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# Food Allergy

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**Abstract**

Adverse reactions to food may be produced by several mechanisms and present a great diversity of symptoms, which may be reproducible or not reproducible (occasional adverse food reactions). The reproducible adverse food reactions to minimal or usual amounts of food are classified as hypersensitivity reactions, which may be derived from immune disorders (food allergies) or derived from non-immune conditions (food intolerance). Here, we review the clinical presentations of food allergies according to the underlying mechanisms and causative agents in order to put perspectives over the treatment possibilities.

**Keywords:** Food allergy; Food intolerance; Food hypersensitivity; Child; Diagnosis; Treatment; Allergoid; Sublingual immunotherapy; Oral immunotherapy; Desensitization

## Introduction

Adverse reactions to food have been a medical concern since the time of Hippocrates, who described individuals who had adverse reactions to the ingestion of cheese. Hippocrates intuitively attributed these reactions to some type of "constituent" or "humor" hostile to the cheese that was present in the patient, in greater or lesser amounts, and that acted on the organism under the influence of this food [1]. Despite scientific advances, physicians sometimes feel like Hippocrates when attending patients with specific or nonspecific complaints involving a suspected adverse reaction to food. The characterization of adverse reactions related to the consumption of food can sometimes be a challenge for clinicians who deal in primary care or even to specialists in pediatrics, gastroenterology or allergy and immunology. The attempt to explain the nature (pathophysiology) of these adverse reactions has limitations due to (A) the diversity of possibilities, (B) an incomplete knowledge of the pathophysiological mechanisms involved and (C) the lack of specific tests for diagnosis. The different mechanisms involved and the overlapping symptoms may turn an accurate diagnosis into an elaborate work, especially when more than one mechanism or food is involved. Despite this complexity, the diagnostic process tends to establish a particular diagnosis or a single pathophysiological mechanism in an attempt to "label" the patient and reduce the anxiety of the unknown. Usually a simplified diagnosis is justified because such a diagnosis is sufficient to dispel the uncertainty of the patient (even when symptoms persist) and to postpone a further laborious investigation [2]. This simplified approach is sometimes quite useful, especially when considering patients who have difficulty in dealing with a considerable amount of information or understanding the subtleties of differential diagnosis. In addition, considering the costs of complementary tests, it is even understandable that the doctor remains satisfied with a simplified diagnosis, especially if the patient is assured that the adverse reaction is not a dangerous disease. Once the "guilty food" has been determined, the next step would be to establish or infer the mechanisms responsible for the clinical symptoms.

## Adverse Reactions to Foods

The use of standardized nomenclature [3], which leaves no room for doubt or ambiguous interpretations, is ideal for researchers to draw appropriate conclusions from their experiments [4] and for physicians to provide convenient prophylactic and therapeutic strategies to their patients [5]. The term "food allergy" is often improperly used by the nonprofessional to represent any type of disease supposedly triggered by the ingestion of a specific food [6]. The medical diagnosis of an allergy, however, must necessarily involve knowledge of the mechanism responsible for the immune hypersensitivity [7]. When the triggering mechanism of the symptoms is unclear, the best term to use is "adverse reaction to food" [8]. When the symptoms are not reproducible this is referred to as an "occasional adverse reaction". When the symptoms are reproducible, caused by specific stimuli and typically caused by doses that are tolerated by most people, the adverse reaction ranks as a "food hypersensitivity" [9], a generic term that does not imply the pathophysiology of the related mechanism. When the nature of the hypersensitivity reaction is reportedly caused by immune mechanisms, one can properly employ the term "food allergy". If the mechanisms responsible for the hypersensitivity reaction are defined as non-immune, one should employ the term "food intolerance" or "non-allergic food hypersensitivity". In food allergies, it is convenient to distinguish between IgE-mediated reactions, non-IgE-mediated reactions and reactions of a mixed nature (mediated by both IgE-mediated and non-IgE-mediated mechanisms) [10].

