

# Food Allergy: When to Think and How to Diagnose

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## Abstract

Food allergy is an adverse reaction that reproducibly occurs following exposure to a certain food. It is always the result of a specific immune response. There is a significant lack of knowledge about its true prevalence and pathogenesis, a situation of concern in the face of a growing increase of this entity. It is estimated that its prevalence can reach a peak of 6%-10% in the first year of life, assuming, in most cases, a transient nature. Different organs and systems can be affected by an allergic reaction to food and, therefore, it should be considered in the presence of a wide variety of clinical conditions. The diagnosis should be phased and based on a clinical history that selects the complementary tests to be performed. It may be necessary to perform an oral food challenge, as it remains the gold standard for diagnosing food allergy. Correct diagnosis is crucial in order to avoid potentially life-threatening exposure of the allergic person to the identified food. On the other hand, exclusion of a food allergy diagnosis is important to prevent unnecessary restrictive diets that often result in nutritional impairment.

**Keywords:** Food Hypersensitivity/diagnosis; Food Hypersensitivity/prevention & control; Review Literature as Topic

## Introduction

Adverse reactions to food include any undesirable effects resulting from ingestion, contact, or inhalation of a food or its derivatives or additives contained therein.<sup>1,2</sup> They may have a non-immunological cause, in which case they are known as a food intolerance, or they may be secondary to an immunological response, mediated by immunoglobulin (Ig) E (IgE-mediated allergy) or other immune mechanisms involving cells and other mediators of the immune system (non-IgE-mediated

allergy). In addition, in some clinical situations, both mechanisms may be involved (Fig. 1).<sup>3-5</sup>

Food allergy seems to result from the failure to acquire oral tolerance to a given food. Whereas the immune system of all individuals recognizes food antigens as foreign, patients with food allergy develop pathological immune responses to these antigens and can rapidly experience harmful adverse symptoms upon repeated exposure.<sup>6</sup>

This is attributed to intestinal immaturity, with increased mucosal permeability, deficiency of gastric secretion and digestive proteolytic activity, and to immunological immaturity, with an absence of intestinal IgA secretion.<sup>7,8</sup> Other factors may be implicated, whether dependent on the patient, such as genetic and age factors, or on the antigens themselves, in their chemical nature, structure, and concentration.<sup>9</sup>

The prevalence of food allergy has been rising in recent decades, with an increasing rate of 1.2% per decade. The reasons for this increase are not yet fully understood.<sup>10,11</sup> Factors such as hygiene and lack of exposure to microbial factors, intestinal microbiota, diet, obesity, vitamin D, and environmental exposure have all been proposed to contribute to the rate of food allergy in so-called developed countries.<sup>12</sup>

Despite the choice of some clinicians to delay the introduction of new, potentially allergenic foods, recent evidence suggests that the development of immune

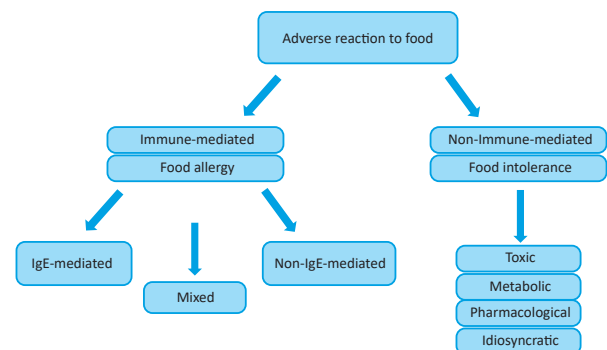


Figure 1. Food reaction mechanisms.

