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Update on Food Allergy 2025: Joint Position Statement of the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Atualização em Alergia Alimentar 2025: posicionamento conjunto da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

Lucila Camargo Lopes de Oliveira[1], Luciana Rodrigues Silva[2], Jackeline Motta Franco[1,2], Alexandra Sayuri Watanabe[1], Abelardo Bastos Pinto Júnior[2], Albertina Capelo[1], Ana Paula Beltran Moschione Castro[1], Antônio Carlos Pastorino[1,2], Ariana Campos Yang[1], Bruno A. Paes Barreto[1,2], Cristina Targa Ferreira[2], Ekaterini Simões Goudouris[1,2], Elisa de Carvalho[2], Elza Daniel de Melo[2], Fabiane Pomiecinski Frota[1], Germana Pimentel Stefani[1], Gustavo Falbo Wandalsen[1,2], Hélcio Maranhão[2], Herberto José Chong Neto[1,2], Ingrid Pimentel Cunha Magalhães Souza Lima[1], Jocemara Gurmini[2], José Carlison Santos de Oliveira[1], José Luiz Magalhães Rios[1], Mauro Batista de Moraes[2], Natália Rocha do Amaral Estanislau[1], Renata Rodrigues Cocco[1], Rossiclei Pinheiro[2], Valéria Botan Gonçalves[1], Clóvis Francisco Constantino[2], Fátima Rodrigues Fernandes[1], Fábio Chigres Kuschnir[1,2], Dirceu Solé[1,2]

ABSTRACT

The global increase in the prevalence of food allergy (FA) has elevated it to a public health concern. FA accounts for a number of adverse food reactions, typically presenting early in life. Its diverse clinical manifestations depend on the specific immunological mechanisms involved (IgE, non-IgE, or mixed). The identification of various clinical presentations and new laboratory methods have enhanced the accuracy of etiological diagnosis. This includes improved understanding of cross-reactivity between foods and the identification of markers indicative of transient, persistent, or severe clinical courses. The standardization oral food challenge tests has enhanced their safety and enabled their inclusion among the tools available for the etiological confirmation of FA, in addition to contributing to a better characterization of both food protein-induced enterocolitis syndrome and eosinophilic esophagitis. Despite the identification of new risk factors and food allergens, elimination of the offending food from the diet remains the primary treatment approach. For patients with cow's milk protein allergy, the availability of specialized formulas has facilitated replacement treatment. This document reviews the current approach to anaphylaxis, the most severe IgE-mediated FA,

RESUMO

A prevalência da alergia alimentar (AA) tem aumentado em todo o mundo, o que a torna um problema de saúde pública. Responde por parte das reações adversas a alimentos, tem início geralmente precoce e suas manifestações clínicas variadas dependem dos mecanismos imunológicos envolvidos (IgE, não IgE ou misto). A identificação das variadas formas clínicas de apresentação, aliada à aquisição de novos métodos laboratoriais, possibilitaram a realização do diagnóstico etiológico de modo mais preciso, sobretudo quanto à reatividade cruzada entre alimentos e mesmo na identificação de marcadores indicativos de formas clínicas transitórias, persistentes e quadros mais graves. A padronização dos testes de provocação oral permitiu a sua realização de forma mais segura e possibilitou a sua inclusão entre as ferramentas disponíveis para confirmação etiológica da AA, assim como a melhor caracterização da Síndrome da enterocolite induzida por proteína alimentar e da Esofagite eosinofílica. Apesar da identificação de novos fatores de risco e de novos alérgenos alimentares, a exclusão do alimento responsável pelas manifestações clínicas continua sendo a principal conduta terapêutica. Entre os pacientes alérgicos às proteínas do leite de vaca, a disponibilidade de fórmulas especiais

1. Associação Brasileira de Alergia e Imunologia (ASBAI).
2. Sociedade Brasileira de Pediatria (SBP).

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since food is the main etiological agent in children. Additionally, it addresses advances in the management of certain gastrointestinal manifestations of FA. Oral immunotherapy is increasingly used in the treatment of FA, and immunobiologicals are also addressed in light of the most recent scientific and clinical evidence, in addition to considerations on the natural history of FA and the available forms of prevention. Based on the 2018 Brazilian Consensus on Food Allergy, this document provides an updated review of diagnostic methods and treatment regimens for patients with FA. A team of experts, including allergologists, gastroenterologists, dietitians, and pediatricians, contributed to this update, with the goal of outlining best practices in therapeutic approaches and patient monitoring.

Keywords: Food hypersensitivity, risk factors, anaphylaxis, skin prick tests, specific serum IgE, diagnosis, immunotherapy, hypoallergenic formulas.

tem facilitado o tratamento substitutivo do leite de vaca para esses pacientes. A abordagem atual da anafilaxia (forma mais grave de AA mediada por IgE) é revisada, uma vez que os alimentos são os principais agentes etiológicos em crianças. Avanços na conduta de algumas manifestações gastrintestinais também são abordados. Na atualidade, a imunoterapia oral tem sido cada vez mais utilizada, e os imunobiológicos também são apresentados à luz das evidências científicas e clínicas atuais, assim como considerações sobre história natural da AA e formas de prevenção da AA. Este documento, baseado no Consenso Brasileiro sobre Alergia Alimentar de 2018, reuniu especialistas no tratamento da AA (alergologistas, gastroenterologistas, nutrólogos e pediatras) que revisaram e atualizaram os métodos diagnósticos e esquemas de tratamento disponíveis e empregados no acompanhamento de pacientes com AA, visando a melhor abordagem terapêutica desses pacientes.

Descritores: Hipersensibilidade alimentar, fatores de risco, anafilaxia, testes cutâneos, IgE sérica específica, diagnóstico, imunoterapia, fórmulas hipoalergênicas.

Introduction

Since the publication of the Brazilian Consensus on Food Allergy in 2018, a document developed by the Brazilian Association of Allergy and Immunology in partnership with the Brazilian Society of Pediatrics, not only has the frequency of complaints related to possible food allergies (FA) increased, but the number of potentially involved foods has also expanded. Advances in the pathophysiological understanding of the different clinical presentations of FA have allowed less expectant and more interventionist approaches, as well as the implementation of primary and secondary prevention measures to improve the quality of life of patients and their caregivers.

In this context, the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics deemed it essential to update the previous document.

Definition

In 1906, Austrian physician Clemens von Pirquet introduced the term “allergy,” derived from two Greek words: “allos,” meaning “other” or “different,” and “ergon,” meaning “work” or “activity.” This combination was chosen to describe an altered or exaggerated immune response by the body to certain substances.[1]

FA is a clinical condition in which the immune system reacts in an exaggerated and consistent manner to a specific food upon exposure. It is important to distinguish FA from food intolerance, which is a nonimmune reaction that involves toxic, metabolic, pharmacological, and undefined mechanisms triggered by the ingestion of certain foods.[2] Therefore, what differentiates FA from other adverse food reactions is its immunological nature.

Classification

FAs are classified into three categories based on the immunological mechanism involved: immediate or immunoglobulin (Ig) E-mediated reactions, delayed or non-IgE-mediated reactions, and mixed reactions involving both mechanisms (Table 1). Understanding these mechanisms is crucial for establishing the correct diagnosis and appropriate treatment in each clinical scenario.

IgE-mediated reactions most often occur from a few minutes to 2 hours after exposure; manifestations after this period may occur in cases of delayed anaphylaxis to red meat and food-dependent exercise-induced anaphylaxis.[3]

Table 1
Classification of food allergies according to the immunological mechanism involved and their clinical presentation[4]

Immunological mechanism	Clinical presentation
IgE-mediated	Contact urticaria
	Systemic urticaria/angioedema
	Immediate gastrointestinal food hypersensitivity
	Oral allergy syndrome
	Anaphylaxis
	Food-dependent exercise-induced anaphylaxis
Non-IgE-mediated	Proctitis and food protein-induced allergic proctocolitis
	Food protein-induced enterocolitis syndrome
	Food protein-induced enteropathy
	Heiner syndrome
	Dermatitis herpetiformis
	Food-related contact dermatitis
Mixed	Eosinophilic esophagitis
	Eosinophilic gastritis
	Eosinophilic gastroenteritis
	Eosinophilic colitis
	Atopic dermatitis (with exacerbation of food-induced eczema)

IgE: immunoglobulin E.

Non-IgE-mediated immune mechanisms are typically responsible for gastrointestinal and cutaneous symptoms, emerging hours to days after exposure.[4] Among mixed manifestations, which involve both mechanisms, the most notable are atopic dermatitis and eosinophilic gastrointestinal disorders.[4]

Epidemiology

FA is a global public health concern, affecting approximately 8% to 10% of children and adults, with varying prevalence worldwide.[5] This variability reflects not only different methodological approaches and diagnostic criteria but also genetic, environmental, and socioeconomic particularities.[6,7]

Over the years, the epidemiological trajectory of FA has been driven by environmental factors that start affecting individuals in the intrauterine period. These factors are associated with lifestyle changes, particularly dietary habits and increased consumption of processed foods, and have contributed – through mechanisms not yet fully understood – to the undeniable increase in FA prevalence.[5]

Epidemiological studies based on questionnaires and forms, in which families and/or patients self-identify as allergic, offer a more accessible and cost-effective method for research but are less accurate for determining true FA prevalence. Large population-based cohort studies using oral provocation tests (OPTs) would yield more reliable data but are more difficult and costly to conduct.[8,9] A recent systematic review estimated the pooled lifetime and point prevalence of FA to be 19.9% and 13.1%, respectively. Point prevalence of sensitization based on specific IgE was 16.6%,

compared to 5.7% with the skin prick test and only 0.8% with the OPT.[10] FA is more prevalent in developed countries and urban areas[10] and is more common in children than in adults.[11] In developing countries, accurate prevalence estimates are difficult to establish due to limited data.[5]

In Brazil, data on FA prevalence are scarce and typically limited to specific populations, making broader assessments challenging. A study by Brazilian pediatric gastroenterologists found a prevalence of suspected cow's milk protein allergy (CMPA) in the study population of 5.4%, with an incidence of 2.2%.[12] In a study by Gonçalves et al., the prevalence of parent-reported FA in infants was 23.5%, but only 1.9% were confirmed by OPT.[13] Cow's milk was the most common allergen.[13] Similarly, the prevalence of parent-reported FA in preschoolers (aged 4 to 59 months) was 17.6%, but only 0.61% was confirmed. Cow's milk and egg were the predominant allergens.[13] Silva et al. investigated the prevalence of FA in Brazilian adults (aged 18 to 65): 10.8% reported symptoms, but only 1.0% were confirmed as allergic upon medical evaluation. The most frequently implicated foods were fruits, cow's milk, shrimp, pork, and vegetables.[14] The dietary profile of Brazil's Northeast region shows unique characteristics. A cross-sectional study involving preschoolers (aged 2 to 6) enrolled in municipal urban schools (March to June 2019) documented a self-reported FA prevalence of 11.7%, lower than most previous studies. The foods most frequently cited by parents were shrimp, pork, and other seafood.[15]

Similarly, data on the prevalence and incidence of anaphylaxis in Brazil are also limited.[16-18] A longitudinal study evaluated anaphylaxis incidence among children and adolescents (< 18 years of age) seen in the emergency department of a private pediatric hospital in São Paulo between January 2016 and December 2018, with diagnoses potentially related to anaphylaxis. Based on the total number of emergency visits, the mean annual incidence of probable anaphylaxis cases was 0.013% in 2017, 0.016% in 2018, and 0.014% in 2019. The most frequently involved foods were cow's milk, nuts, banana, fish, seafood, and wheat.[18] A survey of Brazilian allergists identified the main causes of anaphylaxis in children and adults as medications (nonsteroidal anti-inflammatory drugs and antibiotics), followed by foods (cow's milk and egg white in infants and preschool children; shellfish in older children, adolescents, and adults), and insect stings (fire ants, bees, and wasps). In approximately 10% of cases, no cause was identified (idiopathic anaphylaxis).[16,19]

Food hypersensitivity may be influenced by age at diagnosis and by the type of food involved in the reaction.[20] A limited number of foods account for the majority of FA cases, including peanut, tree nuts, fish, shellfish, egg, cow's milk, wheat, soy, and seeds.[11] In a recent systematic review, Spolidoro et al. compared prevalence estimates for the 8 major food allergens in Europe from 2000 to 2021 and found no significant changes in their prevalence rates.[10]

In Brazil, the multicenter PROAL (Brazilian Allergy Project) study evaluated specific IgE levels in patients seen at referral allergy centers in several regions of the country. The study was conducted in two phases: first in 2004 (PROAL I) and again after 12 years, in 2016 (PROAL II). Among the evaluated foods, a significant increase in sensitization to cow's milk, peanuts, and corn was observed over the period, with a trend toward increased sensitization to other foods as well.[21]

Typically, allergic adults have experienced FA since childhood, indicating that most adult FAs begin early and persists over time. However, recent data from the U.S. suggest that adult-onset FA may be more common than previously thought, potentially affecting up to half of food-allergic adults.[22]

Pathophysiology

The gastrointestinal tract serves as a barrier to the external environment, and its surface is designed for processing and absorbing food. Several immunological and non-immunological mechanisms work together to prevent the entry of external agents, such as microorganisms and food antigens, into the body. Under normal conditions, the absorption of food proteins occurs without their antigens inducing clinical manifestations.[23]

However, proteins and microorganisms in the intestinal lumen interact with the intestinal immune system located at the epithelial surface and lamina propria. This interaction leads to the development

of oral tolerance, which is defined as the active suppression of immune responses to food antigens or potentially beneficial microorganisms that come into contact with the intestinal mucosa. With regard to food proteins, oral tolerance is the default response to the introduction of new foods and beneficial microorganisms.

In this context, when interacting with intact or partially hydrolyzed proteins, the intestinal immune system is normally stimulated toward inducing oral tolerance. During this normal response, IgG and IgA may be produced, but they do not trigger undesired adverse reactions. However, when oral tolerance does not occur, immune reactions to food or microbes can lead to FA. The mechanisms involved in this failure likely include interactions among multiple factors.[24] It is currently believed that changes in the composition of gut microbiota – especially during the first months of life – play a role in this process, interfering with normal immune function and promoting inflammation and allergic disease.[24]

It is worth noting that oral tolerance in animal models is measured by a reduction in the production of antigen-specific antibodies, decreased cytokine production by lymph nodes, and fewer clinical hypersensitivity manifestations upon antigenic stimulation.[24] In humans, no clinically applicable diagnostic method currently exists to identify oral tolerance in non-IgE-mediated reactions. Therefore, in clinical practice, oral tolerance can only be identified through exposure – either supervised (OPT) or unsupervised (home exposure).

The processes involved in the development of oral tolerance can be broadly divided into two stages: (1) antigen uptake from the intestinal lumen, and (2) the natural development of oral tolerance.[25]

Pathways of antigen uptake and transportation to the intestinal immune system include:

– Microfold cells: flattened epithelial cells overlying the Peyer's patches that are specialized in the uptake of particulate antigens such as viruses and bacteria. They are associated with IgA production.
– Transcellular (in vesicles) and paracellular (between cells): involved in the capture of soluble antigens. In the transcellular route, antigens pass in vesicles that are degraded by lysosomes. However, a small fraction of partially degraded antigens may be released into the basolateral space and interact with major histocompatibility complex (MHC) class II molecules and dendritic cells (DCs).
– Goblet cells: involved in the uptake of soluble antigens, producing goblet-cell-associated antigen passages. Goblet-cell-associated antigen passages deliver antigens exclusively to CD103+CX3CR1- lamina propria DCs, a type of DC that participates in the development of oral tolerance. Increased mucin secretion is associated with increased frequency of goblet-cell-associated antigen passages and, therefore, greater delivery of antigens to DCs.
– Other routes of antigen uptake: antigens in the intestinal lumen can be captured by dendrites from macrophages (DCs). This process does not compromise epithelial integrity.[25]

CD103+CX3CR1- DCs transfer peptide-MHC class II complexes to CD103+ DCs, which migrate to the lymph nodes and present antigen to naïve T cells.[25] Following antigen capture, CD4+CD25+Foxp3+ regulatory T cells (Tregs) play a fundamental role in the induction of oral tolerance.[25] Other Treg populations are also involved in this process and express transforming growth factor (TGF)-β, promote Foxp3+ Treg induction, and produce interleukin (IL) 10. After antigen uptake by CD103+ DCs in the lamina propria, naïve T cells differentiate into Tregs through a mechanism dependent on TGF-β and retinoic acid. These Tregs migrate back from the lymph nodes to the lamina propria, where they proliferate.[25]

The gut microbiota also plays a crucial role in oral tolerance. In mice, an altered microbiota was shown to be associated with impaired oral tolerance. Although it is unknown if a specific microbiota species is associated with FA, certain species of *Clostridium*, *Bifidobacterium*, and *Bacteroides* have been associated with FA suppression in mice. The gut microbiota, particularly *Clostridia* species, interacts with Tregs to suppress type 2 helper T cell (Th2) response.

The microbiota also contributes to mucosal integrity, immune regulation, and gut motility.[25]

In summary, food antigens are transported to mesenteric lymph nodes by DCs expressing high levels of retinaldehyde dehydrogenase, indoleamine 2,3-dioxygenase, and TGF-β, facilitating the differentiation of naïve T cells into Tregs. These Tregs express gut-homing markers such as CCR9 and α4β7 integrin and migrate back to the lamina propria. There, expansion of Tregs is induced by high levels of IL-10 produced by macrophages. Granulocyte-macrophage colony-stimulating factor produced by group 3 innate lymphoid cells also contributes to Treg homeostasis by acting on DCs and macrophages. When oral tolerance is not developed, hypersensitivity reactions may occur, leading to the different clinical presentations of FA.

Immunoglobulin E-mediated food allergy

IgE-mediated food-allergic reactions are type I hypersensitivity reactions (Gell and Coombs classification) that occur as a result of loss of oral tolerance following exposure to a food antigen, which is mistakenly recognized as a pathogen by the immune system. The underlying pathophysiology includes disruption of the epithelial barrier – whether gastrointestinal or cutaneous – and genetic predispositions that favor protein absorption and stimulate the release of inflammatory cytokines (alarmins, IL-4, IL-5), which activate DCs into acquiring a Th2 phenotype. This ultimately results in the production of food antigen-specific IgE by B lymphocytes.[26]

Once produced, antigen food-specific IgE binds to the membranes of mast cells and basophils. However, the mere presence of specific IgE does not equate to clinical reactivity: the initial contact may only induce a state of sensitization, characterized by the presence of IgE antibodies without symptoms of allergy. Symptoms are triggered upon subsequent exposure to the same protein if this exposure is capable of provoking the release of preformed mediators (eg, histamine and others stored within effector cells) and newly formed mediators (eg, prostaglandins). Recently, specific IgE physicochemical characteristics (such as glycosylation in the constant region of the antibody) have been associated with a higher risk of developing allergic symptoms in sensitized individuals.[27]

Allergic responses develop in subsequent exposures after sensitization, particularly in genetically predisposed individuals. The production of additional specific IgE antibodies beyond those already bound to mast cells and basophils can lead to membrane rupture and the release of chemical mediators by these effector cells.[28] Prior sensitization is a prerequisite for triggering the described immunological cascade. Antigen exposure can occur via several and sometimes unknown routes, including ingestion, inhalation, transmission through breast milk, or even transdermal exposure. Key components of the immune system involved in the induction of either oral tolerance or sensitization include the epithelium, innate immune cells, T and B lymphocytes, and effector cells such as mast cells, eosinophils, and basophils. The hallmark of IgE-mediated FA is the immediate reaction, with symptoms appearing within minutes to a few hours after exposure to the causal food. These reactions often manifest as cutaneous symptoms, including urticaria and angioedema. IgE-mediated food-induced anaphylaxis represents the most severe expression of this type of allergy.[26]

Non-immunoglobulin E-mediated food allergy

Although its mechanisms are not yet fully defined, non-IgE-mediated FA is believed to occur when there is a defect in the development of oral tolerance – meaning an inability to recognize and ignore food antigens and beneficial bacteria, and instead triggering defensive immune mechanisms.[23,25] Abnormalities in oral tolerance are causal factors in this process and, when restored, may lead to the resolution of FA. Thus, oral tolerance represents a potentially useful target for FA prevention and treatment.[24,25]

Clinical conditions involving increased intestinal permeability, such as disruption of the tight junctions between enterocytes, favor greater allergen penetration. This is thought to increase the risk of CMPA, as observed in food-protein enteropathy associated with epithelial lesions caused by classical enteropathogenic *E. coli*

infections (less common today),[29] in allergic diseases in general, and in other clinical settings such as functional gastrointestinal disorders30 and obesity.[31]

Food-protein enteropathy is characterized by lymphocytic and plasmacytic infiltration of the lamina propria, villous atrophy, increased intraepithelial lymphocytes (> 25 per 100 epithelial cells), crypt hyperplasia, reduced disaccharidase activity, and malabsorption – changes that predominantly affect the proximal small intestine.[29,32] Unlike celiac disease, food-protein enteropathy is generally transient and occurs in early childhood, with cow's milk being the most frequently implicated food. Other triggers may include soy, wheat, oats, egg, rice, and fish. Importantly, in some cases, reactions can occur even to peptides found in extensively hydrolyzed protein formulas.[29]

From a pathophysiological standpoint, re-exposure of the intestinal mucosa to allergenic proteins, particularly those from cow's milk, leads to increased intraepithelial CD8+ lymphocytes and activation of CD4+ helper T cells in the lamina propria. In allergic enteropathies, either a Th1-dominant or mixed Th1/Th2 immune response may be observed.[29] Some authors have reported that inflammation caused by cow's milk proteins involves Th2 cytokines.[32] Reduced TGF-β expression also plays a role in their pathophysiology.