## Epidemiology of Food Allergies

The exact prevalence of food allergies is still unknown. A meta-analysis published in 2007 revealed a significant heterogeneity in the prevalence rates due to the use of diversified methodologies and differences among the populations studied [11]. From 934 articles that were found, only 51 were considered suitable for inclusion. The incidence of self-reported "food allergy" ranged from 3% to 35%. Moreover, the available diagnostic tests are still imprecise and leave room for non-negligible false positives and false negatives. The patient sometimes tolerates the intake of a certain food, and on other occasions presents unequivocal symptoms [12]. Several factors may influence these differences, such as a failure in the protein digestion of the food

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[13], the type of culinary or industry preparation to which the food has been submitted [14], and to engaging in sports after the ingestion of the food [15]. An American estimation situates the prevalence of food allergy at approximately 3.7% of the adult population and 6% of the child population [16].

## Clinical Diagnosis of Food Allergies

The clinical diagnosis of hypersensitivities of an immune nature is based on the symptoms described in the anamnesis, on signs found during the propedeutic examination, on the results of allergy skin tests, on the evidence of oral challenges performed *in vivo*, on the results of laboratory tests performed in vitro and on confrontation tests performed *ex vivo* [17]. The act of diagnosing an immune-allergic disease requires differentiating the disease from a number of other entities with similar profiles of signs and symptoms, which make this, task a complex challenge due to the lack of a gold standard for an unequivocal diagnosis [18]. Some authors have adopted a challenge test with the suspected food allergen under a double-blind placebo-controlled trial as the diagnostic test standard, including electing the challenge test as the "gold standard" [19,20]. However, the challenge tests do not distinguish immune hypersensitivity reactions from non-immune intolerances and are subject to some biases, such as the realization of physical exertion as a trigger of the crisis and/or the use of concomitant adjuvants [21,22]. The challenge tests require the assistance of specialized personnel in the hospital for a prolonged period of observation because these tests are not without risks [23]. The challenge tests have the potential to reveal immediate reactions of relative gravity but are inappropriate for characterizing delayed reactions, such as atopic dermatitis or dermatitis herpetiform. In light of these difficulties, some authors have proposed cut-off levels, based on the concentration of specific IgE at which the chance of a positive challenge test would be significant, in an attempt to make a diagnosis without provocation with the suspected food [24,25]. *In vitro* tests, in contrast, are entirely safe but are usually limited to the serum/humoral component of the patient; however, this compartment is not always the location for the pathophysiology of allergic disease, which often has a delimited anatomical or tissue character. Patients with hypersensitivity mediated by local mediators, such as eosinophilic cationic protein and histamine (indicated by the intestinal luminal dosage after a food challenge), may have normal levels of specific antibodies in the serum, suggesting the local production of the mediators [26]. Thus, a positive specific-IgE measurement confirms a food allergy that clinically manifests while a negative specific-IgE measurement does not exclude the diagnosis of an allergy [27]. Skin tests may also present false-negative and false-positive results, as is the case when food contains nonspecific histamine releasers, such as beta-casomorphin-7, an opioid that is present in bovine milk and is capable of releasing histamine from mast cells [28].

The identification of the responsible food is often a challenge for the clinician, who has few diagnostic tools readily available. The measurement of specific IgE levels and the allergy skin tests have a limited capacity to identify the immediate reactions [29]. Delayed reactions can be identified by the atopic patch test, but this patch test is still far from being standardized for routine clinical use.