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tolerance to an antigen may require repeated exposure, perhaps during a critical early window of time, and perhaps modulated by other dietary factors including breastfeeding.<sup>13-15</sup> Several components of human milk are known to influence immunity and could play a role in reducing the risk of allergies. However, recent studies have shown conflicting data. The lack of evidence was suggested to be due to the heterogeneity in human milk composition and that interventions aiming to modulate human milk composition could influence infant immune responses and potentially help reduce the risk of allergies in early life.<sup>16</sup>

Further studies are needed to define the dose and timing of the introduction of food allergens in order to induce tolerance.<sup>17,18</sup>

Most cases of food allergy occur in the first two years of life, with a prevalence peak of approximately 6%-10% in the first year, followed by a progressive decrease until the end of childhood, after which the prevalence remains stable between 3%-4%.<sup>4,19</sup>

Although all foods are potentially sensitizing, the major food allergens vary depending on the geographic location, food habits of the population, and the age at which there is contact with the food. Food allergens are mostly glycoproteins of molecular weight between 10-70 kDa. In the pediatric age group, about 90% of all food allergies are caused by eight allergens, namely cow milk proteins, egg, soy, wheat, shellfish, fish, tree nuts, and peanuts.<sup>1-3,20</sup>

In most cases, food allergy in pediatric patients is a transient condition and there is a progressive development of food tolerance leading to complete resolution of the symptoms.<sup>3,4</sup> The mechanisms involved, probably multiple, are not yet fully understood. In food specific IgE allergy, most patients present decreasing IgE serum levels over time. The decrease of IgE is the best-known predictor of the development of clinical tolerance. However, some patients become tolerant even with persistently elevated food specific IgE levels. Therefore, IgE decreasing might not be the primary mechanism of the resolution of food allergy, and other humoral changes must be considered, including increasing allergen-specific immunoglobulin G4 and/or immunoglobulin A (IgA). Cellular mechanisms, such as the induction of T regulatory cells, may play a significant part.<sup>1,21-23</sup>

The existence of great homology in the amino acids sequence of the chemical structure of foods from different origins can give rise to cross reactivity phenomena, which are reflected by the occurrence of a reaction to food without previous exposure. Cross-reactivity occurs when an adaptive immune response

to a specific antigen causes reactivity to other antigens that are structurally related to the inducer.<sup>24</sup>

These reactions can be observed between foods of animal source (cow, goat, and sheep milk; cow milk and beef; different fish) or between foods of vegetable origin such as legumes and fruits. There may also be cross-allergy reactions between food and other allergens, such as pollen-plant food syndromes or latex-fruit syndrome.<sup>25</sup>

Several approaches to food allergy prevention and treatment are being investigated including immunotherapy, biologic agents, and microbial therapeutics with promising results. However, the current standard of care for food allergy is still strict food avoidance and use of subcutaneous adrenaline injection pens for administration after accidental exposures.<sup>26-30</sup>

## Food allergy: When to think

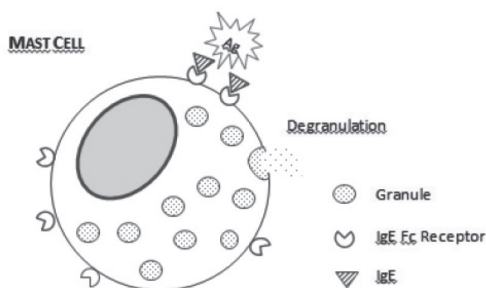
Different target organs can be affected, either singly or simultaneously, making food allergy an entity of broad heterogeneity and wide clinical expression.<sup>3,5</sup>

The type of immune mechanism involved leads to a wide spectrum of clinical manifestations, which may be immediate, occurring from a few minutes to two hours after contact with the allergen (most likely IgE-mediated) or delayed, usually occurring several hours after the exposure (usually non-IgE mediated). In immediate reactions, the symptoms are mostly cutaneous, followed by respiratory, gastrointestinal, cardiovascular, or even potentially fatal anaphylactic reactions. This quick clinical response after exposure usually leads to a clear association to the causative allergen. Delayed and mixed reactions can occur, but they present in an insidious way and with symptoms predominantly involving the gastrointestinal tract and/or the skin, adding difficulties to the clinical investigation.<sup>2,3,5,31</sup>

### IgE-mediated reactions

The pathophysiology of IgE-mediated reactions is based on a shift from the immunological phenotype of T helper 1 (Th1) and T helper 2 (Th2) cytokines with the production of specific IgE antibodies that binds to a specific receptor in mast cells and basophils. In a subsequent contact, the allergen binds to these specific IgE antibodies leading to the activation and degranulation of mast cells and basophils, which triggers the allergic response (Fig. 2).