The mucosal immune response in FA is often associated with infiltration by eosinophils and mast cells, which produce several proinflammatory, vasoactive, and neuroactive mediators. These cells appear to contribute to gut dysmotility and enteric nervous system alterations triggered by the allergic process. During this process, release of tryptase and eosinophilic cationic protein from the lumen may occur, both of which can be detected in stool samples. It is worth noting that the passage of macromolecules through the intestinal barrier – particularly through defects in tight junctions between enterocytes – is a crucial step in this process. Intestinal permeability may increase due to elevated levels of tumor necrosis factor-α and interferon-γ.[29]

In allergic proctocolitis, inflammation primarily affects the rectum and sigmoid colon, although its exact pathophysiology is not fully understood. Similar to other forms of FA, it is associated with increased tumor necrosis factor-α activity and decreased TGF-β expression. Biopsy is not required for diagnosis; however, mucosal erythema and fragility, along with excessive nodular lymphoid hyperplasia, may be observed. Histological findings may include eosinophilic infiltration, often with > 20 eosinophils per high-power field, which does not necessarily correlate with peripheral blood eosinophil levels.[29] It is important to note that approximately half of patients with allergic proctocolitis exhibit eosinophilia.[33]

Mixed food allergy

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by eosinophilic infiltration of the esophageal epithelium. It is considered the prototypical example of mixed FA reactions.

EoE is a chronic inflammatory condition of the esophagus associated with clinical and molecular heterogeneity. It is marked by epithelial barrier defects, eosinophilic inflammation with a Th2-predominant immune response, and tissue remodeling, all of which contribute to progressive esophageal dysfunction. Dysregulated epithelial and immune cell responses are central to the pathogenesis of EoE and its association with chronic inflammation.

In 1995, Kelly et al. reported the first series of children with EoE, noting that both symptoms and histological changes improved with an amino acid-based diet, only to return upon food reintroduction.[34] Since then, several prospective elimination diet trials have demonstrated that dietary restriction can induce histological remission of EoE in 43% to 74% of both children and adults.[31] Peripheral eosinophilia is found in 40% to 50% of patients with EoE.[35] Moreover, between 28% and 86% of adults and 42% to 96% of children with EoE may also suffer from one or more comorbid allergic diseases, such as atopic dermatitis, FA, asthma, or allergic rhinitis.[35]

Although the exact pathophysiology of EoE is not fully understood, it is increasingly recognized as involving a complex interplay of immune dysfunction, epithelial barrier defects, and neuroimmune interactions.

Immune dysfunction

Studies investigating the molecular basis of EoE have focused on chemokines associated with eosinophilia (eg, eotaxin-3) and type 2 cytokines (eg, IL-5, IL-4, and IL-13). IL-5 plays a key role in the maturation and migration of eosinophils to the esophageal epithelium, with increased IL-5 expression observed in the esophagi of patients with EoE.[37] Similarly, IL-13 is markedly elevated in the esophageal biopsy specimens of patients with EoE, and stimulation of esophageal epithelial cells with IL-13 induces the production of eotaxin-3, a major eosinophil chemoattractant, as well the reduction of filaggrin expression, resulting in epithelial barrier dysfunction.[38,39] In a cross-sectional study, Cianferoni et al. found that peripheral blood Th2 cells expressing IL-4, IL-5, and IL-13 were significantly increased in patients without cow's milk-specific IgE during active EoE, further supporting type 2 inflammation as a promising therapeutic target in EoE.[40] Clinical trials with anti-IL-5 and anti-IL-13 antibodies have shown reductions in EoE; however, these trials did not achieve the primary endpoint of symptom reduction, limiting their clinical applicability.[41-44] Conversely, clinical trials with anti-IL-4Rα (dupilumab) have demonstrated positive outcomes for the clinical, endoscopic, and histological remission of EoE.[45]

Moreover, genetic polymorphisms in the thymic stromal lymphopoietin (TSLP) locus have been identified in individuals with EoE but not in healthy controls. TSLP expression is increased in the esophageal biopsy specimens of patients with EoE. TSLP activates DCs, inducing a Th2 immune response. Noti et al. demonstrated the critical role of TSLP in EoE pathogenesis; in their study, TSLP neutralization led to a reduction in food impactions and eosinophilia in a mouse model of EoE-like disease.[46]

An emerging body of evidence supports the involvement of Ig profiles in EoE. For example, IgG4 is increased in the esophageal tissues of patients with EoE.[47,48] Although it was initially expected that IgE-mediated mechanisms might offer diagnostic, therapeutic, or pathogenic insights for EoE, growing evidence does not support a direct role for IgE. Murine models of EoE show that B-cell-deficient mice can still develop esophageal eosinophilia.[49] Furthermore, serum IgE levels are not consistently elevated in patients with EoE, and when they are, it remains unclear whether this is due to EoE itself, to underlying allergic comorbidities, or to sensitization due to epithelial barrier dysfunction. The anti-IgE monoclonal antibody omalizumab has not proven effective in inducing remission of EoE.[47]

The role of epigenetic and environmental factors in EoE is increasingly being recognized. Cesarean delivery, preterm birth, antibiotic exposure in infancy, mixed or formula-only feeding, and living in less populated areas have all been associated with a higher risk of developing EoE.[50,51] Delayed exposure to bacteria (in the first 2-3 years of life) may induce a Th2-dominant immune state, predisposing individuals to allergic diseases.[51,52] Similar to other classic allergic conditions, this Th1/Th2 imbalance – arising from lifestyle changes – could help explain the rising incidence of EoE. For instance, limited bacterial exposure in early life may be linked to a reduced prevalence of *Helicobacter pylori* in the general population.[53] This reduction is particularly notable in developed countries, where EoE incidence appears to be higher. At least one study has demonstrated an inverse relationship between *H. pylori* infection and EoE, although a direct causal link has not been established.[54] A more recent study failed to detect this association, highlighting the need for further epidemiological and pathophysiological studies.[55]

Epithelial barrier dysfunction

Several hypotheses have been proposed for the decreased esophageal barrier function in EoE. First, some patients with EoE may present epithelial barrier defects at baseline even in the absence of inflammation, which predisposes them to allergic sensitization – a model that closely resembles atopic dermatitis. Supporting this idea, transcriptional alterations have been identified in human chromosome 1q21, which encodes for a cluster of genes related to epidermal differentiation, including filaggrin[39] and another tissue-specific proteolytic molecule, calpain 14.[56] Altered expression of these genes may predispose

individuals to barrier dysfunction, either at baseline or following activation by type 2 cytokines such as IL-13.[39] A study measuring esophageal barrier thickness using impedance monitors in adults with EoE found that even after treatment, the barrier remained thinner than in healthy controls, suggesting a potential innate defect.[57]

Second, barrier dysfunction may result from peptic or other type of injury. This hypothesis is supported by clinical observations that EoE can arise following epithelial damage caused by acid injury, trauma, or infection.[58,59] In such cases, food allergens or aeroallergens may come into contact with the damaged epithelium and sensitized microenvironment in the esophageal mucosa, triggering a type 2 inflammatory response.

Finally, barrier dysfunction may emerge as a self-perpetuating consequence of ongoing inflammation. Once an inflammatory process is established, the epithelial surface may become more permeable, allowing more allergens to penetrate and fueling a vicious cycle of allergic inflammation. This hypothesis is supported by histological findings of actively inflamed esophageal tissue, which show dilated intercellular spaces, reduced desmosomes, and abnormal impedance values compared to normal tissue.[60,61]

Each of these hypotheses may help to explain part of the role of barrier dysfunction in EoE, and several lines of evidence have illuminated the molecular pathways involved. Genetic studies have laid the basis for research demonstrating the importance of IL-13 in barrier dysfunction: IL-13 downregulates filaggrin and desmoglein-1, while upregulating calpain 14, all of which contribute to epithelial barrier weakening. Genetic silencing of desmoglein induces barrier disruption *in vitro*.[62] Studies have shown that calpain 14 expression is increased in a subpopulation of patients with EoE,[56] while *in vitro* culture of esophageal epithelial cells with IL-13 has resulted in increased calpain 14 expression and subsequent barrier dysfunction, supporting its central role in EoE pathogenesis.[63]

Another key factor involves eosinophil activity. Beyond their direct effects on epithelial cells, eosinophils contribute to barrier remodeling by promoting tissue repair following injury caused by pathogens, toxins, or cell death. A dual role of eosinophils in both tissue degradation and repair has been described. For instance, eosinophils release eosinophil-derived neurotoxin,[64] which promotes fibroblast proliferation, and major basic protein, which acts synergistically with IL-5 and TGF-β to increase fibroblast activation and stimulate the release of IL-6 and IL-11.[65] In addition to its role in esophageal remodeling, TGF-β1 has also been shown to impair epithelial barrier function *in vitro* by downregulating claudin, a tight junction protein.[66] In conclusion, the presence of an intact epithelial barrier is likely critical to disease regulation in EoE.

Neuroimmune dysfunction

Increased infiltration of eosinophils and mast cells in esophageal tissue may exacerbate vagal sensory neuronal responsiveness to acid, promote barrier dysfunction, and increase epithelial permeability.[67,68] Increased epithelial permeability may enhance the ability of luminal acid to stimulate action potential discharge in nociceptive afferent terminals. Type 2 cytokines can also contribute to hypercontractility of gastrointestinal smooth muscle cells via signal transducer and activator of transcription 6 (STAT6) or mitogen-activated protein kinase signaling pathways, which may be involved in the pathogenesis of dysphagia in EoE.[67]

Transient receptor potential cation channel subfamily V member 1 (TRPV1) and mast cells have been implicated in pain modulation in EoE. A study involving patients with EoE with pain revealed that pain is positively associated with the molecular expression of TRPV1, carboxypeptidase A3, and hematopoietic prostaglandin D synthase but not with eosinophilia.[69] Neuropeptides such as substance P and vasoactive intestinal peptide promote mast cell degranulation and the production of type 2 cytokines and chemokines, leading to a resultant immune cascade.[70]

Symptoms of discomfort and irritation in EoE may be driven by molecular and cellular circuits resembling itch mechanisms rather than traditional pain pathways. This may be explained by the fact that TRPV1-positive sensory neurons, which are prominent within the vagus nerve, have itch-specific transcriptional identity at the single-cell level.[71]

Clinical trials have shown that although agents targeting the IL-5 pathway (such as mepolizumab and reslizumab) reduce eosinophil numbers in esophageal tissue, they have limited impact on symptom relief.[41-44] In contrast, agents targeting IL-13, including the monoclonal antibodies QAX576 and RPC4046 and dupilumab (which inhibits both IL-4 and IL-13 signaling), have yielded positive results.[45,72] Dupilumab is the first medication approved by the U.S. Food and Drug Administration to treat EoE. In clinical trials involving patients with EoE, dupilumab reduced peak intraepithelial eosinophil counts in esophageal tissue and improved clinical, histologic, and endoscopic scores.[45,72]

Risk factors

Several antigen-related, host-related, and environmental factors may influence whether an individual becomes sensitized or tolerant to a particular food antigen. The study of modifiable and non-modifiable risk factors has advanced significantly in recent years, offering opportunities for future preventive and therapeutic interventions aimed at mitigating the impact of FA on the population.[5]

Allergen-related factors

A food allergen is any component of a food capable of triggering a hypersensitivity response. The allergens contained in these foods are mostly water-soluble glycoproteins with a molecular weight between 10 and 70 kDa. They may be classified as sensitizing allergens, which can induce the production of IgE antibodies, or non-sensitizing allergens, which can only cause an allergic reaction if previous contact with a cross-reactive allergen has caused sensitization.[73] The most common routes of allergen entry into the body include the mucosal surfaces of the airways (via airborne particles or aerosol droplets) and the entire digestive tract (including the oral cavity). The skin has also been recently recognized as a route of sensitization – a hypothesis that gained traction after the discovery of filaggrin single nucleotide polymorphisms associated with the development of allergy.

A well-known example of a true food allergen (a primary sensitizer) is tropomyosin, a muscle protein found in shrimp. Its nomenclature varies depending on the type of shrimp (Pen a 1, Cra c 1, Met e 1, Lit v 1, etc.), and it is also found in other shellfish and mollusks, such as lobster (Hom a 1) and crayfish (Pro c 1). Tropomyosin and sarcoplasmic-calcium-binding protein sensitization is most associated with clinical reactivity to shrimp, while arginine kinase and hemocyanin are responsible for cross-reactivity between shrimp and house dust mites. Hemocyanin and hemoglobin are more likely to cause sensitization via respiratory or skin contact in occupational settings, such as seafood handling or fish food production.[74]

Examples of true plant-derived food allergens include 2S albumins from legumes such as peanut (Ara h 2), tree nuts (Cor a 14, Jug r 1, Ana o 3), and seeds (Ses i 1). Although these allergens share similar structural characteristics, based on a common pattern of disulfide bonds, their primary sequences differ significantly, leading to low cross-reactivity between them.[75]

Food allergens may undergo modifications during processing or digestion, resulting in either an increase or decrease in allergenic potential. For example, ovalbumin, a major egg protein, reduces its allergenicity when eggs are cooked at high temperatures, whereas roasting peanuts increases their allergenic potential.

Allergenic epitopes may be conformational, when the tertiary structure of the protein is responsible for provoking an immune response. Their ability to bind antibodies can be lost through cooking, hydrolysis, or other chemical processes. Epitopes may also be linear, composed of sequential amino acids that participate in antibody binding. In such cases, simple chemical processes are often insufficient to alter their allergenicity.[75]

Food allergens associated with severe allergic reactions tend to be heat-stable and resistant to acid and protease digestion. While virtually any food can cause an allergic reaction, the 8 major food allergens are cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish. It is important to note, however, that new food allergens continue to be identified, such as fruits and sesame, and some are region-specific, such as cassava in

certain areas.[76] In fact, sesame was officially recognized in the United States in 2023 as the ninth most common allergen, alongside the previously mentioned 8 major allergens.[77]

The term allergen classically refers to proteins that elicit a hypersensitivity reaction. However, in the context of FA, an important exception involves carbohydrate epitopes. The prevailing explanation for this mechanism is that pure glycans cannot induce IgE antibodies. Classical MHC-II molecules can effectively interact with peptides but cannot combine with pure glycans. However, when glycans are coupled to a protein carrier, the situation is different. In such cases, the cell-anchored antibody on some B cells can interact with the glycan. These B cells bind the glycoprotein via the antibody-glycan interaction, then ingest and digest the glycoprotein and present the peptides in its MHC-II to the T cell. The T cell receptor interacts with the peptide-MHC-II complex on the B cell, leading to T cell activation. The T cell then activates the B cell, which results in differentiation of the B cell into an antibody-secreting plasma cell. Of note, the conventional Th2 cell does not recognize the glycan and yet it can induce the B cell to produce antiglycan antibodies. It is also possible that glycans can be allergenic not only as glycoprotein but also as glycolipid, potentially via sources of IL-4 other than Th2 cells. This mechanism is presumably more relevant for immune responses to invertebrate parasites such as helminths and ticks. Two prototypic glycans with well-established IgE-binding activity are known: cross-reactive carbohydrate determinants (CCDs)[78,79] and the α-Gal epitope.[80]

CCDs refer to a group of glycans that are characterized by a fucose and/or a xylose that are linked in a specific way to the core of the glycan. They are produced by invertebrates and plants but not by vertebrates. They can trigger an immune response and are present in virtually all plants.[81] When specific IgE to this component is detected in cases of suspected allergy to multiple plants, there is a high likelihood of cross-reactivity but no clinical reactivity.[75]

α-Gal (full name: Galα1-3Galβ1-3GlcNAc) is a carbohydrate found in all non-primate mammals and has been associated with allergy to red meat.[82] Sensitization typically occurs through tick bites. For still unknown reasons, the onset of systemic symptoms observed after meat consumption is not immediate but rather delayed, including anaphylaxis occurring 3 to 5 hours after ingestion. In sensitized individuals, infusion of cetuximab can cause immediate allergic reactions due to the presence of Galα1-3Galβ1-3GlcNAc.[75]

The main foods containing the allergenic proteins most involved in FA are listed in Table 2. Patients with FA may exhibit different sensitization profiles, which trigger different clinical symptoms. In FA, certain allergenic components (molecular fractions) have been more clearly associated with both defined clinical phenotypes and symptom severity.[84]

There are three ways through which an individual may become allergic to a specific food:

– direct exposure to the food via the oral route, inhalation, or contact with the skin;
– cross-reactivity between foods;
– cross-reactivity between respiratory allergen sources and foods.

The best-known example of the latter is fruit and tree nut allergy as comorbidity with birch pollen allergy.[85] The mechanism of this association is cross-reactivity of Bet v 1-specific IgE with structurally homologous allergens in foods such as apple, peach, hazelnut, and peanut. These patients typically present a clinical phenotype characterized by mild-to-moderate symptoms restricted to the oral cavity. The explanation for the lack of (severe) systemic symptoms is believed to reside in the protease-sensitive nature of Bet v 1-related food allergens, which are readily digested in the gastrointestinal tract. Apple Mal d 1 or peach Pru p 1, the Bet v 1 homologues of these fruits, are completely digested before they can directly sensitize.[86] However, this does not mean that a fruit like peach cannot directly sensitize atopic subjects through another component.

The allergen involved in peach allergy is Pru p 3, which belongs to the lipid transfer protein (LTP) family. IgE antibodies against Pru p 3 are associated with a higher risk of severe systemic reactions[87] and can broadly cross-react with other fruits, as well as with tree nuts, legumes, and some

vegetables.[88] The heightened allergenic profile of LTPs has been attributed to their high resistance to proteases (and food processing), as well as to the fact that they go into solution effectively only at low pH (ie, only in the stomach), leading to the absence of early oral warning signs. In addition to LTPs and Bet v 1-related allergens, tree nuts, legumes, and seeds contain highly abundant

Table 2
Food proteins and components with demonstrated allergenicity[83]

Cow's milk	Egg
Caseins (αs1-,αs2-,β-, κ-, γ-caseins) Whey proteins (β-lactoglobulin, α-lactalbumin) Proteases and peptones Blood proteins Albumin Immunoglobulins	**Egg white** (albumin, ovalbumin, ovomucoid, ovotransferrin, ovomucin, lysozyme) **Egg yolk** (granule: lipovitellin, phosvitin, low-density lipoprotein) **Plasma** (low-density lipoprotein, livetin)
Fish	**Wheat**
α-Parvalbumin (major allergen) β-Parvalbumin Enolase Aldolase Vitellogenin Tropomyosin	Water-soluble albumin Soluble globulins Prolamins Gliadins A, β, γ, ω Glutelins Glutenins
Legumes	**Shellfish**
Legumins Vicilins	Tropomyosin
Soy	**Peanut**
Globulins 7S: β-conglycinin β-Amylase Lipoxygenase Lecithin 11S: glycinin Whey proteins Hemagglutinin Trypsin inhibitor	Albumins Agglutinins Protease and α-amylase inhibitors Phospholipases Globulins Arachin Conarachin Lectin-reactive glycoproteins
Tree nuts	**Sesame**
Seed storage proteins Vicilins Legumins Albumins **Profilins** Plant defense-related proteins	Seed storage proteins 7S vicilin-type globulin (Ses i 3) 2S albumin (Ses i 2)

seed storage proteins, such as 2S albumins, 7S globulins, and 11S globulins. These proteins are involved in direct sensitization, which typically occurs at younger ages. Similar to LTPs, seed storage proteins, particularly 2S albumins, are notably stable and are strongly associated with severe symptoms. This has been demonstrated for Ara h 2 from peanut and Cor a 14 (2S albumin) and Cor a 9 (11S globulin) from hazelnut.[89,90] Based on these and other findings, molecular diagnosis is increasingly used to more accurately assess the risk of severe allergic reactions.[91,92]

Table 3 outlines the relationship between allergenic food components and their clinical implications, while Figure 1 illustrates the risk of cross-reactivity.

