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Review Article

Laboratory Markers Used for the Diagnoses of Food, Respiratory, Skin, and Drug Allergies

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Abstract

Background: Allergies, as prevalent conditions, significantly impact individuals' health and quality of life. The criticality of accurate diagnosis cannot be overstated, as it is the cornerstone for effective management and treatment, underscoring the gravity of the medical professionals' work.
Objectives: This review aims to provide a comprehensive evaluation of laboratory markers used to diagnose different types of allergies, including food, respiratory, skin, and drug allergies.
Methods: The review analyzed and synthesized data from current literature on essential diagnostic tools such as skin prick tests, specific IgE blood tests, and component-resolved diagnostics. Studies comparing these diagnostic methods' efficacy, specificity, and limitations were discussed.
Results: Skin prick tests remain widely used for diagnosing immediate-type allergies but may have limitations in detecting all allergens. Specific IgE blood tests offer a more detailed assessment of allergen-specific responses, although they can be influenced by factors such as patient age and coexisting conditions. Component-resolved diagnostics provide enhanced precision by identifying specific allergenic components, potentially improving diagnostic accuracy and guiding targeted immunotherapy.
Conclusions: The review underscores the effectiveness of existing diagnostic tools while also highlighting their variability depending on the type of allergy and patient characteristics. The future of allergy diagnosis lies in the integration of advanced technologies, such as component-resolved diagnostics, into clinical practice. This need for further research should instill a sense of urgency and emphasize the importance of efforts to enhance patient outcomes and optimize allergy management strategies.
Keywords: Drug Allergy; Food Allergy; Laboratory Markers; Respiratory Allergy; Skin Allergy.

Introduction

In the context of food allergies, the skin prick test (SPT) is commonly used in addition to serum level determination. However, it's important to note that the SPT method cannot quantify results. On the other hand, the serum level determination method allows for quantification within a range. Genetic diagnosis testing is also feasible, given that most people have been sequenced. This allows for fragment coverage, data analysis, and the sequencing of multiple targets with one experimental design. This section offers a summary of the methods utilized to diagnose specific conditions (1,2,3).

Typically, it is crucial to anticipate and verify allergic reactions through reliable and objective means in the diagnostic procedure. When diagnosing IgE-mediated allergies in children, it's essential to rule out or confirm the specific sensitization that triggers a convincing history of allergic reactions to common food items such as egg, cow's milk, peanut, tree nut, fish, wheat, and soy. Any treatment plan to build tolerance to the allergic reaction or desensitize the patient will only be successful if the relevant allergens are identified (4,5,6).

In certain instances, it can be quite challenging to avoid allergens. In these scenarios, gaining insight into the allergic pathway is key for developing innovative treatment approaches. This can involve comprehension or measurement of precise allergen levels, production of immunoglobulins, and exhaled or nasal nitric oxide (eNO/nNO) (7,8,9).

Definition and Types of Allergies

Immune-mediated adverse reactions can be categorized as sensitization and allergic disease. Sensitization involves the development of allergen-specific T cells that release Th2 cytokines and induce isotype switching in B cells to produce IgE. The IgE produced is then bound by high-affinity receptor-expressing cells such as mast cells and basophils,

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leading to symptoms when the allergen binds to multiple IgE-FcεRI complexes on the effector cells' surface, releasing mediators. A sudden and severe onset of symptoms indicates a severe allergic response, known as anaphylaxis. If no response to the same allergen occurs, the individual is considered sensitized but not allergic (10,11,12).

An allergic disease is a condition in which one or more immune responses to environmental agents (allergens such as foods and pollens) cause distressing or harmful symptoms, repeated in association with the same allergens in the same host. Allergy symptoms may be localized or systemic and might appear as allergic rhinitis, allergic asthma, atopic dermatitis, contact hypersensitivity, urticaria, angioedema, food allergy, and adverse drug reactions (7,9,13).