Immunoglobulin E mediated reactions have an acute onset after allergen exposure, making identification easier. They may present with variable signs and



Fc – Fragment crystallizable; Ig – immunoglobulin.

**Figure 2.** Representative scheme of the mechanism of activation and degranulation of a mast cell.

symptoms, reaching several organs and have potential for serious or even fatal events. Skin reactions, including urticaria, angioedema, and erythema are the most common clinical manifestations of IgE-mediated allergy to food. The typical respiratory symptoms include laryngeal edema, rhinorrhea, and bronchospasm. Gastrointestinal-related signs and symptoms of food allergy include nausea, vomiting, abdominal pain, and diarrhea (Table 1).<sup>32</sup>

Immunoglobulin E mediated food allergy is associated with an increased risk of developing atopic dermatitis and asthma (relative risk 2.4 and 4 times higher, respectively) and with the onset of the allergic march. Asthma as a manifestation of food allergy is uncommon, but food allergy is a risk factor for increased morbidity, mortality, and risk of anaphylaxis in asthmatic patients. Importantly, asthma-related deaths can occur in patients with a history of only mild prior reactions to a specific food.<sup>33-36</sup>

It is important to highlight some IgE-mediated entities, such as the oral allergy syndrome. This typically occurs after the consumption of certain fresh fruits and vegetables in pollen-allergic individuals.<sup>37</sup> Oropharyngeal pruritus and edema of the lips, palate, and pharynx are some of its manifestations. The foods that are usually involved are fruits and vegetables, such as melon, banana, apple, peach, carrot, and celery, among others.<sup>5</sup> In exercise-induced anaphylaxis, exercise itself acts as

a coadjuvant and enhancer of the food allergy (wheat, shellfish, celery), causing serious reactions whenever the ingestion of the culprit food and physical exercise occur close together in time.<sup>35</sup>

### Non-IgE-mediated reactions

Non-IgE-mediated reactions are less frequent and have a non-typical clinical profile, with cutaneous and/or gastrointestinal manifestations usually predominant. As may be an overlap of symptoms with other conditions, differential diagnosis is fundamental.<sup>38</sup> Its pathophysiology is characterized by a cell-mediated mechanism, particularly lymphocytes, eosinophils, and their released mediators.

From the several clinical entities described (Table 2), we emphasize the food protein-induced enterocolitis syndrome (FPIES) as it is a poorly recognized and often underdiagnosed condition. The diagnosis of FPIES is based upon clinical criteria that have recently been defined for both acute and chronic conditions. The major criteria of acute FPIES is the presence of vomiting within 1-4 hours after the ingestion of the suspected food and absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria include diarrhea, lethargy, and hypotension. Although not a criterion for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis. Chronic FPIES presents in a more insidious way with diarrhea, intermittent vomiting, and failure to thrive, with or without dehydration and metabolic acidosis. Importantly, in chronic FPIES, symptoms resolve within days after the elimination of the offending food and return when the food is reintroduced.<sup>39</sup>

Food protein-induced enterocolitis syndrome has a good prognosis during childhood, but it may vary according to the causative food and the age of onset. Usually, if it starts in infancy, tolerance acquisition is expected during infancy. The main recognized culprit foods are cow milk, soy, rice, oats, poultry, and fish, although it may also be caused by vegetables or fruits.<sup>40-42</sup>

