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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Serum allergen-specific IgE testing: How much is too much?

A 25-YEAR-OLD MAN is evaluated for angioedema (swelling of lips and tongue) after eating paella at a Spanish restaurant. He has no history of allergies, but he says he had never eaten such a large variety of seafood before, especially shellfish.

He suspects that he is allergic to shellfish and asks the attending physician to order blood tests for seafood allergies, as he heard from a friend that blood tests are superior to other types of tests for allergy. The physician requests a serum immunoglobulin E (IgE) food panel test for this patient.

SERUM ALLERGEN-SPECIFIC IgE TESTING

Many methods of testing for allergy are available, including the skin-prick test, double-blind and single-blind placebo-controlled food challenges, open food challenges, inhalant challenges, drug challenges, and serum IgE tests. In clinical practice, these tests are often used in combination because when used individually, few of them are both highly sensitive and specific (**Table 1**).[1–6]

Skin-prick testing is generally the method of choice for the preliminary evaluation of IgE-mediated allergies because it is more sensitive and requires less time to get a result.[1] But it is not the preferred test if the patient is at risk of a systemic reaction or has widespread dermatitis, nor is it useful if the patient is taking drugs that suppress the histamine response, such as antihistamines or tricyclic antidepressants.[6] Moreover, skin-prick testing is more invasive and time-consuming than serum IgE testing.

Serum IgE testing is an attractive alternative, and it is more convenient because it requires only a single blood draw and poses a lower risk of adverse effects.

NOT A RELIABLE DIAGNOSTIC TOOL

As serum IgE testing has gained popularity, researchers have tried to improve its diagnostic power (ie, maximize its sensitivity and specificity) by determining the best cutoff values for IgE against specific antigens. Unfortunately, these values are difficult to determine because of confounding factors such as the lack of a reference standard, population diversity, patient atopy, and the overwhelming number of allergens that must be examined.

In addition, some researchers have used positive and negative predictive values to evaluate diagnostic cutoffs for serum antigen-specific IgE values. But these are not the most suitable performance measure to evaluate because they depend on disease prevalence and population characteristics.

Despite these efforts, results are still conflicting, and serum antigen-specific IgE testing is not a reliable diagnostic tool.

In an effort to gain insight from the available research data, we evaluated the clinical usefulness of 89 antigen-specific IgE tests, using an approach of summing their sensitivity and specificity. Previously, Wians[7] proposed that a test is likely to be clinically useful if the sum of its sensitivity and specificity is equal to or greater than 170. **Figure 1** shows the 89 tests, grouped into categories, and their summed sensitivities and specificities. The dashed line indicates a cutoff of 170; any bar that touches or crosses that line indicates that the test may be clinically useful, according to Wians.[7]

Only 7 of the 89 tests (cow, buckwheat, hazelnut, latex, *Alternaria alternata*, honey bee

Tests that have little clinical utility have long-term detrimental effects

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TABLE 1

Suggested evaluations for the five major allergen groups

Allergen	Recommendations	Methods[a]
Food	National Institute of Allergy and Infectious Diseases states food allergy testing is not indicated for evaluation of mild atopic dermatitis or isolated respiratory symptoms, eg, rhinitis or asthma	Skin-prick testing and serum antigen-specific IgE testing, with caveats
	Serum immunoglobulin E (IgE) testing is not indicated for food intolerances, which are not mediated by IgE (see **Table 2** for differing characteristics)	
	Serum IgE testing and skin-prick testing are recommended to confirm suspected allergens; not suitable for indiscriminate screening	
	Serum IgE testing and skin-prick testing do not predict reaction severity	
	Positive serum IgE testing indicates sensitization but not necessarily clinical allergy	
	Serum IgE test results may be negative despite clinical reactivity	
Inhalants	Includes pollen, fungus, epidermis, dust mites	Skin-prick testing
	Serum IgE tests with defined quantifiable threshold levels can predict positive respiratory responses after allergen exposure	
	Skin-prick testing is more sensitive for identifying inhalant allergens and is the preferred method of confirming inhalant allergies	
Latex	The only method for assessing latex allergy approved by the US Food and Drug Administration is serum IgE testing	Serum antigen-specific IgE testing
	Serum IgE tests can be used to confirm latex allergy, but a negative result does not exclude sensitization	
Drugs	There are no validated diagnostic tests of sufficient sensitivity for evaluation of IgE-mediated allergy to antibiotics other than penicillin	Skin-prick testing for penicillin reaction, serum antigen-specific IgE testing for others
	For most drugs apart from penicillin, a serum IgE cutoff of 0.35 kU/L is used for allergy evaluation	
Venom	Predictive inconsistencies exist for both skin-prick testing and IgE testing	Skin-prick testing and serum antigen-specific IgE testing
	Patients with a history of venom reaction should be evaluated by both skin-prick testing and serum IgE testing	
	It is important to perform both skin-prick testing and serum IgE testing in patients with a clear history of severe reaction to insect stings when one test has a negative result	
	Any nonzero value of venom IgE is considered positive, despite the 0.35 kU/L cutoff	
	Performing venom skin-prick testing within the refractory period of the insect sting will result in a high chance of false-negative results	
	Serum IgE testing performed within a short period after the insect sting has a high chance of false-negative results, as serum IgE rises slowly after the sting	