Importance of Accurate Diagnosis:

The reduced efficiency of an employee caused by illness is more significant when suffering from an allergic condition. The mere existence of a respiratory illness, atopic dermatitis, or food sensitivity, even if not outwardly expressed, imposes certain limitations when the worker needs to operate in settings with biochemical hazards, such as areas with high levels of water, air, and noise pollution, as well as in sectors that involve the production of solvents and penicillin, and in monitoring the potential for diseases in daycare workers. For individuals planning to reside or work in the environment of the International Space Station, a predisposition to potential allergens could pose an increased risk of developing allergic conditions due to the changes in the space environment. We have considered diseases that are more prevalent in Earth's environmental circumstances. A precise identification of potential allergic predisposition could provide better protection for these individuals, whether in their professional or domestic environments. The presence of allergies/sensitivities to medications or antibiotics (such as sulphonamides and trimethylamine) used in preventing infections in immunocompromised patients has indicated that at-risk patients may be considered if they meet stringent safety requirements. Infections in immunocompromised or transplanted patients may also be caused by molds, leading to these complications. Awareness of the sensitivity to molds for patient treatment in areas affected by natural or industrial environmental contamination is vital. Inaccurate consumption of certain nutrients or a maladjusted diet in the daily life of a patient allergic to mold antigens could result in the patient's fatality. Understanding the serological and microbiological history of recipients and donors involved in kidney transplants is crucial in determining compatibility and potential adverse co-location (7,9,13). Precise identification of the type of allergy is critical in treating the disease. Additionally, there are other significant implications linked to this information. In conjunction with in-home outpatient assessment and a patient visit, the allergy diagnosis is the initial step toward allergen-specific immunotherapy (SIT). Patients with a heightened risk of infection will require antibiotic prophylaxis for certain orthopedic surgical procedures. Knowing the specific allergens that trigger reactions is valuable for delivering more targeted treatment. Other important implications include preventing further diseases transmitted by certain insects, such as Hymenoptera insects, spiders, or cockroaches. This information is crucial for certain contagious disease vaccines and specific anesthetic drugs. In patients with asthma, allergic rhinoconjunctivitis, or other IgE-mediated allergic diseases, an accurate allergy diagnosis and risk assessment is essential for guiding patients toward allergen-specific immunotherapy (SIT). This step is especially relevant when there is no response or insufficient response to drug therapy, adverse drug reactions, patient refusal of treatment, and a reduction in treatment costs (14,15,16).

Table 1: Comprehensive Classification and Sub-Classification of Allergies, Describing Common Triggers and Diagnostic Tests for each Type

Classification	Sub-classification	Description	Common Triggers	Diagnostic Test
Food Allergy	IgE-mediated	Immediate allergic reactions involving IgE antibodies.	Peanuts, tree nuts, shellfish, milk, eggs, wheat, soy	Specific IgE testing, Skin prick test, Oral food challenge
	Non-IgE-mediated	She delayed allergic reactions that did not involve IgE antibodies.	Gluten (celiac disease), specific proteins	Elimination diet, Food challenge
Respiratory Allergy	Allergic Rhinitis	Inflammation of the nasal passages caused by allergens.	Pollen, dust mites, mold spores, pet dander	Specific IgE testing, Skin prick test
	Allergic Asthma	Chronic inflammatory disease of the airways triggered by allergens.	Pollen, dust mites, mold spores, pet dander	Pulmonary function tests, Specific IgE testing
Skin Allergy	Atopic Dermatitis (Eczema)	A chronic skin condition characterized by itchy, inflamed skin.	Foods, environmental allergens	Clinical evaluation, Specific IgE testing
	Contact Dermatitis	Skin reaction resulting from direct contact with allergens.	Metals (e.g., nickel), latex, cosmetics, plants	Patch testing
Drug Allergy	Immediate Hypersensitivity	Rapid onset allergic reactions to medications involving IgE antibodies.	Penicillin, aspirin, NSAIDs, sulfa drugs	Specific IgE testing, Drug challenge, Skin prick test