Host-related factors

Genetics

A family history of allergic disease in first-degree relatives, diagnosed by a health care professional, is a recognized risk factor for allergy, suggesting a genetic basis. This association is particularly strong among siblings: a child is 2.5 times more likely to develop FA if a sibling has FA, even in the absence of parental history of atopic disease. Twin studies have shown a concordance rate of 82% for peanut allergy among monozygotic twins, far exceeding the 20% concordance observed among dizygotic twins. Overall, heritability estimates for FA reach up to 81%.[95,96]

Although FA prevalence has increased across all demographic groups in recent decades, the increase has not been uniform. In the United States, African American populations have a 4-fold higher prevalence of FA compared to European Americans. Recent studies have shown that variants in several genes that encode Th2-related molecules such as IL-4 and IL-13 show higher allele frequency in African Americans, suggesting that these alleles have been conserved to combat parasitic infections in African populations but not in European populations. This evolutionary trajectory might be responsible for the higher prevalence of allergic disorders in African American individuals.[95]

Genome-wide association studies and candidate-gene studies have suggested significant associations between FA and the human leukocyte antigen (HLA)-DR and HLA-DQ regions, as well as variants in several genes, including *FLG*, *SPINK5*, *STAT6*, *CD14*, and *FOXP3*.[96] Several HLA polymorphisms are being investigated and some have been strongly associated with specific FAs, such as HLA-DRB1 with egg allergy, HLA-DQ7 with cow's milk allergy, and HLA-DQB1 with peanut allergy.[95,97,98]

The role of genetics in the development of FA is further evidenced by monogenic diseases associated with increased risk of FA, such as the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and Loeys-Dietz syndromes. The IPEX syndrome is a rare disorder caused by mutations in the *FOXP3* gene resulting in the defective development of CD4+CD25+ Tregs. In addition to autoimmune conditions, patients with IPEX syndrome exhibit a high risk of FA, atopic dermatitis, and elevated IgE levels. Loeys-Dietz syndrome results from mutations in TGF-β receptors, such as *TGFBR1* or *TGFBR2*.[95]

Other examples include monogenic disorders involving genes responsible for the integrity of the epidermal barrier. In these cases, sensitization may occur due to a defect in skin barrier function, as seen in Comel-Netherton syndrome. This syndrome is caused by autosomal recessive mutations in *SPINK5*, which encodes the lymphoepithelial Kazal-type-related inhibitor, a serine protease inhibitor involved in the regulation of skin desquamation. Comel-Netherton syndrome is characterized by defective cornification, chronic skin inflammation, impaired skin barrier function, and multiple allergies, including FA.[99,100] The association between FA and monogenic hereditary skin diseases further supports the idea that sensitization can occur through a defective skin barrier.

Within this context, the role of FA in the atopic march – the progression of allergic diseases such as atopic dermatitis, FA, allergic rhinitis, and asthma – is not fully understood, but there is a well-established association between FA and atopic dermatitis. According to the dual allergen

exposure hypothesis, a defective epithelial barrier, as seen in atopic dermatitis, facilitates the exposure of allergens to the immune system, leading to sensitization (IgE production).[101] Children with atopic dermatitis have a 6-fold higher risk of developing FA compared to those without the disease. An Australian study showed that 50% of infants with early-onset, severe atopic dermatitis had FA confirmed by OPT at 12 months of age.[102]

Table 3
Key allergenic food components and their association with the severity and persistence of allergic symptoms[93]

Food	Main allergenic components	Possible clinical implication
Cow's milk	Caseins (subset of caseins)	Persistence of allergy
	α-Lactalbumin	
	β-Lactoglobulin	Cross-reactivity with beef
	Bovine serum albumin	
Egg white	Ovomucoid	Greater severity and persistence of allergy
	Ovalbumin	Risk of reactions to raw or undercooked egg and certain vaccines
Egg yolk	Livetin	Cross-reactivity between egg and chicken meat
Wheat	ω-5 Gliadin	Marker of severe allergic reactions and wheat-dependent exercise-induced allergy
Peanut	Ara h 2	Greater clinical reactivity and severity
	Ara h 8	Milder reactions
Hazelnut	Cor a 9	Greater clinical reactivity
Shellfish	Tropomyosin	Cross-reactivity with mites and cockroaches
Meats	α-Gal	Delayed anaphylaxis following meat ingestion
Latex and fruits	Hev b 1 (rubber elongation factor)	Cross-reactivity with papaya and fig
	Hev b 6.01 (prohevein) – PR-3	
	Hev b 6.02 (hevein)	Cross-reactivity with banana, avocado, and hazelnut
	Hev b 6.03 (C-terminal fragment)	Cross-reactivity with kiwi
	Hev b 5 (acidic protein)	Cross-reactivity with potato
	Hev b 7 (patatin-like Hevea latex protein)	Cross-reactivity with banana and avocado
	Hev b 11 (chitinase)	Cross-reactivity with peach and
	Hev b 12 (LTP)	other stone fruits
	Hev b 15 (protease inhibitor)	Cross-reactivity with wheat

Primary food allergy	Cross-reactivity	Risk (varies by region)
Shellfish 	– Other shellfish – Mollusks/bivalves (squid, oyster, mussel, clam)	≈ 75% < 50%
Mollusks/ bivalves 	– Shellfish (lobster, crab, shrimp)	> 70%
Bony fish with fins 	– Other bony fish with fins – Cartilaginous fish (shark, skate, dogfish)	≈ 50% < 5%
Peanut 	– Tree nuts – Lupin – Sesame (co-allergy) – Green bean, pea, soy	≈ 33% ≈ 20% 10-15% 5-20%
Other legumes Soy Chickpea 	– Peanut – Lentil, pea	> 75% > 50%
Tree nuts  If walnut If pecan If cashew nut If pistachio If peanut + nuts	– Other tree nuts – Sesame (co-allergy) – Pecan – Tree nuts – Pistachio – Cashew nut – Sesame (co-allergy)	15-33% 10-15% ≈ 66-75% > 95% ≈ 66-83% > 95% 50%
Cow's milk 	– Goat's milk, sheep's milk – Camel's milk, mare's milk	> 90% < 5%
Wheat 	– Barley and rye	< 25%

α-Gal = Galα1-3Galβ1-3GlcNAc, LTP = lipid transfer protein.

Figure 1
Risk of cross-reactivity between major allergenic foods[94]

The risk of FA increases substantially in cases of early and severe atopic dermatitis, particularly during the first 4 months of life. Children with FA are 2 to 5 times more likely to develop asthma and allergic rhinitis than children without FA. This risk is even greater in those with multiple or severe FA.[103-105] Because intestinal DCs are typically tolerogenic, ideally infants should first be exposed to foods orally.[101]

In summary, there is strong evidence supporting the influence of genetic factors on the development of FA, although the specific genes, their functions, and mechanisms are not yet fully understood. Further research is needed to identify relevant genetic associations and their interactions with environmental factors. Integrative approaches, combining genomics, transcriptomics, proteomics, and metabolomics, are expected to yield valuable insights that will advance our understanding of FA.

Epigenetics

The rapid increase in FA prevalence over the past five decades highlights the role of environmental influences on disease occurrence. This has been illustrated in twin studies involving emigrants to the United States, which demonstrated marked differences in allergy incidence between those who migrated and their counterparts who remained in their countries of origin.[95,106]

Gene–environment interactions may be mediated by epigenetic mechanisms, which involve chemical alterations of the DNA itself or of the proteins with which DNA is associated. Each of these modifications acts as a regulatory and modulating signal in gene expression. Gene expression regulation can be exerted by three different epigenetic mechanisms: histone modifications, DNA methylation, and microRNAs, which are non-coding RNAs that bind to mRNA but are not translated into proteins.[98,107,108]

Among the environmental factors of relevance are mode of delivery (cesarean vs. vaginal birth), feeding method (breastfeeding vs. formula), early exposure to food allergens, dietary habits, vitamin D intake, pollution, hygiene-related factors, exposure to pets, and medication use, such as antibiotics and proton pump inhibitors. These and other factors represent the "exposome," defined as the totality of environmental exposures and associated biological responses that an individual experiences over their lifetime.[109-111] For example, children living on farms with frequent animal contact have a lower risk of developing allergic diseases compared to children raised in urban environments. Similarly, children with older siblings, those who attend daycare at an early age, and those with household dogs have a reduced likelihood of developing FA.[108]

In the gene–environment interaction, the microbiome and the first 1,000 days of life (from gestation through the first 2 years) represent a "window of opportunity" or a "window of susceptibility". During this critical period, environmental factors, including nutrition, microbial infections, and gut microbiota composition, can influence the risk of developing allergic diseases or promote immune tolerance through epigenetic regulation.[106,109]

Microbiome

More recently, the roles of eubiosis and dysbiosis of the microbiome as determinants of health and disease, including FA, have been extensively studied.[111]

The human microbiota is primarily formed and consolidated within the first 3 years of life, progressively increasing in microbial number and diversity starting from the intrauterine period, and especially following birth. Several factors can influence this process, including mode of delivery, antibiotic use (pre- or post-natal), sociocultural and geographic conditions, and especially nutritional factors (eg, diet, infant feeding type, and solid food introduction pattern).[107,112,113]

Two phases are critical for the establishment of the gut microbiota. The first is immediately after birth, during lactation, when the gut microbiota is predominantly colonized by *Bifidobacterium* species. The second phase is when children start eating solid foods. In this phase, they have a greater diversity of bacterial species, including *Enterococcus*, *Enterobacteria*, *Clostridium*, *Firmicutes*, *Streptococcus*, and *Bacteroides*. This promotes the development of a complex, adult-like microbiome.[113] While the gut microbiota of vaginally delivered infants resembles their mother's vaginal

microbiota, primarily dominated by *Lactobacillus*, the microbiota of cesarean-delivered infants is more similar to skin microbiota, typically dominated by *Staphylococcus* and *Clostridium*, among others.[114] Skin colonization by *Staphylococcus aureus*, a known marker of more severe eczema, is also associated with food allergen sensitization. Regardless of eczema severity, such colonization has been linked to sensitization to hen's egg and peanut and to persistent allergy, with a weaker association observed for cow's milk among children up to 6 years old. Additionally, household endotoxin exposure has been associated with increased food allergen sensitization.[105,110,111]

Studies have demonstrated that the gut microbiota of children with FA is characterized by a reduction in butyrate-producing bacteria, accompanied by colonization by *Clostridium paraputrificum* and *C. tertium.* Moreover, there are differences in the gut microbiota composition between children who outgrow FA within the first 8 years of life and those who do not: in the former, *Firmicutes* predominate, whereas in the latter, there is a higher abundance of *Bacteroidetes*.[109]

These observations can be understood through the strong association between diet, microbiome, intestinal barrier, immune response, and epigenetics. Microbiota-derived metabolites may serve as epigenetic substrates capable of modifying gene expression without altering DNA sequences. For example, *Bifidobacterium* and *Lactobacillus* can produce folate, an essential molecule involved in methylation processes. Changes in bacterial composition can thus modify the host's DNA methylation status. At the same time, short-chain fatty acids, produced by commensal microbes during fermentation, can promote histone modifications.[109]

Early alterations in gut microbiota composition and increased intestinal epithelial permeability promote allergic responses. Food sensitization has been associated with a reduction in intestinal microbial diversity, coupled with increased abundance of *Enterobacteriaceae* and decreased *Bacteroidaceae* and *Ruminococcaceae*. Excessive antibiotic use is a major risk factor for inducing gut dysbiosis, as it alters microbial diversity. Commensal intestinal bacteria play a key role in modulating immune tolerance by reducing circulating basophil populations, promoting epithelial barrier integrity, and inducing Treg cell differentiation. Gut microbiota dysbiosis is linked to systemic and local inflammation, leading to intestinal barrier damage, reduction of beneficial bacteria, and increased susceptibility and severity of food allergy. Recent evidence suggests that a high-fat diet may promote increased production of allergenic substances in the gastrointestinal tract due to an imbalance in gut microbiota, characterized by altered proportions between beneficial (eubiotic) and potentially harmful (dysbiotic) intestinal bacteria.[109]

Increasing evidence suggests that human gut microbiota balance and intestinal barrier integrity play significant roles in the development of FA. Environmental factors, such as industrialization and consumption of ultra-processed foods, may contribute to alterations in the gut microbiota and barrier, thereby increasing susceptibility to allergic sensitization. An increase in intestinal barrier permeability facilitates the translocation of allergenic molecules, triggering Th2 immune responses. Under physiological conditions, eubiotic gut microbiota promotes the differentiation of T lymphocytes into Treg cells, leading to immune tolerance. Conversely, in the context of gut permeability and intestinal dysbiosis, epithelial-derived cytokines such as TSLP, IL-33, and IL-25 are released, promoting a pro-allergic microenvironment by activating Th2 and type 2 innate lymphoid cells, resulting in increased release of proinflammatory cytokines (eg, IL-4, IL-5, and IL-13). Moreover, dysbiotic gut microbiota induces Th2 cell differentiation, promoting the IgE class-switching process in B cells. After sensitization to a specific food allergen, allergen-specific IgE antibodies become immobilized on the surface of basophils and mast cells. Upon subsequent exposure to the allergen, these cells release histamine and other proinflammatory mediators (eg, leukotrienes and type 2 cytokines), further increasing gut permeability and amplifying inflammation.[115] Furthermore, the role of the gut microbiota in the human body is not restricted to the intestine itself. It also affects immune cells in the mucosa, including DCs, innate lymphoid cells, T cells and others, which act in the intestine

and migrate to other sites to contribute to host defense.[107]

Gut microbes produce small-molecule metabolites, pattern recognition receptors ligands (such as microbe-associated molecular patterns), extracellular vesicles, neurotransmitters, and hormones that can enter the lymph and circulation, where they impact immune cell development and function in distant organs. Long-distance communication by the gut microbiota can also occur through neuronal communications between the gut and distant organs, including the brain, via the gut-brain axis. Microbiota-derived compounds are detected by the enteric nervous system, and afferent vagal signaling may enable systemic responses coordinated by the central nervous system.[116] All these mechanisms may be involved in the process of immune tolerance, which promotes a Th1 response to antigenic stimuli and nonpathogenic microorganisms encountered in the intra- and extra-corporeal environment from birth. A reduction in Th1 response, along with sustained and enhanced Th2 responses, is observed in children at risk for atopic diseases.[113,114]

Figure 2 illustrates the protective bacterial genera (present in eubiosis) and nonprotective genera (characteristic of dysbiosis) in the gut microbiota of children, while Figure 3 depicts the interaction between genetics, epigenetics, and environmental risk factors associated with FA.

Natural history of food allergies

Understanding the natural history of FA is important for determining the optimal timing for the assessment of oral tolerance.[117] Allergies to cow's milk, egg, soy, and wheat tend to resolve earlier, usually during childhood, whereas allergies to tree nuts, peanut, fish, and shellfish are generally more persistent.[117,118]

However, in general, FA has become more severe and persistent over recent decades.[119-121] For many years, it was believed that adult FA typically began in childhood and persisted; however, the number of patients with adult-onset FA is also increasing, even for egg and cow's milk.[120]

The natural history of the disease varies depending on the specific food and age of onset,

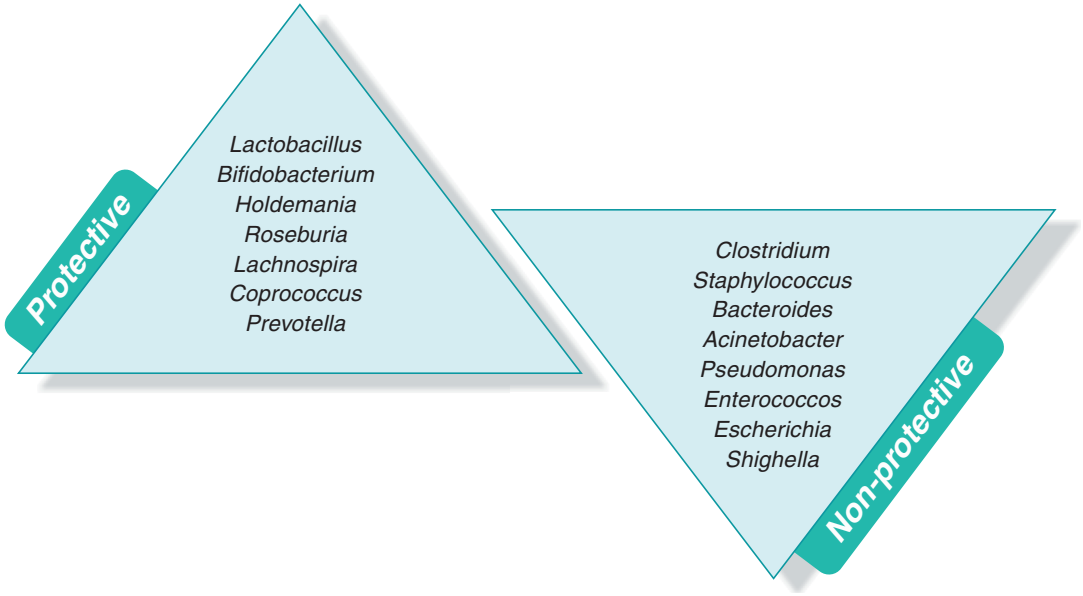


Figure 2
Protective and nonprotective bacterial genera in the gut microbiota of children[109]

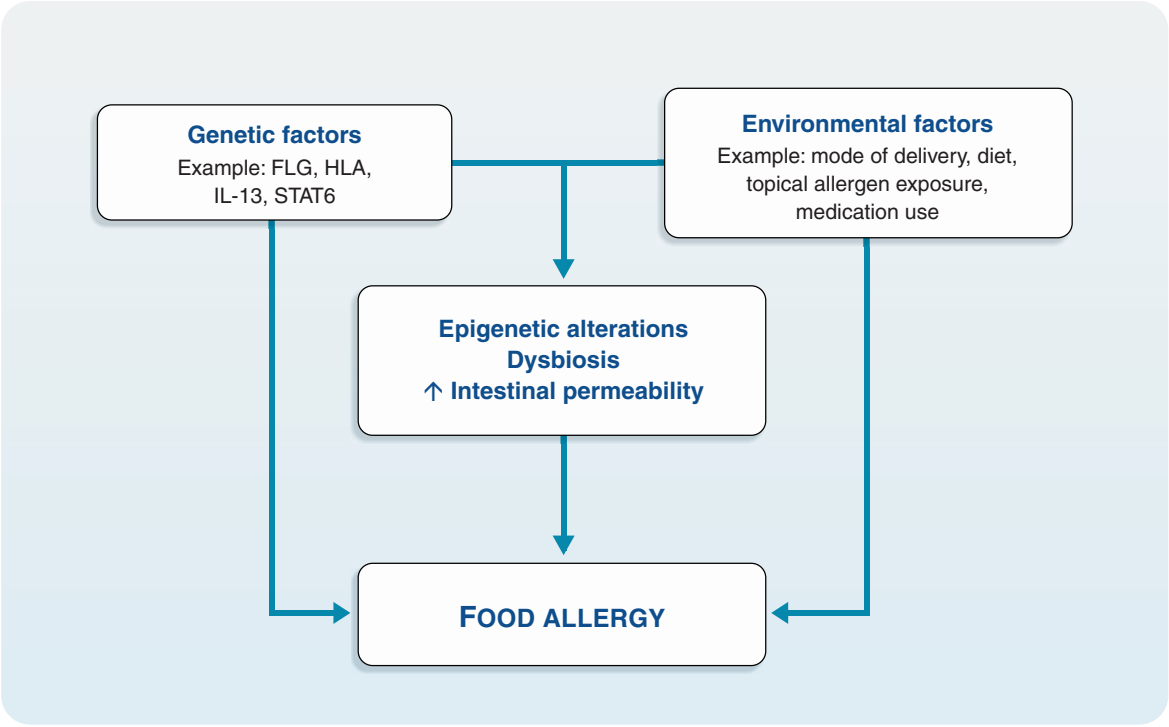


Figure 3
Development of food allergy: interaction between genetic, epigenetic, and environmental factors[95]

as well as the phenotype and endotype. Persistent FA is typically associated with more severe clinical manifestations, early age at diagnosis, personal history of atopic disease, history of multiple FAs, lower threshold dose to trigger a reaction, lack of tolerance to baked forms of the food, and increased levels of specific serum IgE.[121]

IgE-mediated allergies tend to be more persistent, while tolerance acquisition tends to occur earlier in non-IgE-mediated allergies, although 30% of cases persist beyond 2 years of age.[120]

Non-IgE-mediated food allergy

Undoubtedly, CMPA is the most common FA to present with the non-IgE-mediated manifestations described below.[121]

Allergic proctocolitis

Allergic proctocolitis generally resolves within the first year of life; however, some children may acquire tolerance only around 3 years of age.[122]

In a prospective study of 185 children with allergic proctocolitis, Cetinkaya et al. identified the following predictive factors for delayed tolerance development: non-IgE-mediated allergy to multiple foods, concomitant IgE-mediated FA, feeding with cow's milk-based formula prior to symptom onset, and late complementary feeding.[123]

Most international treatment guidelines – including those from the European Academy of Allergy and Clinical Immunology (EAACI), World Allergy Organization (WAO), Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA), and European Society for Paediatric Gastroenterology Hepatology and

Nutrition (ESPGHAN) – recommend at least 6 months of elimination diet or conducting tolerance assessment between 9 and 12 months of age for allergic proctocolitis. Conversely, the Italian group suggests evaluating tolerance 3 months after the last episode of rectal bleeding and even questions whether dietary restriction is truly necessary for these patients.[124-127]

Food protein-induced enterocolitis syndrome

In food protein-induced enterocolitis syndrome (FPIES), an OPT to assess tolerance is recommended every 12 to 18 months after the last reaction. The total remission rate for FPIES ranges from 50% to 90% by 6 years of age. Atypical FPIES (with allergic sensitization) has a worse prognosis. FPIES can also begin in adulthood, but its natural history in this age group requires further investigation.[122,128]

Food protein-induced enteropathy

In food protein-induced enteropathy (FPE), children should be reassessed at 12 months of age, and most cases resolve between 1 and 3 years.[122]

IgE-mediated food allergy

Estimated rates of tolerance acquisition exist for each food, based on studies using different methods and populations. In general, it is estimated that approximately 70% to 80% of patients with allergies to cow's milk, egg, soy, and wheat will have their allergy resolved by age 16, with about 50% resolving by age 5.[117,119,129-132] Most patients can tolerate the food in baked forms, with 69% to 83% tolerating baked cow's milk and 63% to 84% tolerating baked egg. Tolerance to baked forms may indicate a milder and more transient phenotype of allergy.[133,134]

For sesame and peanut, studies indicate that only 20% to 30% of children achieve tolerance by age 5.[117] Regarding fish, approximately 26% of allergic children may acquire tolerance by age 5,[117] whereas for tree nuts, a retrospective study reported resolution rates ranging from 9% to 14%.[135] Most patients who develop peanut, tree nut, and shellfish allergies in childhood tend to persist with these allergies into adulthood. Only 4% of patients with shellfish allergy naturally acquire tolerance.[117]

The likelihood of developing food-pollen allergy syndrome or oral allergy syndrome increases with age, and these conditions tend to be persistent.[117]

A better understanding of the natural history of FA and knowledge of predictive factors for persistent allergy may contribute to the development of new therapies and to improving the management of affected patients.[117]

Prevention

Environmental measures

Recent evidence indicates that, beyond genetic predisposition, a set of environmental factors, including diet, lifestyle habits, and air quality, contributes to the increase in allergic diseases. In all of these contexts, the underlying rationale centers on the modification of the gut microbiota. Generally, the abundant presence of *Lactobacillus* and *Bifidobacterium* appears to be associated with protection against atopic diseases due to their ability to inhibit Th2 immune responses. Conversely, early colonization by *Clostridium difficile* and *Staphylococcus aureus* has been associated with the subsequent development of food hypersensitivity.[136] Barker et al. proposed a theory that the first 1,000 days after conception are a critical period during which several factors could influence the development of chronic diseases in genetically predisposed children.[137] Using a different approach, Haahtela proposed that lack of contact with nature and modern lifestyle habits also predispose individuals to immune imbalance and the consequent induction of allergic and inflammatory diseases.[138]

Within this context, intervening in certain modifiable factors could serve as a potential protective measure against the development of FA and, according to some authors, might even reverse some established negative effects.[139] Based on these findings, several strategies could represent opportunities to prevent FA onset, as outlined below.