**Table 1.** Main clinical manifestations of IgE-mediated reactions

<b>Cutaneous</b>	Erythema Itching Urticaria	Morbilloform rash Angioedema
<b>Respiratory</b>	Cough Dyspnea Chest tightening Wheezing	Laryngeal edema Respiratory distress Nasal congestion and pruritus Sneezing
<b>Anaphylaxis</b>	Systemic reaction of sudden onset with compromise of two or more organ systems	
<b>Other</b>	Ocular Gastrointestinal Cardiovascular	Oral allergy syndrome Exercise-induced anaphylaxis

Ig – immunoglobulin.

**Table 2. Main clinical manifestations of non-IgE-mediated and mixed mechanism reactions**

Non-IgE-mediated reactions	Mixed reactions
FPIES	Atopic dermatitis
Allergic proctocolitis	Eosinophilic esophagitis
Celiac disease	Eosinophilic gastroenteritis
Heiner syndrome	
Allergic contact dermatitis	
Dermatitis herpetiformis	

FPIES - food protein-induced enterocolitis syndrome; Ig - immunoglobulin.

Management relies on allergen avoidance, prompt treatment of acute reactions, anticipatory guidance regarding the introduction of new foods, and periodic reevaluations for tolerance. The ideal timing to determine resolution has not been systematically studied, but can vary considerably by country, nutritional and social food role, and individual preference. In some practices, oral food challenges are usually attempted within 12-18 months after the most recent reaction.

Allergic proctocolitis is also noteworthy, which is a benign transient condition that typically occurs in the first few months of life and presents as bloody stools in a well-appearing infant. Approximately 60% of cases occur in breastfed infants, where the immune response results from the maternal ingestion of the food allergen, usually cow milk, which is passed in immunologically recognizable form into the breast milk. In formula-fed infants, the reaction is associated with cow milk or, less commonly, soy.<sup>43,44</sup> Diagnosis relies on the history of rectal bleeding, exclusion of infections, and other causes of rectal bleeding, and response to an elimination diet, which typically leads to a clinical resolution of gross bleeding within 72-96 hours.<sup>45-47</sup>

In children with atopic dermatitis, late eczematous reactions may occur anywhere from hours to two days following the ingestion of a trigger food. Late eczematous reactions are broadly categorized as non-IgE-mediated, although its pathophysiology is unclear. Food allergen-specific T cells have been shown to be involved. While late reactions may occur in conjunction with immediate reactions, they may also occur as isolated reactions. The overall prevalence of late eczematous reactions is likely underestimated as the existing time gap sometimes hampers the association of food ingestion with the eczema flare.<sup>48</sup>

Heiner syndrome is a rare but reversible non-IgE-mediated hypersensitivity to cow milk resulting in an atypical pulmonary disease in infants and young children. There is often a delay in diagnosis in this disorder due to its unusual presentation with heterogeneous manifestations.<sup>49,50</sup>

### Mixed reactions

Some entities share both IgE and cell mediated mechanisms in their pathophysiology, with expression in different organ systems (Table 2).<sup>5,20,41</sup>