Continuous	Delayed Hypersensitivity	She delayed allergic reactions to medications not involving IgE antibodies.	Antibiotics, anticonvulsants	Patch testing, Clinical evaluation
Insect Allergy	Insect Sting Allergy	Allergic reactions to insect stings or bites.	Bees, wasps, hornets, ants	Specific IgE testing, Skin prick test, Intradermal testing
Contact Allergy	Allergic Contact Dermatitis	Skin inflammation is caused by contact with allergens.	Poison ivy, latex, cosmetics, fragrances	Patch testing
Anaphylaxis		Severe, potentially life-threatening allergic reaction affecting multiple body systems.	Foods, insect stings, medications, latex	Serum tryptase levels, Specific IgE testing, Clinical evaluation
Gastrointestinal Allergy	Eosinophilic Esophagitis	Chronic immune system disease causes inflammation of the esophagus.	Foods (e.g., dairy, wheat, soy, eggs, nuts)	Endoscopy with biopsy, Specific IgE testing
Urticaria (Hives)	Acute Urticaria	Sudden onset of red, itchy welts on the skin lasting less than six weeks.	Foods, medications, insect stings, stress	Clinical evaluation, Specific IgE testing
	Chronic Urticaria	Persistent hives lasting more than six weeks, often with an unknown trigger.	Autoimmune factors, infections	Clinical evaluation, Autoantibody tests

Common Laboratory Tests: The Unique Classification List for individual medical practices outlines the immunological determination of biomarker properties for various allergic diseases in children and adults, indirectly revealing immune responses and allergen conditions. This information is essential for prophylaxis and management of clinical allergic diseases in humans and animals, as well as for evaluating environmental conditions and predicting allergy rates in specific locations. According to the latest findings from the World Health Organization, the most common present and future diseases include asthma, allergic rhinitis, and pollen-related allergies to wormwood, nettle, and the Parietaria weed. Additionally, reactions to pollen from fungi like Alternaria, Clathosporium, and Aspergillus spp. are also of concern (17,18,19,20).

The primary purpose of the supplementary laboratory allergological test is to measure the levels of IgE antibodies and Immunoglobulin E (IgE) in the body. This test is not qualitative but rather a quantitative enzyme test. Values of 0.1 IU/mL indicate a positive result, but there are no specific accepted values, as they can vary depending on the manufacturer of the diagnostic systems and examination methods. If there are recommendations from allergology experts, interdisciplinary agreement should be reached and shared across primary, secondary, and tertiary healthcare facilities. Due to the numerous products available for determining immune component levels and the lack of established currency values, recommendations from healthcare management about device types and immune component levels are complex and long overdue (21,22,23).

Skin Prick Test: A different form of sensitivity to allergens has been identified, known as idiosyncratic or pseudoallergic histamine release syndrome. These reactions are triggered by certain pharmacologically active compounds found in food rather than traditional allergens, indicating that some foods may elicit varying responses in allergic and pseudoallergic individuals. Originally recognized by allergists, pseudoallergic histamine release syndrome is now associated with a range of clinical conditions. This research focuses on cytokines, IgE, and the CD4+ Th1/Th2 ratios, to primarily evaluate the profile of helper T cells in patients with immediate food hypersensitivity and pseudoallergic histamine release syndrome. (24,25,26,27).

The skin prick test (SPT) is a straightforward procedure that a specialist should perform. It involves applying a commercial extract of the allergen onto the patient's skin, ideally on the inner side of the forearm, and then using a small plastic device to prick the skin. This triggers the release of a small amount of histamine as a positive control and, more significantly, disrupts the barrier by causing trauma to the outermost layer of skin cells and stimulates the release of inflammatory mediators. Mast cells gather near the surface, residing on or near the vascular bed, and involve other subtypes of immune cells. Degranulation occurs approximately 30 seconds after the skin is pricked and peaks around 15 minutes later, depending on the patient's allergic status and test quality. Antihistamine medication and reducing dermal swelling are crucial for test accuracy, as these two factors can affect the response size (28,29,30,31).

Specific IgE Blood Test

Initially, tubes containing a base for a specific antibody are combined with the patient's blood. If the patient's blood prompts the antibody to interact with the allergens introduced into the mixture, they are identified chemically. However, incorrect results can occur due to small quantities of food allergens, metal-induced tumors, uncommon substances, or particularly high concentrations of substances. Once certain substances are identified, more dependable methods will be incorporated to validate or refute the

finding. An increase in overall serum IgE levels can indicate allergies, as mast cells produce IgE in response to allergens. However, total IgE levels cannot anticipate conditions such as asthma, anaphylaxis, and other immune system disorders despite elevated allergen levels in some individuals. Although serum IgE levels may be a valuable laboratory-based indicator in food allergy function, they often need to be more utilized despite the potential benefits of anti-IgE antibody therapy for severe throat and peanut allergies (32,33,34).