Prioritize vaginal delivery whenever possible

The translocation of maternal microorganisms through placental tissue and the vagina is crucial for initial colonization of the infant gut during the first hours of life. Evidence suggests a 2-fold increased risk of allergy to cow's milk and egg in infants born via cesarean section.[140]

Avoid indiscriminate/unnecessary use of antibiotics in early life

There is clear evidence linking antibiotic use to allergic outcomes. The effects of antibiotics on the microbiota appear to be long-lasting: penicillins and cephalosporins are mostly associated with FA during the first years of life, while the effects of macrolides may persist into later childhood.[141]

Contact with nature

Cultural evolution and modern indoor lifestyle habits have reduced contact with nature and interaction with biodiversity. Consistent with the "hygiene hypothesis", lack of exposure to microbial agents may lead to microbiome imbalance, resulting in immune dysregulation and a surge of allergic and inflammatory diseases. Thus, regular contact with nature should always be recommended due to its several physical and mental health benefits.[138]

Diet during pregnancy and lactation

In the past decades, guidelines for the prevention of FA have undergone significant changes. Some of these changes reflect a growing understanding of the connection between nutrition, microbiome, the immune system, and epigenetics, emphasizing advances in knowledge about dietary counseling for maternal diet during pregnancy, the promotion of breastfeeding, and the timing of complementary feeding introduction.[142]

Allergy prevention guidelines used to recommend that pregnant and breastfeeding women from high-risk families should avoid peanuts and other common food allergens.[143] However, in 2018, a meta-analysis conducted by the UK Food Standards Agency including five clinical trials concluded that there was no evidence that avoiding food allergens during pregnancy reduces the risk of FA.[144] To date, there are no recommendations supporting dietary restrictions for breastfeeding mothers as a means of preventing FA[145]; on the contrary, dietary restrictions during pregnancy and lactation may compromise maternal and fetal health.[146,147]

There is no evidence suggesting that pregnant or breastfeeding women should consume specific foods unless these are already part of their usual diet. Further investigation into the role of vitamin supplementation, including vitamin D and fish oil, as well as prebiotics, probiotics, and synbiotics in healthy pregnant and lactating women, in FA prevention is still required.[148]

According to the Protocol for the Use of the Brazilian Dietary Guidelines in the Individual Care of Pregnant Women (*Protocolo de Uso do Guia Alimentar para a População Brasileira na Orientação Alimentar de Gestantes*), published in 2021 as a support tool for clinical practice, it is particularly important during pregnancy to consume a wide variety of fresh and minimally processed foods along with water to meet the nutritional needs fundamental at this stage of life, such as iron, folic acid, calcium, and vitamins A and D, among others. Healthy eating during pregnancy favors optimal fetal growth and supports maternal health and well-being, while helping prevent conditions such as gestational diabetes, hypertension, and excessive weight gain. These recommendations apply regardless of the infant's FA risk.[149-151]

Breastfeeding

Breastfeeding is universally recognized as one of the best public health strategies for child survival, as it helps strengthen the bond between mother and child and is considered the gold standard for child nutrition. Breastfeeding promotes greater skin-to-skin contact, influencing the development of the infant's gut microbiota and immune system.[152] For this reason, the World Health Organization, the Brazilian Ministry of Health, and the Brazilian Society of Pediatrics recommend breastfeeding up to 2 years of age, with exclusive breastfeeding for the first 6 months in Brazil.[150,151,153]

Human breast milk contains macronutrients and micronutrients, with its composition varying according to environmental factors. Colostrum is low in fat but rich in proteins and immunoprotective

components. Micronutrients, hormones, and growth factors also play multiple roles in child development. Microbial communities and microRNAs contribute to the construction of the infant's immune system.[154] Human milk oligosaccharides – complex glycans that are indigestible by the human body but serve as the primary substrate for the microbiome, particularly bifidobacteria – play key roles in the proliferation of beneficial bacteria in the infant's gastrointestinal tract, providing both prebiotic and probiotic effects.[145] However, while human breast milk is known for its beneficial effects on the gut microbiota and the infant's immune system, its role in preventing FA remains unproven.[148]

Studies have demonstrated protective effects, no effects, or even a predisposing effect of breastfeeding on the development of FA. A recent systematic review identified five prospective cohort studies that examined the association between breastfeeding and allergy in the general population, along with two studies focused on infants at increased risk for allergic disease. Overall, the relative risk for CMPA ranged from 0.38 to 2.08, but the evidence was weak and diagnostic criteria were lacking.[155] Another systematic review found no association between breastfeeding and allergic disorders, such as asthma or eczema.[145]

From their systematic reviews, the EAACI[156] and the UK Food Standards Agency concluded that breastfeeding does not reduce the risk of FA.[144] This conclusion is further supported by the American Academy of Pediatrics, the American Academy/College of Allergy, Asthma, and Immunology, the Canadian Society of Allergy and Clinical Immunology, and the Japanese and Australian Societies of Pediatric Allergy and Immunology.[157-159]

In summary, pregnant and breastfeeding women are not advised to exclude any foods from their diets, nor is there evidence supporting the active consumption of allergenic foods to prevent FA. Breastfeeding should always be encouraged, given the numerous benefits it provides for the mother, the infant, and the planet.

Complementary feeding

Complementary feeding is defined as the introduction of solid or semi-solid foods during the transition period when the child's nutritional needs can no longer be met exclusively by breast milk (or infant formula, when necessary). Beginning at 6 months of age, other foods should be introduced as part of the child's meals, with a gradual transition to family meals and the complete introduction of foods by 12 months of age.[150,151,153] Based on these milestones, in the Brazilian population, early introduction is defined as the offering of complementary foods between 4 and 6 months of age.

Recommendations from other countries and medical organizations may differ from those advocated by the World Health Organization and Brazilian guidelines.[150,151,153] ESPGHAN recommends introducing complementary foods between 4 and 6 months of age (17th to 26th weeks of life), advising against introduction before 4 months and against delaying beyond 6 months.[160]

Two decades ago, it was believed that early oral exposure to allergenic foods could increase the risk of sensitization and, therefore, the introduction of these foods should be delayed to prevent FA.[161] However, despite delayed introduction, the prevalence of FA continued to rise, prompting experts to reassess previous recommendations and develop new prevention strategies. One of these strategies focuses on determining the optimal timing for introducing allergenic foods into the infant's diet.[161,162]

Randomized, placebo-controlled clinical trials were conducted to evaluate the preventive effect of early introduction of certain foods on FA development. However, they had methodological variations related to the type of food selected, its form of presentation, the dose of allergenic protein consumed, and the target outcome.[163-169] These differences led to different conclusions, at times contradictory, and not always comparable across studies.[170]

The heterogeneity of the randomized clinical trials, combined with differences in the epidemiology of peanut allergy, the forms of consumption across countries, and national complementary feeding guidelines, has led to different recommendations. The 2020 EAACI guidelines suggest that, in populations with a high prevalence of peanut allergy,

peanuts should be introduced between 4 and 11 months of age using age-appropriate peanut-containing foods to avoid the risk of anaphylaxis or aspiration. A weekly consumption of at least 2 g of peanut protein was recommended. However, in countries with low peanut allergy prevalence, such as Brazil, no specific recommendations were made, and peanut should be introduced in accordance with local dietary habits.[156] In 2021, the American Academy and College of Allergy, Asthma, and Immunology and the Canadian Society of Allergy and Clinical Immunology published a consensus on primary prevention of FA, recommending that all infants, regardless of risk, should be exposed to cooked egg and peanut around 6 months of age.[157]

Regarding egg introduction, the EAACI advises introducing cooked (but not raw or pasteurized) hen egg. The initial suggested amount is half of a hard-boiled egg (cooked for 10-15 minutes), twice a week, to be introduced at the start of complementary feeding.[156] The British Society of Allergy and Clinical Immunology guidelines suggest that egg and peanut may be introduced as part of the family diet to high-risk infants between 4 and 6 months of age. However, they recommend introducing egg before peanut, since sensitization to egg appears to occur prior to sensitization to peanut.[173]

Although some allergic reactions occurred in the Learning Early About Peanut Allergy (LEAP) study, there is no recommendation for routine testing for specific IgE antibodies to food allergens prior to their introduction.[163] The exceptionality of FA in this case would not justify such a recommendation, which would be difficult to implement in public health settings and could even cause harm by delaying food introduction. However, testing may be an option for hesitant families, based on the clinician's and family's preferences, with individualized decisions.[157]

Studies on the prevention of FA for other food allergens are less robust and showed evidence of safety but not necessarily of efficacy.[172,173] Evidence on preventing other allergic diseases is scarce and weak, requiring further research.[172,173]

There is no evidence that the order in which different solid foods are introduced is associated with a higher or lower risk of FA.[174] Therefore, timely complementary feeding should follow family dietary practices, allowing the child to be exposed to all food groups between 6 and 12 months of age.[150,151,153] Venter et al. demonstrated that increasing dietary diversity during the first year of life reduces the likelihood of developing FA. They emphasized that for each additional allergenic food consumed between 6 and 12 months, there was a 33.2% reduction in the probability of developing FA within the first 10 years of life.[175]

In cases where exclusive breastfeeding is not possible and infants require breast-milk substitutes under medical recommendation, there is no recommendation for or against the use of standard cow's milk-based formula after the first week of life to prevent FA. A literature review concluded that introducing cow's milk-based formula after the first week had no consistent impact on the development of CMPA during early childhood.[156]

In Brazil, exclusive breastfeeding is recommended until 6 months, with continued breastfeeding up to 2 years or longer.[150,151,153,176] The progressive introduction of foods, including allergenic foods, should begin at 6 months and continue throughout the first year of life, aligned with the child's development.[177]

Complementary feeding should follow current guidelines, including all food groups, while respecting ideology, culture, socioeconomic conditions, and family habits. It is important to emphasize that there is no evidence supporting early introduction of allergenic foods before 6 months. Once an allergenic food is introduced, frequent and sustained ingestion is necessary to maintain tolerance.

Recommendation to avoid ultra-processed foods

A recent study demonstrated a strong correlation between certain additives and emulsifiers, frequently present in the extensive list of ingredients in ultra-processed foods, and intestinal epithelial tight junction dysfunction.[178] This could lead to increased permeability and absorption of protein fragments with allergenic potential.

Furthermore, frequent consumption of ultra-processed foods has also been associated with obesity, metabolic syndromes, systemic

inflammation due to oxidative stress, and an increased predisposition to allergic diseases of any kind.[179]

Infant formula

The role of infant formula in the prevention of or as a risk factor for atopic diseases has undergone significant revisions over the past decades. Current international FA guidelines do not support the use of any infant formula for the prevention of FA,[126] contrary to previous beliefs that partially hydrolyzed formulas could reduce the risk of eczema, or that hydrolyzed formulas might prevent the development of CMPA. This represents a shift from older guidelines that recommended the use of partially and/or extensively hydrolyzed formulas.[10]

Current evidence regarding the relationship between infant formula and the risk of FA is summarized below.

- There is no convincing scientific evidence that avoiding or delaying the introduction of cow's milk-based infant formula reduces or increases the risk of CMPA in infants considered at high risk for allergic diseases.
- It is unclear whether avoiding regular consumption of cow's milk-based infant formula during early life reduces the risk of CMPA in children.
- Supplementary feeding – that is, providing any type of infant formula in addition to breast milk during the first days of life – is not recommended for the prevention of CMPA.
- For infants with a documented family history of allergic disease who cannot be exclusively breastfed, there is currently insufficient evidence to recommend the routine use of partially hydrolyzed formulas or extensively hydrolyzed formulas (based on casein or whey proteins) to prevent CMPA.
- The role of hydrolyzed rice formulas in the prevention of CMPA has not been investigated.
- There is no evidence to recommend the use of soy-based infant formula for the purpose of preventing CMPA.[126]
- Breastfeeding should always be encouraged, except in cases of contraindications or situations where it is not possible.

In situations where breastfeeding cannot be maintained, a cow's milk-based infant formula should be recommended, due to the lack of alternative recommendations.[148]

Clinical manifestations

IgE-mediated food allergy

The typical symptoms of an IgE-mediated FA reaction generally have a rapid onset, with variable severity, and may even be life-threatening. Given that this is an immediate-type reaction, identifying the culprit food can be relatively easier, as symptoms typically occur within 2 hours of ingesting the food. Only in exceptional cases might this timeframe be exceeded, such as in cofactor-dependent FA or red meat allergy triggered by IgE antibodies against the α-Gal oligosaccharide, with manifestations occurring up to 6 hours after ingesting the allergenic food.[181] A detailed description of symptoms, together with a comprehensive dietary history, should always be obtained.[182] This should include questions about usual food intake (meals, snacks, beverages), breastfeeding/bottle-feeding difficulties, growth and nutrition in children, eating disorders in older children and adults, body mass index and weight loss in adults, and dietary adequacy. History-taking focused on FA may also identify cases of overweight, undernutrition, micronutrient and macronutrient deficiencies, as well as developmental disorders, feeding difficulties, and food aversion patterns in infants and young children.[183] While the clinical history is invaluable, it may overestimate the presence of FA, necessitating additional diagnostic steps to confirm the diagnosis. A detailed, allergy-focused history allows clinicians to estimate the probability of IgE-mediated FA and guides the selection and interpretation of allergy tests.[4]

IgE-mediated FA symptoms may involve almost all organ systems, including the skin, respiratory tract, and gastrointestinal, cardiovascular, and nervous systems (Table 4).[4] The skin is the main organ involved in acute IgE-mediated FA manifestations, with urticaria and angioedema being the most prevalent symptoms. Hives consist of circumscribed dermal edema surrounded by erythema which usually blanches with pressure

and are characteristically pruritic. They result from plasma extravasation from small blood vessels or capillaries into the dermis, resolving within 30 minutes to 24 hours without residual lesions. They typically occur immediately after eating the culprit food and may last for a few hours when not treated. Recurrence depends on re-exposure. In angioedema, the process is similar but involves deeper layers of the skin, potentially persisting for up to 72 hours and clinically presenting as swelling of the eyelids, lips, and/or face.[184]

It should be noted that FA accounts for approximately 20% of acute urticaria cases and less than 8% of chronic urticaria cases, requiring caution when attributing food as the trigger. Conversely, urticaria may be the initial symptom of anaphylaxis, as approximately 90% of patients who develop anaphylaxis present cutaneous manifestations. Contact urticaria is also commonly described in FA, characterized by the development of a wheal near or at the exact site of skin contact with the food. Importantly, the presence of contact urticaria does not necessarily indicate a systemic FA manifestation[185,186]; it is IgE-mediated and should be differentiated from contact eczema, which results from chronic exposure to a specific allergen – including food, often in occupational settings – and involves a T-cell mediated response.[185,186]

Food-induced urticaria may be accompanied by gastrointestinal or respiratory symptoms, in which case it represents anaphylaxis. Additionally, erythematous macular rash without hives may also be a manifestation. Eczematous rashes may also be a symptom of IgE-mediated FA, although non-IgE-mediated immune mechanisms also play a role in their pathogenesis.[187]

Respiratory symptoms in IgE-mediated FA can affect both the upper and lower respiratory tracts, but they rarely present in isolation. Isolated and recurrent respiratory symptoms should generally not raise suspicion for a food-related etiology; more prevalent causes, such as respiratory allergies, should be considered.[188]

Laryngeal manifestations in IgE-mediated FA reactions include hoarseness, throat tightness, cough, and voice changes, as well as stridor and airway obstruction in more severe cases. Stridor

Table 4
Symptoms of immunoglobulin-E-mediated food allergy[4]

Organ system	Signs and symptoms
Skin	Contact urticaria Systemic urticaria Angioedema Pruritus Flushing Erythema at eczema sites Itchy ears and hands
Gastrointestinal	Itchy throat/mouth Oral/pharyngeal edema Vomiting Nausea Cramping Diarrhea Abdominal pain
Ocular	Conjunctival erythema Itching Tearing
Respiratory	Rhinorrhea, sneezing, nasal obstruction, pruritus Hoarseness Stridor/laryngeal edema Cough Dyspnea Chest tightness Wheezing Cyanosis
Cardiovascular	Pallor Cold sweating Palpitations Presyncope/syncope Tachycardia Hypotension Shock
Neurological	Anxiety “Impending sense of doom” Behavior change Irritability Apathy Lethargy Seizures Syncope/loss of consciousness
Other	Uterine contractions resulting in abdominal pain and bleeding Tremors

is an abnormally high-pitched sound that occurs during inspiration caused by swelling of laryngeal tissues, including the supraglottic, glottic, subglottic, and tracheal regions. It serves as a warning sign of potential airway narrowing.[189]

Gastrointestinal involvement manifests through subjective and objective symptoms. Subjective symptoms include itchy throat or mouth, nausea, and abdominal pain, while objective symptoms include vomiting and diarrhea. The onset of these symptoms is usually immediate, within minutes to no more than 2 to four 4 after food ingestion.

Symptoms such as growth impairment, bloody diarrhea, constipation, weight loss, prolonged malabsorption, and vomiting or diarrhea occurring more than 4 hours after food ingestion are not observed in IgE-mediated allergies.[26]

Involvement of the cardiovascular and neurological systems occurs in more severe cases. Subjective symptoms include dizziness or weakness, while objective signs may include tachycardia, hypotension, altered mental status, severe cardiovascular collapse, unconsciousness, and death. Cardiovascular and neurological symptoms usually occur together with the involvement of other organ systems, such as associated respiratory or cutaneous manifestations.[189]

Anaphylaxis is a severe form of IgE-mediated hypersensitivity allergic reaction that involves multiple organs. It is characterized by a rapid onset and is potentially fatal. Anaphylaxis symptoms may include the cutaneous reactions previously described, along with respiratory, gastrointestinal, cardiovascular, or neurological involvement. Although rare, anaphylaxis may also present with only cardiovascular or neurological symptoms, such as dizziness, weakness, tachycardia, hypotension, cardiovascular collapse, or unconsciousness.[189]

Many studies have shown that clinical manifestations of anaphylaxis differ among age groups. Infants with anaphylaxis most often present with vomiting and urticaria, while preschool children typically present with wheezing and stridor. Adolescents most commonly report subjective symptoms, such as difficulty breathing or difficulty swallowing. Approximately 3% of children present with hypotension as the first symptom of anaphylaxis.[190]

Non-IgE-mediated allergies

Among the manifestations of non-IgE-mediated FA reactions, the infant's symptoms at first presentation are crucial in the diagnostic process.[124] It is important to consider that these symptoms may vary and overlap with common infant complaints, such as irritability, crying, colic, gas, gastroesophageal reflux, diarrhea, constipation, and blood in stool. These findings may not necessarily be related to CMPA, making differential diagnosis very important.[124,191-194]

Often, the lack of suspicion that symptoms may be allergic in nature is responsible for delayed diagnosis.[126] Conversely, overdiagnosis is also common due to the absence of definitive biomarkers for the diagnosis of gastrointestinal and extraintestinal manifestations in CMPA.[126]

There are some distinctive features in non-IgE-mediated CMPA, particularly in mild to moderate cases, which affect most patients. Skin involvement is less common, and when present, cutaneous manifestations tend to appear later during the disease course, often as sparse lesions, pruritus, and nonspecific rashes. Some patients with atopic dermatitis may experience worsening following repeated exposure to the allergen, especially within the first 6 months of life. Skin manifestations such as hives are very common in IgE-mediated forms and typically appear within minutes after allergen contact.[83,124,195] Conversely, isolated respiratory manifestations are very rare in non-IgE-mediated FA.[196-199]

In children over 1 year of age with non-IgE-mediated allergies, symptoms may be more subtle and often nonspecific, including irritability, fatigue, sleep problems, frequent bowel movements, and impaired growth.[126,198] Typically, older children with non-IgE-mediated allergies do not present with blood in stool or other significant signs and symptoms. These patients are often viewed as normal children with subtle symptoms.