In an attempt to overcome these difficulties, some authors have proposed an ex vivo confrontation with the suspected antigen with the two-fold aim of identifying the causative food and the immune mechanism involved. An ex vivo challenge with bovine beta-lactoglobulin (Bos d 5), which was monitored by analyzing the inhibition of leukocyte migration, was enthusiastically described in a prestigious journal of pediatrics as a promising method to replace the oral provocation tests [30]; however, the relative analytical complexity of the test kept this method from becoming popularized as a routine examination, and it had until now received little attention [31]. Tests of lymphocyte proliferation [32] and basophil challenge [33] are used in scientific research, but they are complex and expensive to put into in clinical practice. Thus, each piece of propedeutic information is just one more piece among many others necessary for the compilation of a definitive clinical diagnosis. Any single isolated test has absolute value for the inclusion or exclusion of the diagnosis of a food allergy, but changes above certain threshold levels are strongly correlated with clinical symptoms. Hence, even in high-impact peer-reviewed scientific papers, the inclusion of patients in a study is reasonably acceptable when they have a "convincing history" of allergy because of the difficulty in standardizing a single diagnostic test as a criterion for inclusion or exclusion [34].

## Non-Immune Adverse Reactions to Foods

Adverse reactions to foods may derive from the inherent properties of the food or the physiological characteristics of the individual [35]. The reactions may be caused by toxins (e.g., due to the contamination of food by pathogenic microorganisms and their products) [36] or caused by the presence of pharmacologically active ingredients in food (as with monosodium glutamate symptom complex) [37]. Some of these reactions are difficult to distinguish from a true allergic reaction, as in the case of poisoning by the scombroid toxin [38]. The scombroid toxin is actually the histamine produced by the bacterial enzymatic degradation of the amino acid histidine and is likely to occur in poorly refrigerated foods, such as scombroid fish (tuna, sardines, mackerel, etc.) or Swiss cheeses. Another type of food intolerance is due to the deficiency of a specific enzyme in the affected individual, for example, migraines induced by the ingestion of tyramine-rich foods in individuals with a metabolic defect for processing this amino acid [39] or individuals with lactase deficiency [40].

## Immune Adverse Reactions to Foods

The line of reasoning that classifies clinical allergic reactions into "IgE-mediated" and "non-IgE-mediated" follows a simplified approach, which is shaped by the diagnostic limitations imposed by clinical practice. Although this classification is useful in the management of patients, it is far from reflecting the pathophysiology of the problem [41]. Several classifications have been proposed for food allergies.

## Classification of Food Allergies

Food allergies can be classified according to the nature of the hypersensitivity reaction, according to the nature of the allergen or according to the immune context in which they are presented.

### Classification according to the nature of the hypersensitivity

Scientific discoveries in the field of immune reactions to food proteins followed the proper characterization of these proteins. In a time when the primary structure of the proteins was unknown, experiments with anaphylactic guinea pigs and their respective antibodies (reagins and precipitins) were considered to be elements for understanding the biochemical nature of the protein itself more than for understanding the allergic phenomenon. The specificity of antigen-antibody interactions and the biological consequences of these interactions generated a branch of study called the "chemistry of anaphylaxis", which in the early twentieth century generated the first reviews. One of the most cited reviews was published by Gideon Wells in 1911 and

focused on the proteins isolated from chicken eggs and cow's milk [42]. Another important landmark was Gell and Coombs' classification of hypersensitivity reactions in 1963 [29]. The IgE-mediated reactions are the Type 1 hypersensitivity reactions and directly degranulate the effector cells (mast cells and basophils) with the release of autacoids and chemotactic agents for eosinophils. The Type 2 reactions are characterized by antigen-antibody interactions that activate complement and stimulate the local production of anaphylatoxins (C3a and C5a) that degranulate mast cells and basophils and recruit polymorphonuclear leukocytes. Type 3 reactions are triggered by circulating immune complexes but also depend on cytotoxic effector cells and the complement system. Type 4 reactions are T cell-mediated and are independent of specific serum antibodies. It has been proposed to include into this classification the type 5 or granulomatous reactions [43]. In addressing the nature of the immune responses, one must distinguish which of the four (or five) types of hypersensitivity reactions may be involved. In clinical practice, this is not always possible, and in most cases, the attending physician simply classifies the immune reactions as "IgE-mediated" (type 1 of Gell and Coombs) or "non-IgE" (types 2I, 3 and 4 of Gell and Coombs) [44]. Some syndromes are understood to have a mixed nature, where mechanisms mediated by both IgE- and non-IgE-mediated mechanisms jointly participate in the pathophysiology of the process [45].