Atopic dermatitis affects 10%-30% of all children and has a multifactorial etiology that appears to result from the complex interaction between defects in skin barrier function, immune dysregulation, and environmental and infectious agents. Children with atopic dermatitis are at high risk of developing food allergies, asthma, and allergic rhinitis. A strong and dose-dependent association between atopic dermatitis, food sensitization, and food allergy has been confirmed by recent reviews, especially in what concerns chronic and severe skin disease. There is also evidence that atopic dermatitis precedes the development of food sensitization and allergy, in keeping with a causal relationship.<sup>51,52</sup> Particularly, the relationship between atopic dermatitis and egg allergy has been well recognized: about 80% of children with egg allergy have atopic dermatitis of varying severity.<sup>5</sup> Eosinophilic gastrointestinal disorders are a manifestation of predominant cell-mediated atopy affecting the gastrointestinal system. Various symptoms may occur depending upon the portion of the gastrointestinal system affected.<sup>53</sup> Eosinophilic esophagitis is a chronic inflammatory disease that affects the esophageal mucosa with the infiltration of eosinophils and consequent impairment of motility. Clinically, and depending on the age of onset, it can manifest itself through vomiting, abdominal pain, dysphagia, gastroesophageal reflux, and food impaction. Although some patients with eosinophilic esophagitis have been found to have positive skin prick tests and/or atopy patch tests to foods and/or aeroallergens, such testing does not accurately identify causative foods in most patients.<sup>54</sup> A thorough personal and family history of other atopic conditions is recommended in all patients with eosinophilic esophagitis. Testing for allergic sensitization may be considered, especially in the 10%-20% of patients who also have symptoms of immediate IgE-mediated food allergy.<sup>55</sup> The main associated foods are dairy, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish, being dairy the most commonly implicated triggering food.<sup>33,35,56</sup>

The management of eosinophilic esophagitis includes dietary, pharmacologic, and endoscopic interventions. Elimination diet of specific foods is associated with clinical and histologic improvement in about 50% of patients, although they do not seem to modify the natural history of eosinophilic esophagitis.<sup>57</sup>

## Food allergy: How to diagnose

### Medical history

The diagnosis of food allergy begins with an exhaustive and complete gathering of the patient's medical history. Factors such as patient age at the time of reaction, time of the first contact with the suspected food, and the time gap between contact and reaction should be investigated. Detailed food diaries are sometimes necessary. It is also important to carefully characterize the food involved, in its natural or cooked form, possibility of co-ingestion, alternative exposure such as cutaneous or inhalation, and the coexistence of other factors such as physical exercise or drugs. Personal and family history should also be investigated for the existence of previous atopic conditions such as asthma, rhinitis, or dermatitis. Detailed physical examination at acute event may demonstrate evidence of an allergic reaction. After resolution, physical examination is most likely to be irrelevant, however, some atopic stigma can be seen.<sup>17,19</sup>

When the suspect food is identified and clinical data is suggestive of an IgE-mediated reaction, complementary diagnostic exams may be performed, always guided by the clinical setting.<sup>58-61</sup>

### In vivo testing

*In vivo* tests have been widely used for its versatility and speed, through skin prick tests (SPT). This method is based on the approach of the allergen to immunocompetent cells, promoting its binding to specific IgE connected to cutaneous mast cells, which activate and degranulate, generating a visible cutaneous inflammatory response in a localized erythematous and itchy papule. A papule with a diameter equal to or greater than 3 mm is considered positive.<sup>62</sup>

Commercial extracts of allergens and lancets of different types can be used to perform the skin tests. Performing skin tests is contraindicated in cases of history of anaphylaxis to the food concerned, significant dermatosis, or use of certain prescription drugs, such as antihistamines.

Although SPT is a simple, safe, and inexpensive method, there are limitations to the availability of the extracts, their stability, and their standardization. As an alternative there is the so-called prick-to-prick test, where fresh foods are used, also placed in contact with the skin and using the same pricking technique. This test is slightly more sensitive than the prick test with commercial extracts. Although it is more sensitive, this test presents a high variability in the

allergenic source, reason why it is less reproducible and it hinders comparative analysis of results.<sup>62,63</sup>