During physical examination, it is essential to evaluate for signs of other allergic diseases, such as atopic dermatitis, and to always conduct nutritional monitoring, including assessments of weight, height, abdominal circumference, and head circumference.[121,199,200]

Contrary to immediate reactions, delayed reactions are responsible for chronic or subacute symptoms. The different conditions included within this group may exhibit overlapping clinical findings, but can be distinguished by their clinical features, age of onset, severity, and natural history.[123,199]

It is important to note that during the first year of life, cow's milk proteins account for most FA cases, frequently involving the gastrointestinal tract. The main clinical manifestations of non-IgE-mediated FA are presented in Table 5.[126] In general, depending on the combination of signs and symptoms, non-IgE-mediated FA can be classified into the following clinical presentations:

1. food protein-induced gastrointestinal diseases;
2. food protein-induced allergic proctocolitis;
3. FPE;
4. FPIES.

Food protein-induced dysmotility disorders

The signs and symptoms of food protein-induced dysmotility disorders are typically nonspecific and may result from abnormalities in neuro-immune-inflammatory interactions and intestinal permeability. This condition is typically triggered by cow's milk protein during the first year of life, especially within the first 6 months, but it may occur at other ages as well.[124,126,192,195,198]

Although an immune mechanism has not been clearly established for all clinical situations, a proportion of patients with dysmotility disorders appear to actually fit within the category of non-IgE-mediated FA.[124,126] In these patients, symptoms typically improve following the elimination of the allergenic protein from the diet, with recurrence upon reintroduction of the food or during an OPT. Several nonspecific gastrointestinal symptoms may demonstrate this pattern of improvement with exclusion and recurrence after reintroduction, including regurgitation, vomiting, colic, irritability, crying, abdominal discomfort, gagging, food refusal, excessive flatulence, loose and frequent stools, constipation, and dyschezia. These symptoms may occur in infants without other clinical manifestations and normal weight gain.[124,126] In addition to these symptoms, there may be skin rashes, pruritus, erythema, and moderate to severe atopic dermatitis.[200] There is limited scientific evidence supporting the role of food allergens in these clinical presentations, indicating that further studies are necessary to better understand the mechanisms by which foods cause these symptoms. Given the lack of laboratory tests for the accurate diagnosis of non-IgE-mediated CMPA, ensuring a correct diagnosis is essential to prevent both unnecessary elimination diets and the adverse consequences of a missed diagnosis or inadequate treatment.[201-203]

Gastroesophageal reflux secondary to cow's milk protein allergy

In infants, differentiating between regurgitation (functional gastrointestinal disorder/disorders of gut-brain interaction), gastroesophageal reflux disease (GERD), and gastroesophageal reflux secondary to CMPA is one of the most challenging diagnostic problems in pediatric care and has been debated for over two decades.[204,205]

It is estimated that in up to half of all infants, GERD manifestations are secondary to CMPA (Table 5). Conversely, regurgitation, crying, or colic – criteria included in the diagnosis of functional gastrointestinal disorders (disorders of brain-gut interaction) – may occur in more than 50% of infants and are considered part of the normal gastrointestinal developmental process in the early years of life.[206,207] Therefore, it is important not to confuse infant regurgitation and other isolated digestive symptoms – which represent a physiological, benign, and self-limiting condition that spontaneously resolves within the first year of life – with GERD or CMPA.[124,126,205,208]

In CMPA-induced GERD, the protein is believed to cause gastric emptying delay, leading to gastric distension and dysrhythmia, which in turn increases the number of reflux episodes.[209] While there is no compelling evidence supporting an immunological mechanism, several studies have shown that eliminating cow's milk proteins from the diet leads to a significant reduction in symptoms.

In this context, guidelines published by the European and North American Societies for Pediatric Gastroenterology, Hepatology, and Nutrition in 2009[210] and 2018[211] recommend eliminating cow's milk protein from the diet

Table 5
Clinical presentations of cow's milk protein allergy with gastrointestinal manifestations

Gastroesophageal reflux due to CMPA	It should not be confused with infant regurgitation – a benign condition with reflux episodes that typically resolves spontaneously during the first year of life. It is estimated that up to half of infants presenting with symptoms of gastroesophageal reflux disease have CMPA. A definitive diagnosis of CMPA must be confirmed through oral re-exposure performed 2 to 4 weeks after the resolution of clinical symptoms, following a diagnostic elimination diet. In rare cases, upper gastrointestinal endoscopy with biopsy may be necessary to exclude eosinophilic gastroenteropathy or eosinophilic esophagitis.
Infantile colic due to CMPA	In most cases, it represents a functional gastrointestinal disorder that occurs predominantly between the second week and the fourth or fifth month of life. It has a multifactorial etiology. The suggested causal relationship between colic and CMPA is based on clinical observations that, in some infants, symptoms significantly improve when breastfeeding mothers exclude cow's milk and its derivatives from their diet or when cow's milk proteins are eliminated from infant formulas. Colic due to CMPA is usually associated with other clinical manifestations of CMPA. Due to the nonspecific clinical picture, oral re-exposure is necessary to confirm the diagnosis.
Constipation due to CMPA	In children, constipation is usually functional in nature, but CMPA may be the underlying cause in some cases. The diagnosis must be confirmed through re-exposure after controlling constipation during the elimination diet phase, without the use of laxatives. CMPA should be considered in cases of refractory constipation. It is more common in infants.
Allergic colitis and proctocolitis	These are common presentations of CMPA. They typically begin within the first 6 months of life. The hallmark symptom is the presence of blood in stool. Other causes of rectal bleeding (such as anal fissures or invasive bacterial infections) should be ruled out. Infants with proctocolitis may also present with difficulty passing stools, hard-to-heal anal fissures, and perianal erythema or diaper rash. It frequently occurs during exclusive breastfeeding. Colonoscopy and biopsy are not required unless other diagnoses are being considered.
Cow's milk protein-induced enteropathy	It is characterized by non-bloody diarrhea that may lead to intestinal malabsorption and nutritional deficiency. It typically occurs in the first 6 months of life and is mainly triggered by cow's milk proteins. It can also be caused or aggravated by proteins from soy, rice, fish, and other sources. Small intestine biopsy obtained through endoscopy reveals villous atrophy not associated with eosinophilic infiltration. This presentation is currently very rare.
FPIES	FPIES is a non-IgE-mediated reaction (though occasionally occurring in sensitized individuals) characterized by a heterogeneous clinical picture. It may be triggered by cow's milk or other foods. Symptoms usually resolve over time, similar to other non-IgE-mediated allergies. FPIES is classified into chronic or acute: 1. Chronic FPIES generally arises in the first 6 months of life in formula-fed infants exposed to cow's milk or soy protein. It presents with intermittent vomiting, chronic diarrhea, and impaired weight gain. Concurrent allergy to cow's milk and soy protein occurs in approximately 30% to 40% of cases. Some cases are more difficult to control, requiring parenteral hydration and hospitalization. Symptoms may recur upon re-exposure to the allergenic food. 2. Acute FPIES occurs with intermittent exposure to allergenic foods (eg, rice, oats, fish, egg, chicken, or cow's milk). Vomiting begins 1 to 4 hours after ingestion. Diarrhea, if present, appears 5 to 10 hours later. This form is often accompanied by pallor and lethargy, and around 15% of cases develop dehydration or hypovolemic shock. Treatment of acute episodes includes hydration, ondansetron, and, in some cases, methylprednisolone. 3. Diagnostic criteria have been proposed. Oral food challenge should be indicated and performed according to specific FPIES protocols.

CMPA = cow's milk protein allergy, FPIES = food protein-induced enterocolitis syndrome, IgE = immunoglobulin E.

of infants who do not improve with positional therapy and dietary interventions for persistent regurgitation and vomiting, prior to initiating acid suppression therapy. According to these guidelines, frequent and persistent regurgitation, even as an isolated symptom, may be the only manifestation of CMPA.[205,210] For this reason, elimination of cow's milk from the maternal diet may be recommended for breastfed infants, while formula-fed infants may benefit from switching to extensively hydrolyzed or amino acid-based formulas as alternatives to those containing intact cow's milk proteins.[205,210]

In Brazil, extensively hydrolyzed formulas are recommended as the first-line treatment in these cases.[83,195] Recurrence of symptoms upon re-exposure (2 to 4 weeks after the recovery period during the elimination diet) is essential for confirming the diagnosis. This involves reintroducing a formula with intact cow's milk protein and observing the return of clinical manifestations. When interpreting responses to exclusion and reintroduction of cow's milk protein, it should be considered that hypoallergenic hydrolyzed and amino acid-based formulas have faster gastric emptying rates and increased digestibility, effects that are not specific to FA.[195,209]

Infantile colic secondary to cow's milk protein allergy

In general, infantile colic is a functional gastrointestinal disorder typically observed between the second week and the fifth month of life. Its etiology is multifactorial, involving gastrointestinal factors such as intestinal immaturity, faster motility, unstable autonomic control, and alterations in the intestinal microbiota, as well as factors related to the central nervous system, sleep cycle, and the environment.[126,212]

In clinical practice, some infants show improvement in colic symptoms following the exclusion of cow's milk proteins from the maternal diet (in the case of breastfeeding) or when intact protein formulas are replaced by hypoallergenic formulas (see Table 5). In such cases, the possibility of CMPA should be considered, especially when colic or inconsolable crying is accompanied by other gastrointestinal symptoms, such as vomiting, feeding difficulties, diarrhea, constipation, or dermatological conditions such as atopic dermatitis. In these situations, re-exposure should be carried out and interpreted with the same caution recommended for gastroesophageal reflux secondary to CMPA.[126]

Constipation secondary to food allergy

This possibility should be considered in cases where functional constipation fails to respond to standard treatment or is associated with other symptoms, such as colic, excessive crying, or irritability (Table 5).[124,198,211,213]

It is estimated that approximately 5% of patients presenting with clinical features compatible with functional constipation may actually have an FA.[213] Constipation is most frequently observed in infants shortly after the introduction of cow's milk protein in the diet, particularly when accompanied by persistent anal fissures, a history of blood in stool, or a lack of response to conventional therapies.[214] Notably, constipation due to FA may also occur in preschool and school-aged children.[213] The link between constipation and an immunological mechanism was demonstrated in a clinical study showing an increased number of mast cells interacting with nerve fibers in the rectal mucosa, which were also correlated with anorectal manometric abnormalities.[209]

As with GERD secondary to CMPA, reintroduction of cow's milk protein should be performed and interpreted with appropriate caution.[126] In these cases, bowel habits must remain normal during the elimination diet without the concurrent use of laxatives.

Food protein-induced allergic proctocolitis

Food protein-induced allergic proctocolitis is characterized by the presence of streaks of fresh blood in stool, with or without diarrhea or mucus. It typically presents within the first 6 months of life, usually in otherwise healthy infants (Table 5).[33,124,126,201,215-219]

Among infants with allergic proctocolitis, approximately half of cases occur during exclusive breastfeeding and the other half in formula-fed infants.[33,126,127] In cases of allergic colitis during exclusive breastfeeding, the condition is triggered by maternal dietary proteins (typically cow's milk

or, occasionally, soy), and not by an allergy to breast milk itself. Allergic proctocolitis is the most frequent manifestation of FA in infants who are exclusively breastfed, making it the most common presentation of non-IgE-mediated FA in this population.[127,218-220]

These infants typically present with rectal bleeding while maintaining overall good health and adequate weight gain. The bleeding is often minor and reported as streaks of blood in stool. Colic, irritability, and excessive crying may also be present. This is a transient condition that resolves within the first year of life in most cases. Reports of allergic colitis triggered by egg, wheat, or cow's milk proteins are rare.[33,126,212,221,222]

In clinical practice, the diagnosis of allergic proctocolitis is primarily clinical and often presumptive, based on symptom resolution following the elimination of a suspected food allergen, usually for 2 to 4 weeks. Oral re-exposure confirms the diagnosis. Eosinophilia may be present in up to half of patients.[33] There are no specific laboratory tests to establish the diagnosis and, thus, testing is usually unnecessary.[124,126].

In formula-fed infants, allergic proctocolitis is generally managed within 3 to 4 days by switching from standard cow's milk-based formula to hypoallergenic formula. A recent study showed that 95% of infants with rectal bleeding due to allergic colitis experienced resolution with an elimination diet, although only 30% had a positive OPT upon reintroduction of the allergen after 2 to 8 weeks.[223] These findings confirm the usefulness of elimination diets for clinical improvement and underscore the importance of reintroducing the allergen to confirm the diagnosis and, when possible, reintroduce the food into the diet. If the reintroduction is positive, it should be repeated every 3 months[223] or, at most, after 6 months.[126]

Notably, at least 20% of infants with allergic colitis during exclusive breastfeeding experience spontaneous resolution of bleeding without any dietary changes or medication.[191,200,224,225] As a result, some authors and even families opt for an expectant ("watch and wait") management strategy.[126] A recent literature review concluded that a 2-to-4-week observation period may be appropriate for managing mild allergic colitis in infants who are exclusively breastfed.[226] The authors compared the pros (eg, reduction or disappearance of rectal bleeding, prevention of iron-deficiency anemia, improvement of child and family quality of life, possible reduction in the risk of developing post-inflammatory functional gastrointestinal disorders, and reduction of health care costs) and cons (eg, adverse effects of maternal of infant elimination diet, risk of recurrence due to poor compliance to the diet, family stress, and high cost of hypoallergenic formulas) of the elimination diet,[127] revealing a largely rhetorical debate lacking scientific evidence that can be objectively measured. A particular concern is iron deficiency, which can be harder to detect in the first 6 months of life but may become clinically relevant after this period due to depleted iron stores, especially if bleeding persists during expectant management.

In most cases, bleeding resolves within 1 to 2 weeks of complete elimination of the allergenic protein from the maternal diet.[126,215] This resolution period may be longer in breastfed infants.[126] Nevertheless, bleeding is not a normal occurrence and is a significant source of parental stress. Elimination diets can reduce the duration of bleeding. Moreover, allergic colitis has been identified as a risk factor for the development of future functional gastrointestinal disorders (ie, "post-inflammatory" brain-gut interaction disorders).[205,211,215,217]

Regarding treatment, breastfed infants should continue breastfeeding due to its many benefits. Instead, dietary restriction should be applied to the nursing mother. These infants are typically allergic only to cow's milk protein and show satisfactory improvement upon elimination of this allergen from the maternal diet.[126] In rare cases, additional dietary restrictions, such as soy, egg, wheat, fish, or nuts, may be required.

For infants fed with standard formulas, a switch to extensively hydrolyzed protein formulas is recommended. In severe or refractory cases, and in those with severe atopic dermatitis, amino acid-based formulas are indicated.

Overall, the prognosis is favorable, with symptom resolution occurring within a few months and typically during the first year of life.[227,228]

Food protein-induced enteropathy

FPE most commonly occurs in the first months of life, particularly after weaning and the introduction of cow's milk or soy-based formulas (Table 5). Following the introduction of these foods, the infant may initially show satisfactory weight gain and favorable clinical progression, which then begins to decline. Clinical symptoms may become apparent days, weeks, or even more than a month after introducing the food, as the reaction is delayed and cell-mediated.[191-193]

FPE has an insidious onset and is characterized by malabsorption, chronic diarrhea (typically watery and acidic stools), perianal erythema, abdominal distension, vomiting, anemia, weight loss, and failure to thrive. Similarly to celiac disease, it may present with protein-losing enteropathy, hypoalbuminemia, edema, and varying degrees of malnutrition.[191-193]

Regarding the diagnosis, histological evaluation of the small intestinal mucosa typically reveals an inflammatory infiltrate in the lamina propria composed of lymphocytes, plasma cells, mast cells, and eosinophils. There may also be varying degrees of villous atrophy and crypt hyperplasia. In these cases, differential diagnosis with celiac disease is critical and should consider the density of intraepithelial lymphocytes, serum levels of anti-transglutaminase antibodies, and HLA DQ2 and DQ8 typing.[126,196]

Villous damage results in a reduced absorptive surface, decreased disaccharidase concentrations, and increased intestinal barrier permeability. This facilitates the absorption of macromolecules, which may promote sensitization to other dietary proteins, perpetuating a cycle of immune activation. In addition, villous damage and disaccharidase deficiency may lead to carbohydrate malabsorption, contributing to the production of watery, acidic stools. Infants often present with abdominal bloating and perianal diaper rash. In such cases, it is important to clearly communicate to the family that the infant may experience lactose intolerance due to villous damage. However, the absorptive capacity can be restored after appropriate treatment, which includes elimination of the allergenic proteins and adequate nutritional support.[126,196]

Food protein-induced enterocolitis syndrome

FPIES is a non-IgE-mediated FA. Unlike food protein-induced proctocolitis and enteropathy, FPIES is characterized not only by gastrointestinal symptoms but also by systemic manifestations such as lethargy, acidosis, cyanosis, and shock. For this reason, patients are often initially misdiagnosed with sepsis. In addition to cow's milk and soy, rice, banana, and oats may also trigger FPIES (Table 5).[228-232]

In infants < 6 months of age, cow's milk and soy are the most common FPIES triggers. Among older children, typically above 9 months of age, solid foods such as cereals, fruits, and fish are more frequently involved.[225,231]

There are two clinical forms of FPIES: acute and chronic, with vomiting being the hallmark symptom in both. In acute FPIES, sudden and repetitive vomiting is the most prominent symptom. Other manifestations may include pallor, lethargy, and apathy. Diarrhea, dehydration, hypotension, and even shock can also occur. In contrast to IgE-mediated allergies, signs such as anaphylaxis or respiratory and cutaneous symptoms are not present. Acute FPIES usually arises when the triggering food is consumed intermittently or after a period of dietary restriction. In such cases, symptoms resolve within 24 hours, and patients remain asymptomatic between episodes.[228,230]

Chronic FPIES is more often seen in younger infants who are regularly and repeatedly exposed to the offending food.[216] Symptoms include chronic or intermittent vomiting, diarrhea, poor weight gain, and failure to thrive. Tables 6 and 7 outline the diagnostic criteria for acute and chronic FPIES, respectively.[216,231]

As with other forms of FA, treatment is based on dietary elimination of the offending food. However, in FPIES, due to the risk of hypovolemic shock, hemodynamic stabilization may be required. In mild cases, management with oral rehydration therapy may be sufficient. Moderate to severe cases may require hospitalization, intravenous access, fluid resuscitation (10-20 mL/kg of normal saline), ondansetron (0.15 mg/kg per dose, maximum 16 mg per dose in children over 6 months), methylprednisolone (1 mg/kg intravenously, maximum 60-80 mg per dose in severe cases),

Table 6
Diagnostic criteria for acute food protein-induced enterocolitis syndrome (FPIES)[216]

Major criterion
Vomiting 1-4 h after ingesting the suspected food but no classic IgE-mediated symptoms (skin or respiratory).
Minor criteria
1. At least 1 further episode of repeated vomiting after eating the same suspected food. 2. Repeated vomiting episode 1-4 h after eating a different food. 3. Extreme lethargy with any suspected reaction. 4. Marked pallor with any suspected reaction. 5. Emergency room visit needed for any suspected reaction. 6. Intravenous fluid support needed for any suspected reaction. 7. Diarrhea within 24 h (usually 5-10 h). 8. Hypotension. 9. Hypothermia.
FPIES diagnosis = major criterion plus > 3 minor criteria

Table 7
Diagnostic criteria for chronic food protein-induced enterocolitis syndrome (FPIES)[216,231].

Mild
Low doses of the suspected food (eg, solid foods or food allergens in breast milk) lead to intermittent vomiting and/or diarrhea, usually with poor weight gain/failure to thrive, but without dehydration or metabolic acidosis.
Severe
Regular ingestion of suspected food (eg, infant formula) leads to the development of intermittent but progressive vomiting and diarrhea (occasionally bloody), sometimes with dehydration and metabolic acidosis.