## Classification according to the nature of the allergen

According to the nature of the allergen, food allergies can be divided into two groups or classes. In the so-called class 1 food allergy, the allergens are resistant to gastric digestion, and the sensitization process occurs in the gastrointestinal tract [46]. A class 1 food allergy is rare in adults but affects children as one of the first manifestations of the atopic syndrome. The most prevalent allergens in this class are cow's milk, hen eggs and some vegetables. Generally, these manifestations disappear during the course of childhood and are replaced by other manifestations (allergic march) [47]. The class 2 food allergy is elicited by allergens susceptible to gastric digestion. Class 2 food allergies are seen predominantly in adults and develop as a result of sensitization by inhalation. The immunological basis for this form of allergy is the cross-reactivity (which may be manifested or clinically irrelevant). The symptoms range from an oral allergy syndrome (pollen-fruit syndrome) to anaphylactic shock [48]. Most of the proteins that elicit this class of allergies are highly labile and difficult to extract and characterize, which makes the diagnostic procedures even more complex [49]. In addition to these classical clinical manifestations associated with different forms of hypersensitivity, there are a number of others reported in the literature, in which a possible association with some form of food hypersensitivity is not well-established [50]. Although extremely useful, laboratory tests and skin tests are not always able to identify the various forms of food allergies and the mechanisms responsible for the hypersensitivity in certain patients, and the insight and experience of the attending physician are essential for the establishment of a strong suspicion or diagnostic conclusion [51].

## Classification according to the immune context

A classification of allergic phenotypes according to the immune context presented by the individual has also been proposed, which separates the allergies into three classes (atopy, monoallergy and non–IgE-mediated allergy). These classes are not mutually exclusive because they can overlap [52].

**Atopy:** Atopic diseases include atopic dermatitis, allergic rhinitis and asthma and develop within a complex genetic background. The concept of atopy, initially described by Coca in 1923 [53] refers to a personal or familial predisposition to produce IgE antibodies in response to specific allergens [54]. Atopy is characterized by increased levels of total serum IgE. The atopic allergic disease often begins in children when an allergic inflammation affects a single organ, such as the skin, the lung, the nose, or a combination of all of these. Cutaneous manifestations of an allergy usually represent the beginning of the atopic march. Approximately two-thirds of the affected individuals with atopic dermatitis develop allergic rhinitis and half develop asthma. The onset of an atopic march is characterized by the IgE-mediated sensitization to food allergens, which subsequently evolves to inhaled allergies [52].

**Monoallergy:** Monoallergy (allergic breakthrough) is characterized by the development of a specific IgE-mediated hypersensitivity in the absence of an increase in the level of total IgE in non-atopic individuals. The monoallergy can develop at any time of life without any predisposing factors. It manifests itself as an anaphylactic event with insect venom, some foods or medicines or with the involvement of a particular organ, such as rhinitis, asthma or dermatitis. Usually, monoallergies respond well to allergen-specific immunotherapy [52].

**Non–IgE-mediated allergy:** Some individuals with atopic dermatitis, asthma and/or rhinitis have normal levels of total and specific-IgE and non-reactive allergy skin tests. This third type of allergy has been called a "non-atopic", "non-IgE associated" allergy or, formerly, intrinsic asthma, dermatitis and/or rhinitis [52].

## Classification according to clinical presentation

As a systemic disease, an allergy may theoretically manifest itself in any organ system. When classifying food allergies, it is useful to differentiate the digestive manifestations from the non-digestive manifestations. This separation leads us to a local and/or systemic pathophysiology [45].