It is essential to make an effective selection of the allergens to be tested, always considering the history of each patient in the relationship between allergen exposure and symptom occurrence. Conducting and interpreting the test results requires experience and expertise. A positive skin test for a given food does not necessarily imply the existence of allergy, but rather a sensitization, not proving that this food is the cause of allergic symptoms. On the other hand, a negative skin test does not immediately rule out the diagnosis of food allergy but makes it less likely. Using an oral food challenge (OFC) as a reference standard, a number of studies have demonstrated a SPT weal diameter at and above which a positive reaction invariably occurred.<sup>64</sup> In 2014, the British Society for Allergy and Clinical Immunology reached a consensus regarding milk, egg, and peanut allergy, establishing SPT values at which the positive predictive value was  $\geq 95\%$ , thereby obviating the need for an oral challenge.<sup>65</sup> More recently, some authors performed a large study that included testing for 11 different food allergens with a standardized oral food challenge to a cumulative dose of 500 mg protein in patients with elevated SPT or specific IgE. This study presented SPT and specific IgE values that were highly predictive of a positive challenge, suggesting oral food challenge may be unnecessary in the subset of patients with values falling above reported cut-offs (Table 3).<sup>66,67</sup>

### In vitro testing

#### Specific IgE assay

When skin tests cannot be performed, serum specific IgE assay will be the test to elect.<sup>6</sup> This is a less sensitive, time-consuming and costly method. Positive IgE serum values ( $\geq 0.35$  kU/L) may indicate allergy or only sensitization, so the clinic becomes essential for its correct interpretation.<sup>68</sup> It is also noteworthy that the probability of occurrence of a clinical reaction increases with the rising concentration of IgE, whose values are standardized in classes for easier interpretation.<sup>69</sup> As for SPT, there are predictive cut-offs pointed with positive predictive value of 95%-98%, which are often referred to as diagnostic values (Table 3).<sup>65,68,70</sup> However, for the vast majority of foods, it is not yet possible to establish the relationship between the IgE values and the occurrence of clinical response, nor its severity. The progressive decrease in serum IgE values may be associated with a likely transient allergy, while stable or increasing specific IgE values point to a permanent situation.<sup>71,72</sup>

**Table 3. Positive predictive value for immunoglobulin E and skin prick test values to specific allergy tests with oral food challenge**

Food allergen	IgE kU/L	PPV (%)	SPT (mm)	PPV (%)
Egg	9.6	100	13.0	100
< 2 years	2.0	≥ 95	5.0	≥ 95
Milk	20.1	96	8.0	100
< 2 years	5.0	≥ 95	6.0	≥ 95
Peanut	10.7	95	9.0	100
Pecan	1.8	100	7.0	95
Wheat	43.1	100	5.5	100
Almond	12.2	100	12.0	100
Cashew	1.2	98	4.5	100
Hazelnut	14.6	73	7.0	100
Sesame	7.5	64	11.0	100
Walnut	13.5	100	4.0	100

Ig - immunoglobulin; O - oral food challenge; PPV - positive predictive value; SPT - skin prick test.

Adapted from Luyt D, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy* 2014;44:642-72.<sup>65</sup> and Sindher S, et al. Analysis of a large standardized food challenge data set to determine predictors of positive outcome across multiple allergens. *Front Immunol* 2018;9:2689.<sup>66</sup>

There are also commercialized kits with groups of food allergens, usually including foods with a high prevalence of sensitization or foods that are similar from the molecular point of view, which may result in a much higher degree of positive IgE test results among related foods than clinical reactions. As an example, more than half of patients with peanut allergy test positive to other legumes, but less than 5% have symptoms of allergy from the ingestion of legumes. Cross-reactivity between aeroallergens and food allergens may result in positive tests to foods, often without clinical allergy (e.g. birch pollen with hazelnut, peanut, soy).<sup>73,74</sup>

The variability observed between different foods and populations, and the accessibility to new techniques, reduced the enthusiasm with which, in the past few years, the relations between specific IgE and clinic settings were analyzed. Despite these limitations, specific IgE assay remains a valid instrument, whenever it is well interpreted.

### Molecular testing

Molecular technology allowed the progression from the study of the allergen extract, which is the mixture of allergenic and non-allergenic components obtained from the allergen source, to the molecular component capable of binding to IgE antibodies, triggering the allergic reaction.<sup>75</sup> These molecular components are divided into groups with a similarity of composition and functionality, called protein families, such as lipid transfer proteins, PR-10, profilins, tropomyosins, and parvalbumins, among others.