Note:

– The most important criterion in chronic FPIES diagnosis is whether symptoms resolve within days after eliminating the suspected food(s) and acute symptoms recur when the food is reintroduced, including vomiting within 1-4 h and diarrhea within 24 h (usually 5-10 h).
– Without an oral provocation test, a diagnosis of chronic FPIES remains presumptive.

and/or vasoactive agents. Epinephrine and antihistamines appear to have limited efficacy in FPIES management.[215,216]

Another important step in FA diagnosis is the exclusion of other conditions. The differential diagnosis of FA includes: food intolerance, anatomical abnormalities of the gastrointestinal and respiratory tracts, inborn errors of metabolism, celiac disease, cystic fibrosis, GERD, pancreatic insufficiency, intestinal lymphangiectasia, immunodeficiencies, infections (gastrointestinal and sepsis), and early-onset inflammatory bowel disease, among others.

Mixed food allergy

Mixed FA involves both IgE-dependent and IgE-independent pathways. Allergic manifestations resulting from mixed mechanisms include FA-associated atopic dermatitis (6-48 h after exposure) and eosinophilic gastrointestinal disorders.[233,234]

Atopic dermatitis

Some moderate and severe cases of atopic dermatitis in children can be aggravated by food. There are 3 patterns of clinical reactivity to food in patients with atopic dermatitis: immediate-type reactions (IgE-mediated in the first 2 hours after consumption), late worsening of atopic dermatitis (non-IgE-mediated), and mixed reactions, which involve both IgE-mediated and non-IgE-mediated clinical features.[235]

Immediate-type reactions in atopic dermatitis

Immediate reactions in atopic dermatitis manifest with cutaneous symptoms (urticaria, angioedema, flushing) or, in the context of anaphylaxis, respiratory tract symptoms and/or gastrointestinal and/or cardiovascular symptoms. These reactions generally occur within the first 2 hours after consumption, ranging from mild reactions in a single organ to anaphylaxis.[235]

Late worsening of atopic dermatitis

Delayed non-IgE-mediated reactions in atopic dermatitis usually occur 6-48 h after consuming the suspected food allergen. The late worsening pattern in adult-onset atopic dermatitis has not been clearly defined. An oral provocation test (OPT) is essential for objectively assessing suspicion, given the high rate of food sensitization compared to healthy controls, which is often not clinically relevant.[236]

Mixed reactions in atopic dermatitis

Some patients present with more complex symptoms, combining IgE-mediated symptoms and worsening atopic dermatitis.[237] In a study of 64 children with atopic dermatitis who underwent 106 double-blind, placebo-controlled OPTs with chicken egg, cow's milk, wheat, or soy, a mixed reaction occurred in 45%, while a delayed reaction occurred in only 12%.[238] However, in the Danish Allergy Research cohort study, 95% of patients during double-blind, placebo-controlled OPTs had an immediate-type reaction.[239] However, the frequency and pattern of clinical reactivity vary among patients with atopic dermatitis.

Eosinophilic esophagitis

EoE has been recognized with increasing frequency in the last two decades, which may or may not be due to the apparent increase in diagnostic awareness.[240] It is characterized by eosinophilic infiltrate in the esophagus without compromising other segments of the gastrointestinal tract.[241] This chronic, immune-mediated disease of the esophagus is characterized clinically by esophageal dysfunction and histologically by predominantly eosinophilic inflammation.[241,242] EoE can begin in the first few years of life, and its clinical presentation varies with age. In the first few years of life, EoE often presents as GERD, and it is believed to be responsible for approximately 10% of the infants who need treatment for GERD. The clinical presentation includes regurgitation, vomiting, sometimes rumination, lack of appetite, crying after feeding and, sometimes, crying immediately after beginning to feed. This condition results in food refusal and, at times, abnormal head and neck posture and significant arching of the spine (Sandifer syndrome). It may also be associated with melena and iron deficiency anemia.[243] The presence of nonspecific symptoms,

such as vomiting, nausea, abdominal pain, food refusal, choking, low weight gain, and difficulty introducing solid foods occurs in infants and preschool children. More specific symptoms, similar to those seen in adults, are observed in older children and adolescents, such as dysphagia and food impaction, in addition to vomiting and abdominal pain.[244] According to current evidence, in pediatric patients, the time of disease progression without therapeutic intervention can cause remodeling of the esophageal tissue through fibrosis, which is clinically expressed as dysphagia and food impaction.[244]

The symptoms of EoE and GERD are similar, especially in infants and preschool children, which hampers differential diagnosis. Approximately 5% to 10% of pediatric patients who respond poorly to GERD treatment may have EoE. In such cases, a lack of response to proton pump inhibitors should raise suspicion of EoE.[245]

The current diagnostic criteria for EoE are symptoms of esophageal dysfunction and, in the esophageal mucosa, a blood eosinophil count ≥ 15 cells per high-power field in the area of greatest eosinophilic density in at least 1 tissue sample obtained by endoscopy.

Clinical trials have used 3 scales to measure and standardize changes in EoE symptoms, endoscopic findings, and histological findings: the Pediatric Eosinophilic Esophagitis Symptom Score,[246] the Endoscopic Reference Score, and the EoE-specific histologic scoring system, respectively.[247] However, these scores have not yet been validated in the pediatric population for diagnosis or disease activity monitoring. The most recent treatment guidelines from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters attributes a supporting role to these instruments without dismissing intraepithelial eosinophil count as the primary factor in diagnosis and disease activity monitoring.[248]

Non-esophageal eosinophilic gastrointestinal diseases

Apart from EoE, eosinophilic gastrointestinal disorders are rare, chronic, inflammatory conditions with unknown long-term consequences.[249] They are usually nonfatal and are characterized by various gastrointestinal symptoms, eosinophilic infiltration of the gastrointestinal tract, and sometimes peripheral eosinophilia. Diagnosis requires the exclusion of other causes of eosinophilic infiltration and the involvement of other organs. The estimated prevalence of non-EoE eosinophilic gastrointestinal disorders is 2.1-5.1 per 100,000, compared to 10-57 per 100,000 in EoE.[240]

Non-EoE eosinophilic gastrointestinal disorders are a group of diseases subdivided according to the site they affect: eosinophilic gastritis, eosinophilic duodenitis, eosinophilic enteritis, eosinophilic ileitis, and eosinophilic colitis. In addition to the affected area of the digestive tract, their clinical presentation depends on the extent and depth of eosinophilic infiltration. Diagnosis is based on symptoms of gastrointestinal dysfunction, an increased number of eosinophils and eosinophilic inflammation in biopsies, and the exclusion of other causes of eosinophilia (Table 8).[250] Due to the limited literature on non-EoE eosinophilic gastrointestinal disorders, the most recent European and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus standardized the related terms and definitions and provides assistance in diagnosis and treatment. This consensus also suggests maximum acceptable limits or average peak eosinophils to be considered in each intestinal segment (Table 8).[249]

Allergic eosinophilic gastroenteritis

Allergic EoE is much less common than EoE. It affects both adults and children and is rarely seen in the first year of life.[251] In young children, it can cause abdominal pain, irritability, early satiety, vomiting, diarrhea, weight loss, anemia, and hypoalbuminemia due to protein-losing enteropathy. However, the symptoms depend not only on the patient's age, but the organ affected, and the extent (infiltration through the layers of the intestinal wall).[252] Peripheral eosinophilia is found in approximately 50% of patients with allergic EoE. Skin testing and/or serum food-specific IgE tests reveal a food trigger in < 50% of cases. Marked eosinophilic infiltration of the gastric and/or duodenal mucosa, totaling ≥ 30 eosinophils per high-power field, is seen in allergic EoE. However,

Table 8
Suggested peak eosinophil count for diagnosing non-esophageal eosinophilic gastrointestinal diseases[249]

Affected area	Peak eosinophil count per high-power field	Peak eosinophils count per mm²
Stomach	> 30	> 110
Duodenum	> 50	> 185
Terminal ileum	> 60	> 220
Cecum and ascending	> 100	> 370
Transverse and descending	> 80	> 300
Rectum and sigmoid	> 60	> 220

a differential diagnosis must be performed to exclude other causes of gastrointestinal hypereosinophilia.[252]

Eosinophilic colitis

Eosinophilic colitis is the least common form of eosinophilic gastrointestinal disorder, although, like the others, its overall frequency appears to be increasing.[253] It is observed in adolescents in association with inflammatory bowel disease and/or celiac disease and, more rarely, in other atopic conditions.[254] Its association with FA is unclear, but it probably decreases with advancing age. In a retrospective study of 69 children with eosinophilic colitis, FA accounted for 10% of the cases, inflammatory bowel disease for 32%, irritable bowel syndrome for 33%, and other diagnoses for 25%.

Differential diagnoses

Several differential diagnoses should be considered in patients with FA. In previous sections, relevant differential diagnoses of non-IgE-mediated allergy have been mentioned. Table 9 lists the main non-immunological adverse reactions to food that should be considered as differential diagnoses of FA.

Diagnosis

Anamnesis and physical examination

Anamnesis is fundamental in FA diagnosis. At the end of a complete and detailed anamnesis, it should be possible to recognize whether the symptoms are compatible with some manifestations of FA and determine the most likely food and immunological mechanism involved (mediated and/or not by IgE). Additional tests and/or procedures should be planned, such as an oral provocation test (OPT) in cases of greater risk or a restricted diet followed by re-exposure in milder cases.[3,26,158,264] The consultation should investigate:

– characterization of the symptoms, the affected organ, and episode duration (when applicable) and severity;
– age at symptom onset should be related to the age at which the food was introduced (for foods such as cow's milk, manifestations tend to occur during initial exposure);
– time until symptom onset after exposure (a few minutes to 2 h in most IgE-mediated cases) and whether symptoms spontaneously resolve or medication is required;
– reproducibility, ie, whether the symptoms occur only after exposure to the food and if they occur after each exposure;

Table 9
Differential diagnosis of food allergies with other conditions affecting the gastrointestinal tract

Major non-immunological food-related reactions	
1. Gastrointestinal problems	
Non-celiac gluten sensitivity	Although the pathophysiology is undefined, patients may manifest gastrointestinal or extraintestinal symptoms after gluten ingestion, but there are no laboratory results compatible with celiac disease or wheat allergy.[255]
Gastroesophageal reflux	More than 50% of healthy babies regurgitate after feeding in the first few months of life, with symptoms disappearing by 12 months of age. Reflux is only considered pathological if it is associated with peptic mucosal injury (esophagitis, peptic stricture, Barrett's disease, metaplasia, adenocarcinoma), growth retardation, or respiratory complications.
Irritable bowel syndrome	This functional disorder is characterized by abdominal distension, meteorism, abdominal pain, and changes in bowel habits, but no biochemical or structural changes are detectable through available methods.[257]
Intolerance to fermentable oligo-di-mono-saccharides and polyols	These naturally occurring carbohydrates are found in various foods. When not absorbed in the small intestine, they reach the colon and undergo fermentation by intestinal bacteria, which produces gases and liquids.[255]
Small intestinal bacterial overgrowth and small intestinal fungal overgrowth	Excessive bacteria and/or fungi in the small intestine cause the following symptoms: diarrhea, bloating, gas, abdominal discomfort, constipation, and nausea.[255]
Cystic fibrosis (pancreatic insufficiency)	This autosomal recessive genetic disease is characterized by pulmonary manifestations, specifically chronic obstructive pulmonary disease, sinusitis, malabsorption due to exocrine pancreatic insufficiency (leading to malnutrition), biliary cirrhosis, and cystic fibrosis-related diabetes.[258]
Gallbladder diseases	Sclerosing cholangitis, cholelithiasis and cholecystitis.[258]
2. Toxic reactions	
Seafood	
Scombroid syndrome	This syndrome involves skin and respiratory symptoms due to histamine production in response to the histidine decarboxylase produced by bacteria in fish and seafood.[259]
Ciguatera poisoning	Herbivorous fish feed on macroalgae and coral reef substrates from which ciguatoxins are derived, which accumulate in their muscles. There are no routine tests to identify contaminated fish or to determine when this toxin occurs on reefs. Ciguatera poisonings are characterized by severe gastrointestinal and neurological symptoms.[260]
Saxitoxin	This toxin, produced by cyanobacteria and dinoflagellates, is absorbed by shellfish such as oysters and mussels and can reach humans through food. It can cause respiratory paralysis and death.[255]
Fungal toxins (mycotoxins) *Aflatoxins, trichothecenes*	Aflatoxins, the most common and heat-stable toxins, are mainly produced by *Aspergillus spp.* They can be found in corn, peanuts, walnuts and Brazil nuts. The clinical consequences vary, depending on the frequency and quantity ingested, from bloody stool to carcinogenesis.[255]
Bacterial toxins *Clostridium botulinum, Staphylococcus aureus*	Botulism is a potentially fatal disease that often presents with subtle symptoms that can progress to paralysis and respiratory failure.[255]

Table 9 *(continued)*
Differential diagnosis of food allergies with other conditions affecting the gastrointestinal tract

Major non-immunological food-related reactions	
3. Intolerances	
Enzyme deficiencies	
Disaccharidase deficiency:	
Lactose, Sucrose-isomaltase	This is a deficiency of certain substances, mainly enzymes, necessary for the absorption and digestion process of some foods.[255]
Inborn errors of metabolism	This is a class of rare genetic diseases in which the enzymatic defect can lead to interruption of a metabolic pathway, altering cellular processes in different ways. Some examples include phenylketonuria, galactosemia, and fructosemia.[255]
Pharmacological intolerance	These are reactions caused by direct pharmacological action (on tissues or receptors), of certain substances present in some foods, which cannot be adequately metabolized by some individuals.[255]
Caffeine	Coffee, green tea, black tea, guarana.[255]
Theobromine	Tea and chocolate.[255]
Histamine	Aged cheese, processed meat, wine.[255]
Tryptamine	Tomato, plum.[255]
Tyramine	Cheese, canned fish.[255]
Serotonin	Banana, tomato.[255]
Solanine alkaloid	Potato.[255]
Alcohol	Wine, sparkling wine, beer, spirits.[255]
Food additives	
Antioxidants	Butylhydroxyanisole, butylhydroxytoluene, propylgallate.[255]
Stabilizers	Guar gum.[255]
Spices	Cinnamon, ginger, mustard, pepper, paprika.[255]
Colorants	Saffrona, carmine red, annatto, tartrazine.[255]
Flavorings	Monosodium glutamate.[255]
Preservatives	Sulfites, benzoates, nitrates.[255]
4. Infections	
Bacteria	*Salmonella, Shigella, Escherichia coli, Campylobacter.* [255]
Parasites	*Giardia, Trichinella, Amoeba.* [255]
Viruses	Enterovirus, rotavirus, hepatitis.[255]
5. Neurological reactions	
Auriculotemporal syndrome (Frey syndrome)	This syndrome, which is characterized by gustatory sweating and/or flushing, results from damage to the parasympathetic nerve fibers of the parotid gland, with subsequent reinnervation of the sweat glands in the skin.[261]
Gustatory rhinitis	This condition is characterized by a watery rhinorrhea a few minutes after ingesting spicy foods, such as pepper or foods containing capsaicin.[262]
6. Psychological disorders	
Food aversions	Aversion to certain foods or drinks can be caused by trauma, psychological blockage, or food selectivity.
Munchausen syndrome and Munchausen syndrome by proxy	These disorders characterized by the fabrication or induction of signs or symptoms of a disease, as well as abnormal laboratory results.[263]
7. Accidental contamination	
Pesticides	Glyphosate, pirimiphos-methyl.[255]
Antibiotics	This occurs when the patient is allergic to an antibiotic added to the food.[258]

[a] Can trigger IgE-mediated reactions.

– the quantity and processing level (raw, cooked, etc.) of the suspected food, as well as the route of exposure (oral, inhalation, or cutaneous);
– factors associated with the episode, especially physical activity, infections, alcohol or medication intake, and hormonal factors;
– whether symptoms improve after excluding the suspected food and worsen after re-exposure to it.

When the patient is not having an acute allergy episode, a detailed physical examination can detect other allergic comorbidities, such as asthma, allergic rhinitis, and atopic dermatitis, which favor a diagnosis of IgE-mediated FA.[3,26,158,260]

Investigating allergic sensitization

Investigating FA sensitization by specific IgE testing is only relevant if IgE-mediated FA is suspected or as an initial step in the investigation of mixed allergies. It is important to emphasize that investigation of specific IgE for multiple foods, suspected and non-suspected, does not benefit late FA diagnosis; on the contrary, it may lead to unnecessary exclusions.

To diagnose immediate-type FA, the specific IgE can be determined from the source, such as cow's milk, egg, and peanut, or to components (example: casein, ovomucoid, or Ara h 2).

Allergic sensitization can be detected by *in vivo* and *in vitro* tests.

Since not all *in vivo* or *in vitro* tests are absolute, their results should always be interpreted in light of the patient's clinical history. If the clinical history is highly suggestive, FA cannot be ruled out if the tests are negative; further investigation will require OPT or, when possible, a basophil activation test for peanut and sesame allergy.[4]

In vivo

Skin prick tests are used for *in vivo* sensitization assessment. These semi-quantitative tests should always be performed in a suitable environment (ie, clinic, office, or hospital) by a trained physician, as they must be carefully performed and interpreted. Although the use of standardized extracts gives these tests positive predictive values of up to 60%, they are rarely positive in the absence of IgE-mediated allergies (negative predictive value of up to 95%). There are few standardized food extracts, and an additional internationally recognized strategy is the use of prick tests with fresh food, a technique called "prick-to-prick" testing. The fresh food is punctured and then the prick is inserted percutaneously. The results, which can be assessed after 15 to 20 min, consist of measuring the papule that forms at the puncture site, the positive control (histamine) site, and the negative control (saline solution) site. Fresh food increases the test's sensitivity to heat-labile or lipophilic allergens that could be destroyed or removed during extract preparation.

In vivo tests provide rapid results that can be viewed by the patients themselves and can be used as an educational resource. They have high sensitivity, a high negative predictive value (negative results exclude up to 95% of IgE-mediated allergy cases), a low positive predictive value (high false-positive rate), allow testing with fresh food, have low specificity, and generally have a low risk of systemic allergic reactions.[258,265,266]

The basic requirements for performing and interpreting *in vivo* tests include a trained professional, having discontinued antihistamines for 5-7 days, prior skin cleansing and selecting a site without skin lesions.

The results are considered positive when a papule forms with a mean diameter of ≥ 3 mm in patients whose positive control was also positive negative control was negative. Some international guidelines consider the possibility of "deducting" the mean diameter of the negative control papule from the allergen result. For this method, the food papule must also be ≥ 3 mm. There are no age restrictions on the test, although in it should be remembered that children < 6 months of age may have low levels of skin reactivity.

In vivo tests depend on the operator and high quality extracts, and the results may vary. There are also limitations regarding the use of medications and the presence of skin lesions.

In vitro

The detection of circulating specific IgE for suspected allergens also presents high sensitivity, low specificity, and high negative predictive value.

In this context, negative tests result practically rule out a diagnosis of IgE-mediated FA. The positive predictive value of specific IgE is highly variable in different populations, as it differs with age, geographic location, ethnicity, as well as the presence of other allergic diseases, especially atopic dermatitis. In atopic dermatitis, due to the high serum levels of total IgE, sensitization to multiple foods is very common, although it may not necessarily be related to clinical reactivity.[256,257]

Another important aspect in specific IgE testing is the method the laboratory uses, eg, whether it is performed using fluoroenzyme or chemiluminescence immunoassays. The methods provide different and non-interchangeable results, with results generally higher in chemiluminescence. These differences can lead to false interpretations and interfere with the case management.[258]

Specific IgE detection for some food components can facilitate FA diagnosis, especially when the history and/or whole-source IgE do not clarify the case (eg, patients with atopic dermatitis and positive tests, multisensitized patients, or situations of laboratory reactivity). In these cases and for certain foods, testing for component-specific IgE to may be relevant.[4,257]

In suspected peanut and hazelnut allergy, peanut components Ara h 2 and Ara h 6 and hazelnut components Cor a 9 and Cor a 14 showed moderate sensitivity and high specificity, aiding in the diagnosis of more complex cases. Cashew nut component Ana o 3 has high sensitivity and specificity values and may be useful in diagnostic confirmation. Components of cow's milk (alpha lactalbumin, beta-lactoglobulin, casein) and egg (ovalbumin, ovomucoid) can be more useful in determining the severity and persistence of the allergy than in diagnosis. Table 10 shows food components related to FA. Multiplex specific IgE testing is possible, given that small amounts of serum allow assessment of several components simultaneously. ImmunoCap ISAC® (Thermo Fisher Scientific Inc., Waltham, MA, USA) is the multiplex specific IgE testing platform currently available in Brazil.[4,257]

One advance in the diagnosis of *in vitro* sensitization is the basophil activation test. In this test, circulating basophils from individuals suspected of FA are stimulated with food allergens and the degranulation of these cells is quantified in comparison with positive and negative controls. This test appears to have a higher positive predictive value, but there is a need to standardize each tested allergen. The mast cell activation test is similar to the basophil activation test but is more expensive and has a lower negative predictive value.[4]

Table 11 compares diagnostic tests for foods in IgE-mediated FA.