Specific IgE is quantified in conjunction with clinical data, allergen testing, and consultation. There are various methods for measuring specific IgE that are faster and simpler than skin testing, but they are also more expensive. It is feasible to order specialized tests for specific antigens to confirm the diagnosis and assess treatment efficacy. The levels of specific IgE antibodies are commonly assessed using the enzyme-linked immunosorbent assay (ELISA) or the radioallergosorbent test (RAST). The RAST system utilizes radioactive substances to quantify the amount of allergen in the blood, although the susceptible chemiluminescent test is gradually replacing it. Commercially available IgE antibodies are employed in blood tests, where cells release chemicals when mixed with various allergens (35,36,37,38).

"Innovative Technological Advancements for the Diagnosis of Allergies"

It is difficult to know the real prevalence of allergic diseases, but it is estimated that nowadays, the prevalence can vary from approximately 20 to 30% of the population. Diagnosing an allergic disease involves obtaining a medical history and performing a clinical examination complemented by diagnostic testing. The specificity and sensitivity of the tests used in the diagnosis may differ significantly, being confronted with a high number of false positives. Determination of the molecular allergens responsible for the symptoms, as well as the patient's specific predisposition to develop the allergies, surely contributes to the improvement of the diagnostic tests and subsequent treatment of each patient suffering from an allergic disease (39,40,41).

Many emerging tests with various index mechanisms are being considered for diagnosing allergic diseases. This highly innovative field leads to frequent changes and many newly developed strategies, thanks to updated protocols. Some of these tests include the basophil activation test, lymphocyte activation test, novel in vitro assays using CD-sens combined with the major urine protein, and the Micronucleus test, among others developed in recent years. These tests can potentially become valuable tools to confirm, complement, or even replace traditional methods for diagnosing allergic diseases (7,9,42,43).

Component-Resolved Diagnostics

Component-resolved diagnostics (CRD) utilizes a collection of recognized allergenic molecules from key allergenic sources in immunological diagnostics. The implementation of CRD tests in clinical settings has the potential to enhance standard procedures, customize treatment, and diminish the need for unnecessary oral food challenges. The reliability and precision of specific IgE and CRD tests are contingent upon the circumstances in which the test is conducted. Across the complete range of allergic conditions, from rhinitis to anaphylactic reactions, the precision of in vitro allergen-specific tests differs (4,44,45).

Despite the importance of reaching a positive diagnosis based on clinical symptoms, exposure history, and context, several additional diagnostic options are available. In routine clinical allergy, the measurement of total IgE and allergen-specific IgE through commonly available *in vitro* assays is often conducted as the initial test. This is typically followed by the component-resolved diagnostics assay to detect allergenic components. Furthermore, additional tests such as basophil activation tests (flow-cytometry tests), provocative tests, patch tests, nose scratch indexes, throat biopsies, and skin biopsies may also be utilized (10,37,42,46).

The different cut points determined in the populations studied make it impossible to have a common threshold for all populations and to have a result after consulting the flow. Furthermore, the BAT should be tested well in research and within the public health system to identify IgE determinants, such as allergen molecules, in such high-alert patients, and it should be closely linked with the detailed clinical history in determining the threshold of clinical activity. Otherwise, in conditions of availability, it is undoubtedly the method of choice for diagnosing hypersensitivity reactions to drugs, whose diagnosis is sufficiently accepted, as only it or a basophil activation test with a similar experimental approach, based on the patient's cells, detect non-IgE-driven mechanisms, such as cross-reactivity with the pharmacological compound and linked to idiosyncrasies present in active, nonreactive and tolerant patients treated with the suspected drugs (6,7,9).