[a] Diagnostically invalid tests: cytotoxic tests; provocation-neutralization; electrodermal testing; applied kinesiology; iridology; hair analysis; food-specific IgG, IgG4, IgG/IgG4 antibody tests.

Compiled from information in references 1–6.

venom, and Johnson grass) satisfied this criterion. This suggests that a significant number of serum antigen-specific IgE tests perform suboptimally, and we are left with the question of why they are so commonly ordered.

Inappropriate use can lead to false-positive results, a situation in which patients may be subjected to unnecessary food avoidance that can result in nutritional deficiencies and decreased quality of life. It can also lead to false-negative results, when life-threatening diagnoses are missed and further excessive downstream testing is required—all leading to negative outcomes for both patients and healthcare providers.

CHOOSING WISELY

The Choosing Wisely campaign in the United States has partnered with the American Academy of Allergy, Asthma, and Immunology to advocate against indiscriminate IgE testing in evaluating allergy.[8] Allergy diagnosis and evaluation should be based on a combination of clinical history and judicious ordering of specific IgE tests, whether through skin or blood testing. Ordering of serum allergen-specific IgE tests for food allergies should be consistent with a clinical history of potential IgE-mediated food allergy[8] and not food intolerance (**Table 2**).[4,5]

Some jurisdictions in Canada have followed suit by restricting the number of serum IgE tests each physician is allowed to order per patient, to encourage more responsible ordering and to lower the number of potential false-positive results, which can lead to increased downstream costs as well as unnecessary patient worry and lifestyle modification.

CLINICAL BOTTOM LINE

Ordering diagnostic tests that have little clinical utility has long-term detrimental effects on both patient safety and healthcare sustainability.

In the case of the 25-year-old evaluated for shellfish allergy, the clinician should first explain that the swelling of the lips and tongue (angioedema) does suggest an IgE-mediated allergic reaction and not a non–IgE-mediated allergic reaction or a food intolerance. Non–IgE-mediated food allergies and food intoler-