Each food may have components sorted in different families, and each family has a different potential to cause symptoms of varying severity. The molecular

structure and physiochemical properties of allergens are major determinants of their clinical relevance. The stability/lability of a molecule (along with the clinical history) helps the clinician to evaluate the risk of systemic versus local reactions. Stable allergens are generally associated with severe systemic reactions, whereas labile allergens are associated with low/mild reactions and cooked food is often tolerated. For instance, in the case of allergies to lipid transfer proteins, located on the skin of some fruits (such as peaches) and resistant to heat and digestion, serious systemic reactions may occur with raw or cooked food, whereas PR-10, because they are thermolabile, can be harmless in cooked foods. International classification ranks the allergenic source first by its scientific name, from which it takes the first three letters of the generic name and the first letter of the species (or two letters when confusion is possible). For example, peach is scientifically called *Prunus persica* and, therefore, *Pru p* indicates the allergen source; different allergenic molecules identified are then order chronologically (e.g. *Pru p 1*, *Pru p 2*, *Pru p 3*).

Molecular based diagnosis is defined as single or multi-plexed IgE assay microarray. By the single-plexed diagnostics, the choice of the components to be tested relies on the clinician's judgment and based on the patient's profile. In poly-sensitized patients it may be reasonable to use the multi-plexed allergen microarray that allows for the detection of specific reactivity to over 100 allergen components. This is particularly useful in patients presenting symptoms of a cross-sensitization to inhalant and food and clinical evidence of food allergy.<sup>76</sup> Molecular testing has allowed a better understanding of the cross-reactivity between foods, and a better awareness of the possible severity and prognosis of food allergy.<sup>75</sup>

It should be noted that the complementary tests described should always be requested in a clinical context and not as a form of random screening. They should be analyzed in a critical and attentive manner, considering that allergen sensitization does not necessarily mean the existence of allergy and, therefore, can never be used as an isolated diagnostic method.

### Other tests

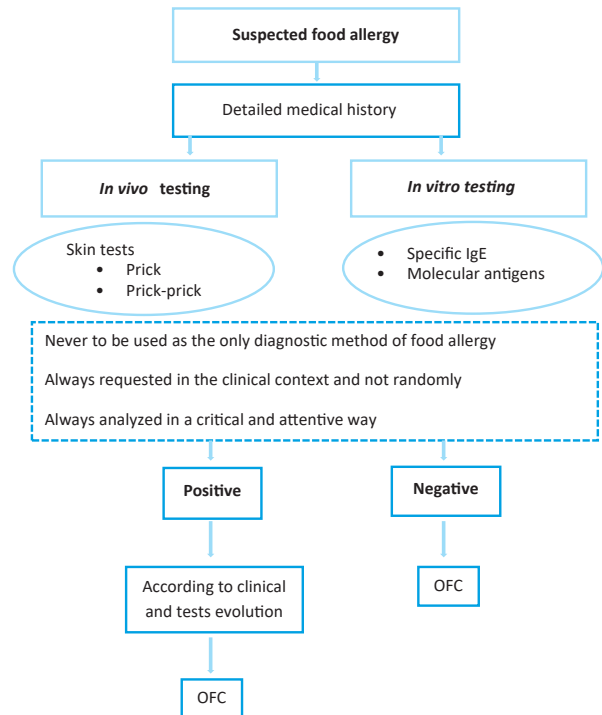
Other diagnostic tests may be considered individually in each clinical setting, including patch test, and basophil activation test, among others. These can be particularly useful in non-IgE-mediated reactions.<sup>36</sup>