The test evaluates the quantity of basophils in circulation with IgE-FcεRI bound to them. This test involves using flow cytometry to stimulate these cells with an allergen in a test tube and then identify specific markers on their surface, such as CD63, CD203, or other markers. This examination is appropriate for monitoring the responsiveness of patients who have undergone allergen-specific immunotherapy, particularly in cases of immunotherapy with multiple independent allergens that have caused severe allergic reactions. Despite the inability to conduct allergy skin tests, there are no recommendations for the duration of various types of immunotherapy, including total or accelerated immunotherapy, monotherapy, or combination therapy with anti-IgE/anti-IL inhibitors. Although the test is being conducted in an increasing number of laboratories, qualitative and semiquantitative results have not yet been achieved, meaning that patient activation values are not correlated with the percentage of activated basophils (2,7,17).

Challenges and Limitations in Allergy Testing

The determination of cutoff levels is based on the sensitivities and specificities of the test in providing accurate diagnoses. However, it is important to note that these tests have limitations as they do not provide information on the allergen's clinical relevance or molecular structure. It should be emphasized that a positive IgE result indicates sensitization rather than clinical relevance. Additionally, it is worth noting that in young children, a low level of IgE is often required to trigger airway reactions, as well as for food-specific IgE and food allergies. Therefore, clinical symptoms play a crucial role in allergological diagnosis. Furthermore, while an increased presence of IgE in the nasal epithelium may stimulate airway secretions, it may not be specific to clinical symptoms related to seasonal allergens. Moreover, using IgE isotype to diagnose local IgE vasomotor allergic cerebral edema in the brain cannot determine its involvement in developing edema observed in the migraine phenotype. Consider the necessity of demonstrating the clinical safety of pharmacological treatment for potential atopic conditions, including its local effects (47,48,49).

There are three main approaches to allergy testing: serum immunoglobulin E (IgE) testing, skin prick testing (SPT), and component-resolved diagnosis (CRD). These methods assess how the immune system responds to proteins and glycoproteins found in allergens. Serum IgE testing measures allergen-specific IgE and is particularly important for patients with eczema who cannot undergo SPT and those with dermatitis from an unknown allergen. *In vitro* serum tests can be used as primary tests for allergic rhinitis and asthma, as they do not require the provocation necessary for *in vivo* tests, resulting in more allergy symptom-free days. It is important to note that serum IgE levels can increase in individuals without allergic symptoms due to the pollen priming effect, potentially leading to a false allergy diagnosis. Different tests establish varying cut-off levels to identify this possibility accurately (33,46,50).

Cross-Reactivity and False Positives

The use of combinations of allergens in skin prick tests (SPT) and *in vitro* tests (IgE multiPLEX, ImmunoCAP ISAC) poses a significant challenge. When pan-pollen or tree pollen groups are included in the combination of allergen sources, it often interferes with *in vitro* assays and clinical masking of underlying allergen profiles. For instance, patients sensitized to grass pollen with pure IgE may not be accurately diagnosed if they are only tested with timothy and pollen allergens. This leads to misinterpretation of lab tests and potentially negligent clinical judgment by physicians due to limited allergen sensitivity (13,46,51).

Certain unidentified laboratory markers may be present in specific instances. However, the test results could be more *in vitro* and *in vivo* tests and the clinical symptoms of affected patients. Cross-reactivity occur when the immune system’s IgE antibodies recognize and bind to secondary allergens that share high structural or amino acid sequence homology with the primary sensitizing allergen. For example, patients sensitized to grass pollen (such as timothy grass) may have elevated specific IgE to timothy pollen. Cross-reactivity among grass pollen allergens from various sources within the "pan-allergen" group often leads to false positive test results that do not reflect true sensitization (52,53,54,55).

Cost and Accessibility Issues

When discussing expenses and availability, it is essential to consider the financial cost of laboratory procedures and the time and effort required for an appointment with a specialist. In the former Soviet Union, appointments can take anywhere from a few days to three weeks; in some other countries, it can take a year or longer. For many patients, pollen allergies occur during specific times of the year, and the need to see a doctor during these flare-ups can make the consultation cost the most significant expense. Private medical consultations with allergists are often unaffordable for patients, and the availability of necessary testing is limited due to a lack of appropriate equipment in some laboratories. Unfortunately, diagnosing allergies can be expensive for many patients and those who pay for these services, regardless of the number of antibodies tested. In most countries, healthcare systems do not cover the cost of all diagnostic tests for every patient, and the expenses increase depending on the type and complexity of the test. Rarely are all markers for a specific clinical case used in the same patient (3,7,9,41).