**Digestive manifestations of food allergy:** In general, it is difficult to classify all types of presumed immune hypersensitivity reactions to foods under a single unifying concept. From a mechanistic standpoint, most reactions are often more so presumed rather than proven to be of an immune nature. The best criteria are the involvement of IgE antibodies and mast cell activation. The finding of mucosal eosinophils is suggestive of immunoreactivity but does not constitute in itself a diagnosis of immune hypersensitivity. Regardless of the mechanism involved, the symptoms of gastrointestinal hypersensitivity are similar and differ according to the type of onset, severity and persistence [55].

- Immediate gastrointestinal hypersensitivity: Immediate gastrointestinal hypersensitivity is defined as an IgE-mediated gastrointestinal reaction that is often accompanied by manifestations in other organs, such as the skin and lung. The most prominent symptoms after eating the offending food are gastric hypotonia, pylorospasm and subsequent alteration of the bowel, leading to vomiting and diarrhea. After contact with the antigen, the mucosa becomes hyperemic and edematous. Biopsies taken before and after the confrontation indicate a decrease of stained mast cells and tissue histamine after the food challenge [55].

- Oral allergy syndrome: The oral allergy syndrome usually affects individuals who are allergic to pollen. This syndrome is a form of IgE-mediated allergy usually confined to the oral cavity and is characterized by a rapid onset of itching, tingling and swelling of the lips, tongue, palate and throat. The oral allergy syndrome involves cross-reactivity with fruits and latex proteins and is usually triggered by conformational epitopes denatured by boiling and/or by peptic digestion [56].

• Eosinophilic esophagitis: Eosinophilic esophagitis is a mixed hypersensitivity (IgE-mediated and non-IgE-mediated) that occurs more frequently during childhood and adolescence and involves chronic esophagitis with or without gastroesophageal reflux. It is manifested by dysphagia, vomiting, refusal to eat, abdominal pain, irritability, sleep disturbance and esophageal strictures refractory to antacids. The patients are often reactive to various foods. A biopsy reveals mucosal and submucosal infiltration with eosinophils [57].

• Allergic eosinophilic gastritis: Allergic eosinophilic gastritis is a mixed hypersensitivity (IgE-mediated and non-IgE-mediated) that occurs most often between the ages of childhood and adolescence. It is manifested by postprandial vomiting, abdominal pain, anorexia, early satiety, hematemesis, poor weight gain and pylorospasm. A gastric biopsy reveals eosinophilic infiltration of the mucosa and submucosa, particularly in the antrum [58].

• Allergic eosinophilic gastroenterocolitis: Allergic gastroenterocolitis occurs at any age and manifests with symptoms similar to allergic gastritis and esophagitis. Weight loss and stature delay are prominent. Enteropathy can trigger a loss of proteins and cause hypogammaglobulinemia and hypoalbuminemia. The esophagus and duodenum biopsies reveal eosinophilic infiltration of the mucosa and submucosa and a biopsy of the colon may reveal cryptic abscesses [59].

• Dietary protein enterocolitis: This condition is not mediated by IgE and is more frequently observed in the first months of life, manifested by irritability, vomiting and diarrhea, which can lead to dehydration. Vomiting occurs 1-3 hours after feeding and diarrhea occurs 5-8 hours afterwards. In children, dietary protein enterocolitis is usually caused by cow's milk, soy, egg, wheat, rice, peanuts, chicken or fish. In adults, similar symptoms can be caused most commonly by seafood. The examination reveals occult blood, neutrophils, eosinophils and Charcot-Leyden crystals in the fresh stool. It has been suggested that this condition is mediated by the antigen-induced secretion of inflammatory cytokines by T lymphocytes [60].

• Dietary protein proctitis: IgE does not mediate this condition, and it is more common in the first months of life. Dietary protein proctitis presents with diarrhea, steatorrhea, inadequate weight gain, vomiting, bloating and malabsorption. The most frequent cause is non-IgE-mediated hypersensitivity to cow's milk, but the reaction can be caused by soy, egg, wheat, rice, chicken or fish in older children. The biopsy reveals villous atrophy with increased crypt length and intraepithelial lymphocytes [61].