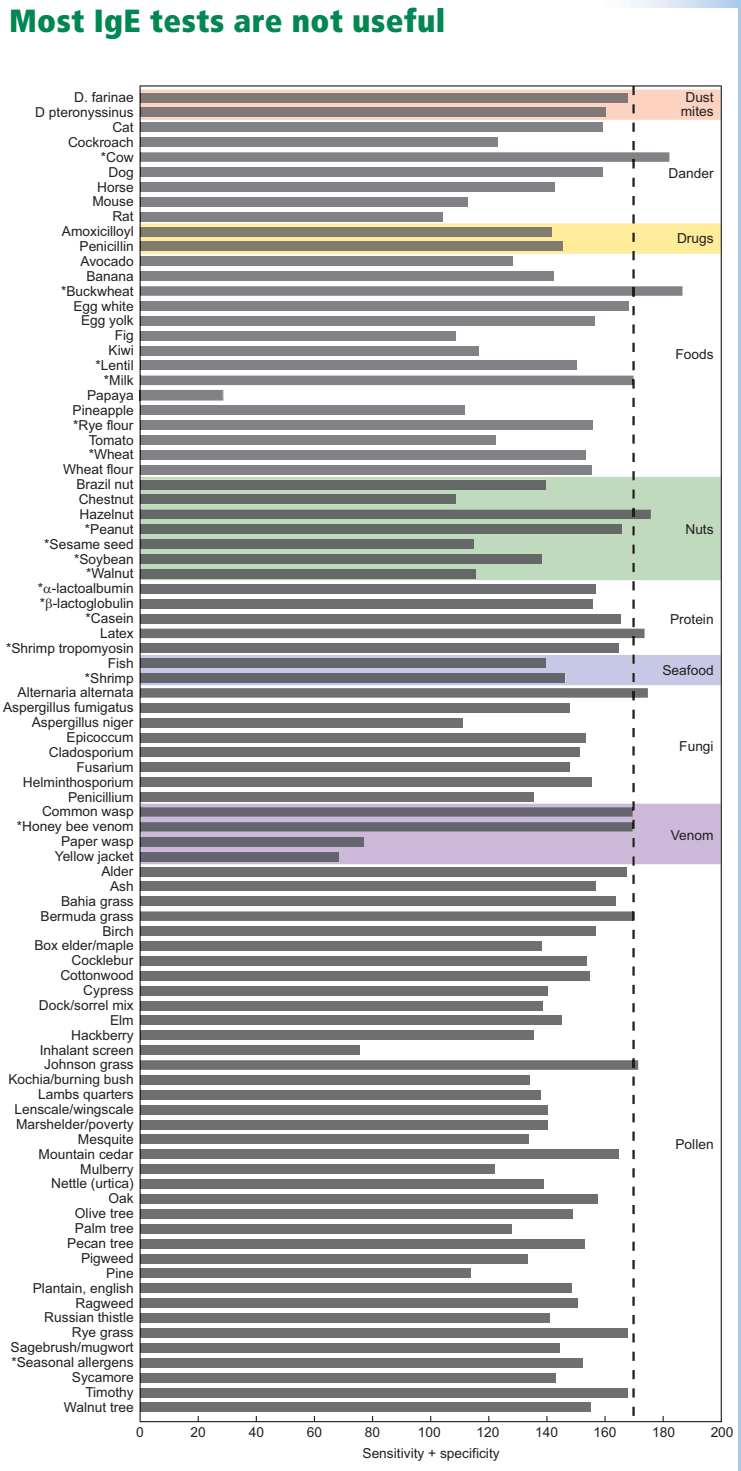

FIGURE 1. Sum of sensitivity and specificity of serum antigen-specific IgE tests of different ImmunoCAP allergens. A sum of 170 or greater (dashed line) is considered clinically relevant; tests with IgE cutoffs greater than 0.35 kU/L are noted with an asterisk.

TABLE 2

IgE-mediated vs non–IgE-mediated food allergy

Factors consistent with IgE-mediated allergy
Onset within 2 hours of ingestion
Resolution within 12 hours
Vomiting, diarrhea, gastrointestinal pain
Symptoms of anaphylaxis (urticaria, angioedema, pruritus, cardiovascular collapse)
Acute wheezing, coughing, stridor
Factors consistent with non–IgE-mediated allergy or food intolerance
Onset hours or days after ingestion
Resolution after more than 12 hours; days
Nonspecific symptoms (diarrhea, bloody stool, food refusal, colicky pain)
Symptoms mainly associated with digestive system

Compiled from information in references 10 and 11.

Only 7 of 89 serum IgE tests were likely to be clinically useful

ances are marked by symptoms relating mainly to nonimmune aspects of the digestive system, whereas IgE-mediated food allergies affect the immune system and can involve a multitude of organs, including the skin and the respiratory and digestive systems (**Table 2**).

However, clinicians should avoid indiscriminately ordering food allergen IgE panels and instead should focus on foods likely to be the culprits based on the clinical history.[9] Indiscriminate testing can lead to false-positive results and unnecessary food avoidance.

Since the patient developed symptoms of angioedema when he was exposed to his allergen, he may be apprehensive about a skin-prick test and the possibility of being subjected to the same discomfort. Therefore, in this situation, it may be best to perform serum IgE tests, but on a few targeted seafoods rather than the food panel the physician had ordered. A patient can be sensitized to an allergen (possess IgE antibodies) but not experience symptoms when exposed to it (ie, have tolerance).[5] Also, false-negative results may occur, so a negative serum allergen-specific IgE test should likewise be interpreted in light of the pretest probability of allergy to a specific antigen.

If the history and the results of testing are not clear and congruent, the patient should be referred to an allergist for diagnosis or for management. The allergist can provide management techniques and periodic assessment as to the progression and resolution of the allergy. **Table 2** highlights symptoms that differentiate an IgE-mediated from a non–IgE-mediated food allergy.[10,11] **Table 1** presents clinical indications and suggested diagnostic methods to the five most common allergen groups and the diagnostically invalid tests.[1–6]

The bottom line is that we must consider the poor performance of serum allergen-specific IgE tests when diagnosing and treating suspected type I allergies and avoid ordering food allergen IgE panels whenever possible.

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