## Oral food challenge

Oral food challenge testing is the gold standard to establish the definitive diagnosis of food allergy, to assess the resolution of an allergy and to evaluate the response to an avoided food. In clinical practice, most tests are open (both patient and physician know the food that is being tested), although the gold standard for the diagnosis of food allergy is the double-blind, placebo-controlled food challenge, in which the tested and placebo food are prepared and coded by a third party, not involved in the evaluation. This method is particularly useful in scientific protocols.<sup>77</sup>

The protocols for conducting food challenge tests are not consensual and show some variability between centers, although with common points. Generally, it is accepted that the test must be performed in a facility with means for approaching anaphylaxis (hospital ward, day hospital), always under medical supervision and with collaboration of health personnel trained in emergency response. Not less important is the obtaining of informed consent, with previous clarification about the procedure to both caretaker and child. The challenge should not be undertaken in cases of recent history of anaphylaxis, uncontrolled asthma, current infectious disease, or use of medication interfering with the test. Prior to the test, a complete physical examination should be performed, a peripheral venous access should be placed, and the patient should be monitored. Emergency drugs should be accessible and doses pre-calculated. Permanent monitoring should be ensured. The test protocols must always be adapted to the clinical condition of the patient. In general, only one food should be tried per test, giving less priority to the most easily avoidable food, in case of multiple allergies. The concept of the challenge is the administration of the food to be tested, in increasing quantity, at regular time intervals,

until reaching the total daily dose. The occurrence of symptoms during the challenge leads to its immediate interruption and treatment of the patient, meaning that the test was positive and implying strict avoidance of the food tested. If no symptoms occur during the test, including within two hours of surveillance after the last ingestion, the diagnosis of IgE-mediated food allergy is excluded. The suspected food ingestion should be gradually liberalized, and outpatient follow-up should be ensured (Fig. 3).<sup>78,79</sup>



Ig - immunoglobulin; OFC - oral food challenge.

**Figure 2.** Simplified approach to the diagnosis of food allergy.

## Final remarks

Food allergy has a strong impact on the quality of life of children and caregivers and represents a considerable burden, with physical, psychological, and socioeconomic repercussions. Patients and their families need to be educated and motivated in order to cope with the daily need for food avoidance and awareness for potential allergens. The health professional should be able to diagnose food allergy as well as advise and guide the patient. Furthermore, the health professionals dealing with food allergy should stress the need for creating adequate health policies and implement well-defined strategies.

As food allergies keep growing, there is a need for awareness in our society that can only be achieved by interdisciplinary cooperation between health care, education, and social structures.

### Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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### Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### Provenance and peer review

Not commissioned; externally peer reviewed

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**Alergia Alimentar: Quando Pensar e Como Diagnosticar****Resumo:**

A alergia alimentar é uma reação adversa que ocorre de forma reprodutível após a exposição a um alimento, sendo sempre o resultado de uma resposta imune específica. Verifica-se um acentuado desconhecimento sobre a sua verdadeira prevalência e patogenia, situação preocupante face à constatação de um aumento crescente desta entidade. Estima-se que a sua prevalência possa atingir um pico de 6%-10% no primeiro ano de vida, assumindo posteriormente, na maioria dos casos, um carácter transitório. A alergia alimentar pode atingir diferentes órgãos e sistemas, pelo que deve ser pensada perante uma ampla heterogeneidade e expressividade clínica. É fundamental

o seu diagnóstico ser sempre faseado, alicerçado numa história clínica selecionadora dos exames complementares a realizar, podendo haver necessidade de culminar numa prova de provocação oral que continua a ser o *gold standard* para o diagnóstico de alergia alimentar. Um diagnóstico correto é crucial para evitar exposição ao alimento, com risco de vida do doente verdadeiramente alérgico e para evitar dietas restritivas desnecessárias e muitas vezes com prejuízo nutricional, nos restantes casos.

**Palavras-Chave:** Hipersensibilidade Alimentar/diagnóstico; Hipersensibilidade Alimentar/prevenção & controlo; Literatura de Revisão como Assunto