Patch test

The food patch test is a variation of the standard test for contact dermatitis. Its adaptation for FA diagnosis arose from the search for complementary tests to diagnose mixed mechanism or non-IgE mediated allergies. Since the early 2000s, efforts have been made to standardize this test so that it can play a reliable diagnostic role. For now, the results are very heterogeneous and it should not be recommended for diagnosing FA, except in specific situations, such as suspected allergic contact dermatitis due to food.[260]

Other examinations

Coprological examinations

Due to the scarcity of FA diagnostic tests, especially for non-IgE mediated allergies, there is a growing interest in biomarker identification. Fecal alpha-1-antitrypsin levels are used to assess gastrointestinal protein loss, which could be altered in cases of dietary protein-induced enteropathy. However, this non-specific test cannot establish or rule out FA as the cause of protein loss.[177,261]

Fecal hemoglobin tests may be positive in cases of FA, especially in children < 1 year of age with allergic proctocolitis. Like fecal alpha-1-antitrypsin tests, it is nonspecific and cannot establish or rule out FA as the cause of bleeding. Furthermore, when following up children, it should not be used to assess the resolution of allergic proctocolitis. In addition to not having been validated, requesting fecal hemoglobin tests in FA follow-up may lead to overdiagnosis and is not supported by international FA guidelines.[200,221]

Table 10
The relevance of main food components in food allergy[4,257]

Food	Main components	Specific IgE to this component could indicate
Milk	Caseins (set of caseins)	Allergy persistence
	α-Lactalbumin	
	β-Lactoglobulin	
	Bovine serum albumin	Reaction to meat proteins
Egg, white	Ovomucoid	Greater allergy severity and persistence
	Ovalbumin	Greater clinical relevance of egg white proteins
Egg, yolk	Livetin	Egg yolk allergy, related to chicken-egg syndrome
Wheat	ω-5 gliadin	Severe reactions in adults and clinical reactivity in children
Peanut	Ara h 2, Ara h 6, Ara h 9	Greater clinical reactivity/severity
	Ara h 8, Ara h 5	Minor reactions
Nuts		
Hazelnut	Cor a 14, Cor a 11, Cor a 9	Greater clinical reactivity/severity
	Cor a 1, Cor a 8, Cor a 2	Minor reactions/oral allergy syndrome
Almond	Pru du 1, Pru du 3	Minor reactions/oral allergy syndrome
Cashew	Ana o 3, Ana o 2	Greater clinical reactivity/severity
Pistachio	Pis v 1, Pis v 3, Pis v 2	Greater clinical reactivity/severity
Walnut	Jug r 1, Jug r 2, Jug r 4	Greater clinical reactivity/severity
	Jug r3	Minor reactions/oral allergy syndrome
Brazil nut	Ber e 1	Minor reactions/oral allergy syndrome
Crustacean	Tropomyosin	Cross-reactivity with animals of very different species
Meat	Alpha-gal	Delayed anaphylaxis after meat ingestion
Latex and fruit	Hev b 1 rubber elongation factor	Cross-reactivity with papaya and fig
	Hev b 6.01 (prohevein) PR-3 Hev b 6.02* (hevein) Hev b 6.03 c-terminal fragment	Cross-reactivity with avocado, banana, and hazelnut
	Hev b 5 Acid protein	Cross-reactivity with kiwi
	Hev b 7 Patatin homolog	Cross-reactivity with potato
	Hev b 11 Chitinase	Cross-reactivity with banana and avocado
	Hev b 12 (*Hevea brasiliensis* lipid transfer protein)	Cross-reactivity with peach and other stone fruits
	Hev b 15 Protease inhibitor	Cross-reactivity with wheat

IgE = immunoglobulin E.

Calprotectin, a cytosolic protein that binds calcium and zinc, has immunomodulatory and antimicrobial properties. It is derived primarily from neutrophils and can be measured in various body fluids, including serum and feces. Levels increase with inflammation, infection, and malignancy. Fecal calprotectin is widely used in diagnostic screening and monitoring for patients with inflammatory bowel disease. However, as a marker of FA, inconsistent research results have been found. Using the Cow's Milk-Related-Symptoms Score, a recent study found a strong relationship between symptom severity and calprotectin levels in children.[262] Similarly, a meta-analysis concluded that fecal calprotectin may be a simple and reliable biomarker for the diagnosis of CMPA, especially for infants with non-IgE-mediated CMPA.[263] Another study found improvement (ie, a reduction) in calprotectin levels in children with CMPA after 3 months of a cow's milk protein-restricted diet.267 In contrast, other authors have concluded that fecal calprotectin does not discriminate between healthy infants and those with CMPA.[259] In 2021, ESPGHAN determined that fecal calprotectin levels show considerable variability in children with atopic diseases, making it difficult to draw definitive conclusions about the effectiveness of this test for diagnosing or monitoring of allergic conditions. Thus, fecal calprotectin measurements are not recommended for diagnosing or as a prognostic marker for CMPA in children.[268]

Upper gastrointestinal endoscopy

In patients with FA, upper digestive endoscopy may reveal the presence of esophagitis, gastritis, and lymphoid nodular hyperplasia, but it should only be requested in individual cases and must be carefully evaluated by experienced pediatric gastroenterologists. The histological study of endoscopic biopsies is important because it quantifies the distribution of eosinophils along the esophagus and, thus, distinguishes between GERD and EoE, which may have similar clinical manifestations in infants. Intestinal villous atrophy may be observed in cases of FPE and FPIES syndrome. Antral and/or duodenal biopsies in children with CMPA can show a large number of intraepithelial lymphocytes and eosinophils in the lamina propria and eosinophilic cryptitis. Such findings add information, but cannot establish or exclude the diagnosis of CMPA, since they can be found in other upper gastrointestinal diseases or allergies to other foods. Therefore, because it is an invasive test that requires sedation, it should be reserved for more severe cases or for differential diagnosis. Upper gastrointestinal endoscopy should be requested by a specialist in pediatric

Table 11
Characteristics of diagnostic tests for food allergens[4]

Test	Sensitivity	Specificity	PPV	NPV
Skin prick test	High	Low	Moderate	High
Specific serum IgE	High	Low	Moderate	High
Component-specific t IgE [a]	Moderate	High	High	Moderate
Basophil activation test [b]	High	High	High	High
Oral Provocation Test	High	High	High	High

[a] Useful for some allergenic components.
[b] Useful for some allergens.
PPV = positive predictive value, NPV = negative predictive value, IgE = immunoglobulin E.

gastroenterology and should be performed by a trained endoscopist.[126]

Colonoscopy

The most common colonoscopy findings in FA are focal or diffuse colitis, with edema and erosions, focal erythema of the mucosa, loss of vascular patterns, ecchymoses, and nodular lymphoid hyperplasia, all of which are nonspecific. Nodular lymphoid hyperplasia is a common finding in infants with CMPA and can be found in the colon and/or terminal ileum. In histological findings, it is important to quantify eosinophils in different segments of the colon. In neonatal transient eosinophilic colitis, the endoscopic and histological findings are the same as in CMPA, but the bleeding observed in this condition is self-limited and stops without a cow's milk protein-restricted diet. Despite these findings, routine upper or lower gastrointestinal endoscopy should not be recommended for CMPA diagnosis due to the unspecific nature of the endoscopic and histological findings. Invasive tests should be reserved for the most severe cases and/or for differential diagnosis, evaluated on a case-by-case basis. Colonoscopy should be requested by a specialist in pediatric gastroenterology and should be performed by a trained endoscopist.[126]

After clinical suspicion, the diagnosis is confirmed by symptoms upon re-exposure to the suspected food, ie, if the clinical condition improves after restricting the suspected food for a time, it must be reintroduced, and the symptoms must be reappear.

Using amino acid formula as an initial option for a cow's milk protein elimination diet may represent a dominant diagnostic tool from a pharmacoeconomic point of view, considering that a lack of clinical response, in practice, rules out FA in infants. A Brazilian pharmacoeconomic study on CMPA diagnosis, which has recently been cited in international guidelines, investigated the cost-effectiveness of using amino acid formula in an elimination diet, followed by re-exposure, finding that this strategy resulted in a 9% cost reduction and 25 fewer days of symptoms.[126,223] Other countries, including Australia, China and Turkey, also follow this practice.[126]

Non-recognized tests

There has been a real increase in both the prevalence of FA and its overdiagnosis based on alternative tests with no evidence of diagnostic efficacy (ie, specificity, sensitivity, justification, and reproducibility). Patients should be warned about the risks of indiscriminate testing, which causes financial, psychosocial, and nutritional harm and often delays appropriate therapy. Table 12 lists tests that are not recognized as effective for FA diagnosis, as well as scientific evidence for not performing them.

Food re-exposure and oral provocation test

Diagnosing FA remains a challenge, especially non-IgE-mediated allergies, which involve delayed reactions and often have nonspecific manifestations, such as nausea, vomiting and diarrhea, and which may occur in other diseases or clinical conditions. Thus, overdiagnosis and underdiagnosis occur frequently. Underdiagnosis entails nutritional and allergic reaction risks, including acute reactions, failure to thrive, micronutrient deficiencies, impaired quality of life for patients and caregivers, increased morbidity, and even mortality. However, overdiagnosis has been associated with several undesirable consequences, such as unjustified elimination diets and the economic burden on families and the health system. Therefore, correct diagnosis of FA is very important, and dietary re-exposure, whether through OPT (when there is a risk of severe and acute manifestations) or at home, plays a fundamental role.[273]

After diagnostic suspicion of severe reactions (IgE-mediated, FPIES, etc.), an elimination diet is recommended for a period, followed by an OPT (diagnostic stage). When tolerance to the food can be acquired, it is important to perform a new OPT (tolerance assessment stage). Whether for diagnosing FA or assessing the development of tolerance, there are 3 formats of OPT:

– open: both the patient and doctor aware of the food;
– single blind: conducted in 2 stages, only the doctor knows the difference between the test and placebo foods;

Table 12
Tests of dubious value for diagnosing food allergies

Test	Scientific evidence
Specific serum IgG and subclass measurement	IgG4 is part of the immune response to a food, and specific IgG4 is present in the tolerance response to allergens. IgG does not identify intolerance to a food.[4]
Hair analysis	A British study on 9 people with fish allergies (proven in OPT) and 9 healthy controls. Hair samples were sent to different laboratories. No laboratory identified the fish allergy, but several other "allergies" were diagnosed for which no clinical indication was found.[269]
Cytotoxic test	This examiner-dependent microscopy test analyzes morphological changes in leukocytes after the addition of antigens (up to 180 different food allergens per test).[270] The studies lack reproducibility and are unable to detect allergy in patients with proven allergic conditions in OPT.[270]
Kinesiology	In this test, the investigated allergens are prepared in stoppered glass vials. The patient holds the bottle in one hand, and decreased in muscle power in the contralateral arm is considered a positive result.[271] It was concluded that this method is no more useful than random guessing.[270]
Iridology	This method uses iris patterns and colors to diagnose food allergies. A systematic review found no scientific support for the validity of iridology as a diagnostic tool.[270] The possibility of false positive and false negative results may result in harmful therapies.[270]
Bioresonance, Vegatest, and electrodermal test	These tests observe changes in the electrical impedance of the skin at an acupuncture point in allergic response to foods placed at another point in an electrical circuit.[272] In a randomized double-blind trial of 30 individuals with positive (15) or negative (15) results in skin prick test for mites or cat hair, these tests failed to distinguish between sensitized and non-sensitized participants.[270,272]
Genetic analysis, polymorphism detection	Although alterations in a number of genes have been implicated in the development development of food allergy, no validated genetic markers for FA diagnosis have been found.[4]

IgG = immunoglobulin G; OPT = oral provocation test.

– double-blind, placebo-controlled: conducted in 2 stages, neither the patient nor the doctor knows the difference between the test and placebo foods; the food must be prepared by a third party, usually the nutritionist.

The double-blind, placebo-controlled OPT is the gold standard for FA diagnosis, but it is time-consuming and must be performed by specialists in a hospital setting. Due to its high cost and difficulty, this test has been used only in special situations to avoid interpretation bias or when the objective is scientific research. Therefore, due to its simplicity and socioeconomic reasons, the single-blind and the open formats are considered satisfactory for diagnostic purposes in clinical practice.[177,273]

OPT involves careful clinical and laboratory evaluation, and risk stratification is based on several factors:

– the occurrence of a reaction after contact in the last 6-12 months;
– a history of anaphylaxis;
– uncontrolled asthma or exercise-induced asthma;
– a history of reaction to foods that are associated with more severe reactions;
– cofactors such as menstruation, infectious diseases, fasting, proton pump inhibitor use, and alcohol intake;
– elevated levels of specific serum IgEs, especially to protein markers such as ovomucoid, casein, ω-5-gliadin, and storage proteins.[274,275]

Elimination diet

After diagnostic suspicion, an elimination diet should be implemented. For infants with CMPA who are exclusively breastfed, the mother should begin a cow's milk-restricted diet that includes calcium and vitamin D supplementation. For infants with CMPA who are not breastfed or are mixed-fed, extensively hydrolyzed formulas are the first choice for treatment.[201] If there is diarrhea lasting > 1 week, lactase deficiency may be suspected and, in these cases, lactose-free extensively hydrolyzed formula is recommended.[126,276,277] Amino acid formulas are indicated when symptoms persist during use of extensively hydrolyzed formula or in more severe cases, such as: (i) anaphylaxis; (ii) significant nutritional impact and/or failure to thrive; (iii) multiple and severe FA; (iv) severe acute and chronic FPIES; (v) EoE that does not respond to an allergen elimination diet; (vi) clinical situations that require avoiding any risk of sensitization.[278,279]

Although not widely applied, some guidelines recommend a step-down approach that begins with amino acid formula in the diagnostic elimination diet. If re-exposure is symptomatic, extensively hydrolyzed formula is then used for the therapeutic elimination diet. In Brazil, this is considered a pharmacoeconomical approach that results in fewer days with symptoms.[223] Other publications have also recommended amino acid formula for diagnostic elimination diets.[276]

Where available, rice hydrolysate formula is an option for infants with CMPA,[280,281] although compared to extensively hydrolyzed and amino acid formulas, only a limited number of studies have used it.[126] Since the arsenic content in rice hydrolysate formula is 10 times lower than the World Health Organization's recommended limit, it is considered safe by the ESPGHAN Nutrition Committee.[282,283] To date, no data have been published on the efficacy of rice hydrolysate formula as an alternative to amino acid formula in infants who cannot tolerate extensively hydrolyzed formula. Rice hydrolysate formula has not been evaluated for safety or nutrition in the same way as extensively hydrolyzed formula or amino acid formula.

Table 13 summarizes the ESPGHAN consensus recommendations on elimination diets for non-breastfed infants, and Figure 4 illustrates the modified algorithm for CMPA oral re-challenge. Given the specificities of each hydrolysate, if allergy is confirmed, the same the formula used in the diagnostic elimination phase should be used in the therapeutic diet.

The doctor and the family should decide together on the re-exposure type, whether OPT (in a controlled environment with a trained team) or at home (if the risk of a severe reaction is low), and at what point re-exposure should take place. The decision should consider factors such as clinical history, age, symptom types, time of last reaction, *in vivo* and/or *in vitro* sensitization test results, and the nutritional value of the suspected food.

FA symptom resolution varies from a few hours in immediate and FPIES to several weeks in FPE.[196] In general, an elimination diet is recommended for 2-4 weeks and could take up to 8 weeks in severe cases of FPE.[273] If symptoms persist, the diet should be carefully re-evaluated due to the possibility of cross-contact, or another diagnosis may be considered.[260] After this period, if there is clinical improvement, food re-exposure should be attempted to define the diagnosis.

OPT should not be performed on patients with acute febrile illnesses, respiratory symptoms, and/or who have used beta-agonists to treat asthma attacks in the previous 48 h, since these conditions may increase the risk of reactions. Likewise, beta-blockers should be discontinued, if possible, because they compromise the action of adrenaline. Pregnancy, decompensated heart failure, and severe chronic lung disease are relative contraindications. Antihistamines should be discontinued an average of 7 days before the test.[275] For diagnostic purposes, the food should be reintroduced in its natural form after 2-4 weeks of dieting.[197]

The setting for oral provocation tests

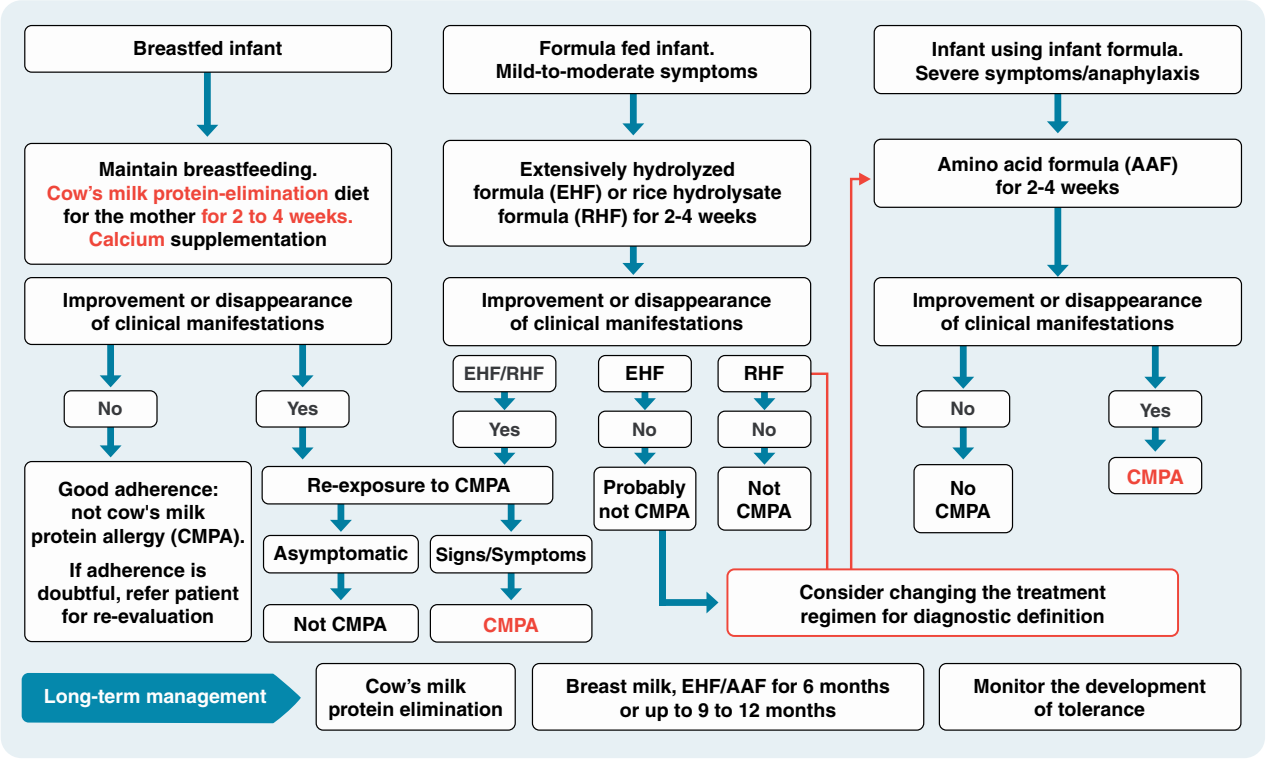
The OPT, a medical procedure performed in an environment prepared for an anaphylaxis reaction by specialists and trained staff, is indicated for:

– IgE-mediated FA.
– severe non-IgE-mediated FA, such as FPIES;
– atypical FPIES (associated with food-specific IgE positivity).

Table 13
European Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus recommendations on diagnostic elimination diets for non-breastfed infants[126]

In formula-fed infants, extensively hydrolyzed formula derived from cow's milk protein is the first choice for the diagnostic elimination diet.
Only formulas tested in randomized clinical trials should be used.
Not enough comparative trials have been conducted to recommend whether cow's milk whey protein hydrolysates should be preferred over casein protein hydrolysates.
In patients with CMPA and severe diarrhea and/or severe malnutrition, 2-4 weeks of a lactose-free hydrolyzed formula may be recommended.
For formula-fed infants, in the elimination diet (diagnostic phase), AAF should be reserved for severe cases or those with persistent symptoms after using extensively hydrolyzed formulas. AAF should be used from the beginning in severe cases involving anaphylaxis, FPIES, eosinophilic esophagitis, and when there is no response to hydrolysates.
Some publications recommend a step-down approach, but there is insufficient evidence to recommend AAF as a diagnostic elimination diet for all children with suspected CMPA.
Although less studied than extensively hydrolyzed formulas derived from cow's milk protein, rice hydrolysate formula can be considered as an alternative for a diagnostic elimination diet.
Soy-based infant formula should not be used as a first choice for a diagnostic elimination diet, but it may be considered in some cases for economic, cultural, and palatability reasons.

CMPA = cow's milk protein allergy, AAF = amino acid formula, FPIES = food protein-induced enterocolitis syndrome.



CMPA = cow's milk protein allergy, AAF = amino acid formula, FPIES = food protein-induced enterocolitis syndrome.