In certain nations, Western blot and EliA Tests are not utilized. Meanwhile, Russian scientists frequently need to request the most informative and commonly used tests (ImmunoCAP, CDR-FEIA) for their patients from other countries, which restricts the number of patients in their studies. Furthermore, limitations are imposed based on the laboratory's profile or the personnel's qualifications. ISO 9001 regulations are only feasible for laboratories with high-quality technology, reagents, and responsible staff. Insurance companies often cover the expenses of additional tests for individuals deemed at risk. Diagnosis is determined by identifying a specific allergen using the patient's serum, and an allergic nature is always confirmed through a skin test. These two tasks are crucial in clinical practice for a specific allergen extract. The advantages of serum components over 48 extracts and their cost benefits have yet to be established (32,33,46,56,57,58).

The total IgE level is measured alongside specific allergens in a water-based, allele-specific extract. This extract contains allergens from plants and animals that can cause various allergic reactions. It includes allergens from common receptor proteins like dust, dairy, cow's milk, oats, corn, wheat, barley, turtles, chickens, dogs, and cats. The extract also covers important plant species and includes 40 fungi allergens. When specific allergies and total IgE are analyzed, a single test is used, given that the total IgE level remains under 50 units as the first step in determining high-quality results. In the diagnosis of different types of allergies, and with clear clinical

symptoms and seasonal ingestion, an atopic status can be identified. The total cost of diagnostics will be significantly lower when the absolute value of the total IgE is determined for each allergen, compared to using specific allergens, with a decrease of 160% or more (32,33,46,56,57,58).

Regarding cost and accessibility, allergen-specific IgE testing is relatively expensive; however, it is widely performed in developed countries due to its standardization, automation, and direct relevance to IgE-mediated (Type I) hypersensitivity reactions. In contrast, cellular immune assays are generally more complex, expensive, and less accessible in routine clinical practice. Standard diagnostic methods, such as skin prick testing, may offer high sensitivity and are often used as first-line investigations depending on the clinical context. Furthermore, the cost of allergy diagnostics can be optimized through the use of standardized commercial kits and targeted testing strategies (10,46,59,60).

Future Directions in Allergy Diagnosis

Despite the promising findings regarding using carefully selected allergen components for diagnosing and managing allergic diseases, more evidence-based data is still needed. Interpreting allergen component-based IgE testing within the full clinical context of a patient's allergic disease may improve the prescription of specific allergen immunotherapy over the whole extract. These components can help predict the risk of severe allergic reactions and sensitization, identify cross-reactive allergens, and assist in effectively avoiding problematic foods. Employing personalized treatment strategies based on a patient's profile of aeroallergens and food components adds value by increasing treatment efficacy and reducing unnecessary therapeutic interventions (15,61,62,63).

Today, already in routine practice, the molecular component-resolved IgE diagnosis or microarray technologies, capable of testing at the same time a large number of molecular allergens, make it possible to determine the sensitivity profile of the patient with greater precision. These methods are not only indicated in polysensitized patients but also in cases of localized symptoms, in selecting food that is safe for a patient, in preventing and evaluating the immunotherapy development, in children with wheezing symptoms, in patients who had an anaphylactic episode, and in drug and Hymenoptera stings allergy, since they help the avoidance measures and subsequent treatment (64,65,66).

Conclusion

There is significant activity in the search for reliable assays that can determine the trigger type and its control. Recent publications have shown promising techniques integrating both *in vitro* and *in vivo* tests. In this context, transcriptomic data is critical in diagnosing allergies and assessing the effects of anti-IgE treatment, tolerance induction, and reactivity to the same food in cases of pollen-food syndromes. Furthermore, tests based on the IgE response to allergen components have improved patient diagnoses. However, the limited number of patients in these studies suggests the need for more extensive clinical trials. While no published markers can determine the route of tolerance induction on their own, there are new and more effective protocols for testing and understanding these mechanisms. In addition to cell-based methodologies such as basophils, mastocytes, and microarray data, technical facilitators can change how an old method, like the skin test or RASTs, is used.

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