• Celiac disease: Celiac disease is associated with an increased transglutaminase activity toward the glutamine linked to gliadin in the mucosal tissue. The glutamine residues are deaminated by transglutaminase, which creates epitopes that are able to bind to T DQ2 lymphocytes in the intestine. The transglutaminase is also the target of anti-endomysium and anti-transglutaminase antibodies. These antibodies, as well as antibodies against deaminated gliadin peptides, can be used as diagnostic tools. It is believed that the formation of a single gliadin epitope altered by the action of transglutaminase leads to the activation of T DQ2 lymphocytes, which in turn leads to the breakdown of tolerance and the initiation of the autoimmune process that generates the intestinal inflammation [62].

• Irritable bowel syndrome and food allergy: Irritable bowel syndrome is a complex functional entity that is still unclear. It is believed to be due to a nervous system disorder with a central visceral component suggested by changes that were detected with the aid of magnetic resonance imaging and evoked potential [63]. Nevertheless, there is an associated inflammatory component, and several studies have shown an increased production of cytokines and an increase in the number of immunocytes, such as intraepithelial lymphocytes, macrophages and mast cells, in the biopsies conducted in these patients. These changes are often interpreted as being secondary to the changes in the intestinal microbiota. Because there is no characteristic finding, the diagnosis is made by exclusion and algorithms based on the clinical symptoms (Manning, Rome I, Rome II, Kruis) [64]. Patients with symptoms similar to irritable bowel syndrome underwent elimination diets and were monitored with regard to the levels of eosinophil cationic protein and trypsin, which showed evidence of a concomitant food allergy in 25% of the cases [65,66].

**Non-digestive manifestations of food allergies:**

• Cutaneous manifestations: Food allergy is one of the causes of atopic dermatitis [67], urticaria [68], exercise-induced urticaria [69] and contact urticaria [70].

• Respiratory: Food allergy is associated with asthma [71-73], pulmonary hemosiderosis (Heiner syndrome) [74], persistent cough and rhinitis [75].

• Systemic manifestations: Food allergy can trigger anaphylaxis by ingestion [76] and other means than ingestion. There are reports of cases caused by skin contact, and inhalation of food components added to inhalers [77-79]. Food allergies can also produce anaphylaxis triggered by exercise [15].

## Treatment

The treatment of food allergy consists on removing the allergens identified as sensitizing agents. Therefore, the correct diagnosis of the causative agents is essential to the treatment. Sometimes, a patient develops allergies to more than one food so a broad triage with cutaneous tests with habitual ingested ingredients can alert about sensitization to unsuspected antigens. The subsequent exclusion diet and re-introductory oral challenge will confirm (or not) the hypersensitivity. The development of appropriate strategies for desensitization is a need for changing the clinical course promoted by food allergies [80]. Protocols for induction of oral tolerance have been described with unmodified allergens, however, the use of natural antigens have a greater chance of eliciting allergic reactions that halt the progression of immunotherapy [81-83]. Modified allergens (allergoids) have been used for desensitization protocols to minimize allergic reactions produced by natural antigens [84,85]. Proteins with equivalent epitopes, but less allergenic, can be obtained by gene recombination technology, but this is an expensive methodology [86]. Extended cooking, a more accessible approach, have been used on the assumption that the destruction of conformational epitopes may become the protein less allergenic and, therefore, safer for oral administration [87,88]. However, this physical denaturation may destroy the linear epitopes which are necessary to induce the state of tolerance [89]. The rational design to a safe and effective tolerance induction protocol includes the use of immunogenic proteins (that retain relevant linear epitopes) with reduced allergenicity (submitted to inactivation of the relevant conformational epitopes) [90]. The inactivation of conformational epitopes may also be achieved by the use of enzymatic polymerization, a technique already used by food engineers to modify the consistency of industrial food, as well a promising strategy for food allergy desensitization [91,92]. Studies are been designed to analyze better ways to achieve this goal, either

by oral or sublingual/oral administration, with a focus on the innate tolerogenic properties of the oral mucosa [93,94].

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