allergy, leading to unnecessary psychosocial and economic burdens for patients and caregivers, including food avoidance, difficulty maintaining a nutritionally balanced diet and added financial burden (both direct and indirect) for safe food and medical expenses.[18–20]

HOW SHOULD I APPROACH EVALUATION IN A SIBLING OF A RECENTLY DIAGNOSED PATIENT WITH PEANUT ALLERGY?

A 2-year-old boy presents with no history of allergic reaction but with an older sibling recently diagnosed with peanut allergy. Should testing be offered? Pretest probability for a sibling of a peanut-allergic patient to have peanut allergy was determined to be 5% on the basis of available data. If a test is ordered, Ara h2 would provide the highest specificity and positive and negative likelihood ratios of 5.5 and 0.17, respectively. Based on pretest probability, pretest odds and likelihood ratio, post-test probability was between 0.8% and 25% (figure 1). This range indicates that the patient has a low likelihood of peanut allergy, which can be confirmed through an OFC.

Improved practitioner education on identifying patients in need of testing for IgE-mediated food allergy, determining the correct tests to perform and knowing how to interpret testing results can improve patient safety and reduce the burden of overtesting.

Test your knowledge

1. Among the following food allergens, which is not one of the eight most common food allergens?
   A. Soy
   B. Wheat
   C. Chocolate
   D. Milk
2. Which of the following tests identifies an increased probability of IgE-mediated food allergy?
   A. Food sensitivity tests
   B. SPT
   C. Cytotoxicity tests
   D. Hair analysis
3. What external factors can impact sIgE levels?
   A. Age
   B. Geographic location
   C. Allergic diseases
   D. All of the above
4. If patient history is discordant with the SPT result, which test is used to confirm or rule out food allergy?
   A. Another SPT
   B. sIgE panel
   C. OFC
   D. Component testing

Answers to the quiz are at the end of the references.

Clinical bottom line

- Testing for IgE-mediated food allergy should only be performed in patients with a medical history demonstrating possible allergic reaction.
- Antigen-specific tests, such as SPT and sIgE tests, can establish the probability.
- OFC is the gold standard for confirming diagnosis of IgE-mediated food allergy.
- Overuse of IgE-mediated food allergy testing leads to overdiagnosis, unnecessary dietary restriction and psychosocial and economic burden.

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Answers to the multiple choice questions

1. C.
2. B.
3. D.
4. C.