Figure 4
Clinical management after cow's milk protein allergy is suspected, including description of the formulas used in the diagnostic elimination diet

Modified from Vandenplas, et al.[126]

However, re-exposure can be performed at home under the supervision of with:

– mild or moderate forms of non-IgE-mediated allergy, such as food protein-induced proctocolitis;
– mild, nonspecific manifestations of non-IgE mediated allergy (abdominal pain, nausea, gut dysmotility).[284]

Recommended oral provocation test protocols according to the involved immunological mechanism

Before beginning the OPT, the patient's parents or guardians should read and sign an informed consent form, and the patient's health status be assessed, including verification that no medications are being used that could interfere with the outcome. Furthermore, any equipment or medications necessary in the event of reactions must be easily accessible.

In IgE-mediated allergies, the normal regimen consists of 4-6 increasing doses administered at intervals of 15 to 30 minutes, culminating in the normal portion for the patient's age. Greater fractionation of the doses is not recommended due to the risk of desensitization and false negative results. However, patients at high risk of reaction can start with 1% of the total dose, while low-risk patients can receive a 2-dose regimen (10% and 90%). There is also a low-dose protocol, in which the final dose is much lower than traditional protocols. Low-dose OPTs release small amounts or traces of the food, thus improving the patient's quality of life.[285] Yanagida et al. suggest 2 mg of

boiled egg protein and 102 mg of protein from heated milk as initial doses.[286]

In IgE-mediated allergies, the OPT results are considered positive when the patient presents ≥ 1 of the following symptoms:

– cutaneous: ≥ 3 hives, angioedema, or a pruritic erythema;
– respiratory: wheezing, persistent cough, stridor, dysphonia, aphonia, or respiratory distress;
– gastrointestinal: vomiting, diarrhea and/or abdominal pain for > 3 min;
– hypotension.

Or if ≥ 2 of the following symptoms occur:

– pruritus for > 3 min, itchy eyes or nose for > 3 min, runny nose for > 3 min, diarrhea.[275]

For patients with FPIES with a history of severe reactions, peripheral venous access is indicated, since approximately 15% may develop hypotension. The protein dose is 0.06 to 0.6 g per kilogram of body weight, reaching a maximum dose of 3 g (10 g from whole food/100 mL from liquid). The classic protocol consists of 3 stages with equal doses, administered at 30-min intervals. A regular portion may be added after 2 h, and clinical observation should continue for at least 4 h. A lower initial dose or longer observation time should be considered in patients with a history of severe reactions.[275]

It is important to note that some authors have criticized the classic protocol, since the dose would progress before the usual time of symptom onset, which is 1-4 h. An alternative would be to offer the doses on different days, with a 48-hour interval between each dose: 25% dose on the first day, 50% dose on the third day and 100% dose on the fifth day. Although such an arrangement would apparently involve a lower risk of severe reactions, it involves time and cost difficulties.[287] The results are considered positive if typical symptoms appear 1-4 h after ingestion (Table 14). Vomiting in the absence of skin symptoms is considered the major criterion and lethargy, pallor, hypotension, hypothermia, diarrhea, and neutrophilia are considered minor criteria. It should be noted that prompt treatment with ondansetron could prevent the minor criteria, so each case should be evaluated separately.[192]

Observation time after oral provocation testing and test completion

In IgE-mediated allergy, the response to OPT is more easily recognized, since the symptoms are specific and immediate, ranging from a few minutes to 2 h after ingesting the allergen. In FPIES, manifestations occur within the first 4 h after ingestion. In non-IgE-mediated allergies, the time interval between ingestion and symptoms varies from a few hours to a few days. Thus, to complete the test in non-IgE-mediated phenotypes, patients should be followed up for 4 weeks, even if they remain asymptomatic for the first few days. After re-exposure, the recurrence of clinical manifestations confirms the diagnosis of FA.

Oral provocation testing to assess tolerance

Once FA has been diagnosed, the development of tolerance should be assessed during follow-up through an OPT. Where the test is performed and how to interpret the results are similar to the diagnostic phase. There are some particularities related to when and how to perform the test.

When to perform oral provocation testing

The ideal time for re-exposure to assess tolerance depends on the clinical phenotype of FA and the severity of the patient's condition. The resolution rate of IgE-mediated CMPA may be later than that of non-IgE-mediated CMPA. In these patients, serum levels of specific IgE or wheal size measured in the prick test should be evaluated in particular. Although no single value can be applied universally, a reduction of > 50% in serum levels over a 12-month period, is considered a marker of good prognosis.[289,290] Asymptomatic dietary transgressions may also indicate tolerance acquisition.

For mild cases of allergic proctocolitis in children who are exclusively breastfed and have shown good progress after eliminating cow's milk and derivatives, consider reintroducing cow's milk protein to the mother's diet after 3 months of an elimination diet, although the approach should always be individualized. However, children with enteropathy and malnutrition may require a longer recovery time (1-2 years of age). As in FPIES,

Table 14
Interpretation of oral provocation test results in patients with a history of food protein-induced enterocolitis syndrome[288]

Major criterion
Vomiting 1-4 h after ingesting the suspected food and no classic IgE-mediated symptoms (cutaneous or respiratory)
Minor criteria
1. Lethargy 2. Pallor 3. Diarrhea 5-10 h after eating 4. Hypotension 5. Hypothermia 6. Neutrophil count >1,500 above baseline
Positive oral provocation test
Major criterion plus ≥ 2 minor criteria

Observations:
- With the rapid use of ondansetron, repetitive vomiting, paleness, and lethargy can be avoided.
- Because neutrophil counts cannot always be performed at the time of testing, the attending physician may decide that only the primary challenge has been met. However, research must adhere to strict criteria to conclude a positive response.

the minimum time for an elimination diet is 12-18 months after the last reaction.[197,261,270,275]

How to administer oral provocation tests

For IgE-mediated allergies and more severe cases involving late manifestations, such as FPIES, the procedure should be performed as described for diagnostic OPT. However, since a significant proportion of patients allergic to eggs and cow's milk can tolerate the baked forms of these foods, their regular consumption could allow for an expanded diet and possibly accelerate oral tolerance to their natural forms. The lack of 100% reliable laboratory markers to determine which patients can tolerate these foods implies the need for OPT (Table 15).

The oral provocation test and baked foods

For IgE-mediated allergies, OPT for baked goods should be performed in a healthcare setting and use an adequate amount of protein to avoid underdosing, which could result in false negative results. The recommended serving is 1.3 g of cow's milk protein and 2 g of egg protein, which should be added to a matrix (wheat flour) and baked for ≥ 30 min at 180 °C.[291]

Milk ladder

In cases of CMPA and mild-to-moderate egg allergy, reintroduction can be performed at home according to recommended methods of staggered CMPA reintroduction (milk ladder, egg ladder) after a therapeutic elimination diet, a practice increasingly used internationally. A controlled

environment is recommended for cases of IgE-mediated allergy.

In this protocol, egg or cow's milk in baked foods is first introduced in small quantities, followed by increasing doses and progressively less thermally processed forms. The progression begins with baked foods (cakes, muffins), followed by cooked forms (tapioca crepes, mashed/boiled eggs), then cooked forms with cheese and, finally, prepared foods (ice cream, whipped egg whites).[292.293] Preparation options should take family habits and nutritional value into account.

Reintroduction should progress slowly and gradually. Neither the minimum/maximum time for completing the escalation nor how long each step should take has been determined, since it is adjusted to individual patient characteristics, such as history, reactions, age, and clinical phenotype, etc. Table 15 summarizes the prerequisites for re-exposure to these foods. Figures 5 and 6 summarize the step-by-step process for cow's milk re-exposure in children < and > 1 year of age, respectively.[133]

If symptoms recur with reintroduction of the allergen after a therapeutic elimination diet, the elimination diet should be continued for another 3-6 months and before further re-exposure attempts.

Food Allergy Diagnosis in Patients with Atopic Dermatitis

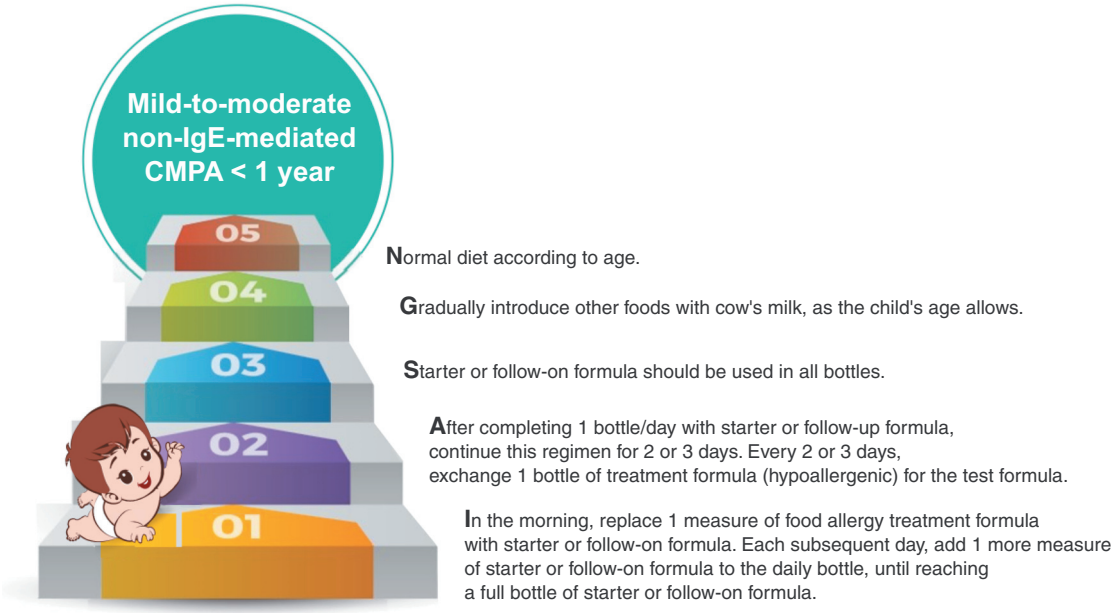
Extra care is required when diagnosing FA in patients with atopic dermatitis. Anamnesis, an important diagnostic tool, requires greater attention, since the collected information could be biased, with a tendency to blame food for worsening dermatitis. The effectiveness of the classic instruments for investigating specific IgE may also be compromised. In the prick test, for example, no area of healthy skin may be available or the patient may chronically use antihistamines, which makes the test unfeasible. In such cases, specific serum IgE may be an alternative, but panels should be discouraged, since the immune dysregulation in atopic dermatitis may lead to an excess of positive specific IgEs with no clinical relevance.[284]

The diagnostic approach includes the patient's clinical characteristics, such as early disease onset and moderate or severe manifestations, for which specific IgE testing is performed. It is worth noting that 80% of FA in patients with atopic dermatitis are to cow's milk, peanuts, and eggs, although wheat has been reported as well. Negative results rule out FA with a high degree of certainty (the negative predictive value of specific IgE tests is 90%). In

Table 15
Prerequisites for home-based staggered dietary re-exposure (milk ladder) to cow's milk protein after a therapeutic elimination diet[126]

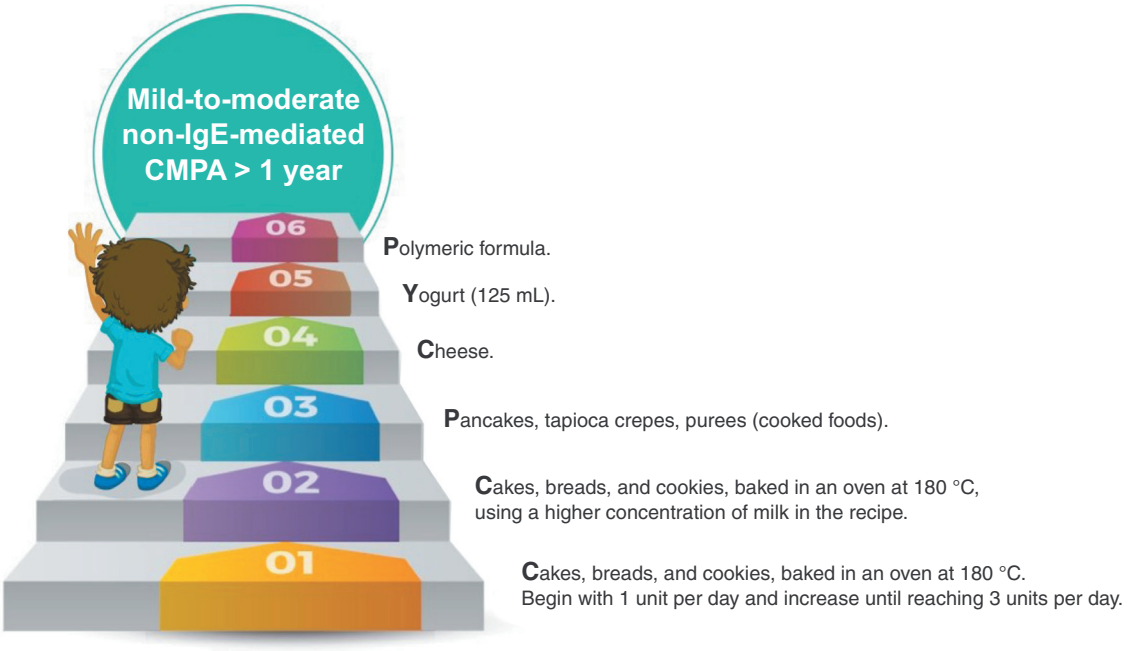
Non-IgE-mediated allergy (except FPIES).
Preferably non-asthmatic patients; asthmatic patients should be stable and appropriately treated.
Patients and family members should be willing and prepared, with complete understanding of the procedure.
Ideally, families should have immediate access to emergency services if necessary.
The patient should have a high pre-reaction threshold (ie, only reacted to large quantities).
Younger patients (eg, preschool children) are preferred, although this group is not without risk, since older patients may be prone to persistent allergy and suffer from coexisting allergies.

FPIES = food protein-induced enterocolitis syndrome, IgE = immunoglobulin E.



CMPA = cow's milk protein allergy, IgE = immunoglobulin E.

Figure 5
Prerequisites for home-based staggered dietary re-exposure to cow's milk protein (milk ladder) in children under 1 year of age with mild-to-moderate non-IgE-mediated cow's milk protein allergy[192]



CMPA = cow's milk protein allergy, IgE = immunoglobulin E.

Figure 6
Prerequisites for home-based staggered dietary re-exposure to cow's milk protein (milk ladder) in children over 1 year of age with mild-to-moderate non-IgE-mediated cow's milk protein[192]

patients with positive results, the recommendation is to eliminate the food for 2-4 weeks, followed by re-exposure.

Two considerations should be highlighted: these measures should be performed on patients at a stable stage of the disease. No medication should be suspended, and the severity of the dermatitis should be assessed using classic severity scores such as Scoring Atopic Dermatitis or the Eczema Area and Severity Index. Significant variations in the criteria aid in the diagnosis. The atopic patch test, a non-standardized method with highly variable results, is not recommended as a diagnostic tool for FA in patients with atopic dermatitis.[284,294] Eliminating foods due to inadequately diagnosed FA in patients with atopic dermatitis increases the risk of IgE-mediated clinical manifestations upon reintroduction. The exclusion time associated with this risk ranges from 5 weeks to years.[260]

Management

Diet

Dietary management is based on the following pillars: eliminating the food allergens responsible for the reaction, including nutritionally appropriate and safe foods, and treating any acute reactions.[126,177] In this context, the aim of nutritional guidance is to avoid FA symptom onset, prevent nutritional disorders, and provide what the child needs for adequate growth and development.[294]

Eliminating food allergens

Removing allergenic foods is the basis of dietary FA treatment and should include, in most cases, total elimination of the suspected food, including products derived from it and products that contain it. However, the strictness of the elimination diet should be based on the various characteristics of the allergens, the pathophysiological mechanisms involved (whether mediated or not by IgE) and the different phenotypes of FA, and it may be relaxed in some situations. Differences in clinical reactivity thresholds, concepts such as tolerance to trace amounts in industrialized products and home cooking, and tolerance to thermally processed (cooked/roasted) foods should be considered to avoid unnecessary exclusions, which can affect quality of life and the process of acquiring oral tolerance.[126,273,295]

The impact of eliminating an allergenic food from a patient's diet depends on several factors, such as age, previous nutritional status, allergen representation in the diet, ease of access to adequate food substitutes, and food selectivity. Thus, dietary guidance must be individualized. It is important to specifically identify the allergens in each case to maintain a qualitatively and quantitatively adequate food supply, avoiding overly or unnecessarily restrictive diets. Every effort must be made to find substitutes for the restricted foods to ensure adequate nutritional supply, which must meet current nutritional recommendations for age group and sex.[296]

Elimination diets can affect macro- and micronutrient intake, especially in children, in whom nutritional deficiencies can affect growth and development. Since major food allergens change across age groups, the overall impact of FA on nutrition is variable.[297] Although eliminating peanuts, shellfish, or a specific fruit has practically no nutritional impact on adults, eliminating allergens such as cow's milk and eggs can have a significant effect on young children.

Nutritional education for the patient/family is essential for successful treatment and goes beyond recognizing and excluding the allergen in a variety of food scenarios. It should clarify the best nutritional choices and describe strategies for accepting permitted foods. Guidance on environmental and domestic hygiene, as well as caution when handling foods containing allergenic proteins, should be highlighted. Depending on the mechanism and severity of the case, non-oral contact while cooking (inhalation or skin contact) can trigger a reaction.[298] Multidisciplinary teamwork, including periodic reassessments, is a valuable aid in dietary planning, adhering to recommendations, and addressing difficulties. The aim is to prevent malnutrition, height impairment, and other deficiencies.[177,297-299]

In Brazil, allergen labeling is controlled by Brazilian Health Regulatory Agency resolution 26/2015,[300] being applied to beverages, foodstuffs, food additives, and processing aids that are not packaged in the presence of consumers, including

those intended exclusively for industrial processing and those intended for food services. Warning labels are mandatory for the following substances: wheat, rye, barley, oats and their hybridized strains, shellfish, eggs, fish, peanuts, soybeans, milk from any species, almonds, hazelnuts, cashew nuts, Brazil nuts, macadamia nuts, walnuts, pecans, pistachios, pine nuts, chestnuts, and natural latex.

If a lack of cross-contact (ie, when the same industrial equipment is used to produce foods that do and do not contain the aforementioned allergen) cannot be guaranteed, the label must include the statement "Allergens: may contain (eg, wheat)". This information must be printed in bold capital letters immediately above or below the list of ingredients in a color that contrasts with the background of the label, having a minimum height of 2 mm.[300]

Because labels and products can change without prior notice, the labels should be checked with each purchase. It is worth noting that such labeling does not apply to products prepared in bakeries, snack bars, or restaurants and similar establishments, or to artisanal production or foods sold without packaging. Other products may also contain allergenic proteins, including animal feed, cosmetics, soaps, lotions, sunscreens. Since most of these products are not subject to mandatory allergen labeling, careful inspection of their ingredient lists is required prior to use. According to Brazilian Health Regulatory Agency resolution 768/2022, medications must contain the warning "Attention: this medication/vaccine contains (eg, wheat), in accordance with Annex I of resolution 26/2015 and its updates)".[300]

There are regular infant formulas, for example, that in addition to cow's milk contain allergy warnings about soy, eggs, or fish. Due to the large number of possible risk situations, families should be fully informed about action plans in the event of an allergic reaction.[177] Below are guidelines for specific elimination diets, according to the allergen, focusing on cow's milk.

Elimination diet for nursing mothers

Maternal diet directly influences the nutritional composition of breast milk, and proteins and peptides from the maternal diet may be transferred to breast milk in sufficient quantities to evoke immune responses in the infant. Food allergens (including beta-lactoglobulin [cow's milk], ovalbumin, ovomucoid [egg], gliadin [wheat], and Ara h 1 and Ara h 2 [peanut]) have been isolated from human milk.[301,302] Nevertheless, not all breastfeeding women must adhere to an elimination diet.

For infants with FA who are breastfed and have a reaction to allergens transmitted through breast milk, an elimination diet is recommended for the mother. If symptoms are triggered only after the child ingests the food directly, excluding the food from the mother's diet is not recommended. If eliminating cow's milk and derivatives from the mother's diet is recommended, she should receive calcium and vitamin D supplementation.[125,126,273,303.]

It is important to encourage exclusive breastfeeding until 6 months of age, introducing complementary feeding thereafter.

Elimination diet for infants and children

The aim of dietary guidance is to eliminate the allergen from the patient's diet. The risk of macro- and micronutrient deficiencies must be assessed for each food or food group excluded.

Eggs are rich in protein, vitamin B12, and riboflavin, which can be replaced by other sources of protein. However, eggs are an important ingredient in Brazilian cuisine and, hence, the social impact of their exclusion may be significant, despite the availability of egg substitutes for recipes. Wheat is also widely consumed food in Brazil, especially in processed foods. It can be replaced by several other grains. It is worth noting that "gluten-free" foods also do not contain wheat, but that "wheat-free" foods may contain gluten (rye and barley). Soy is a nutritionally dense food, rich in protein and many micronutrients but, because it does not appear in large quantities in the Brazilian diet, it can be easily replaced by other foods. Studies show that the vast majority of individuals with soy allergy can tolerate highly refined soybean oil and soy lecithin, which are widely used for various industrial purposes. Nuts and peanuts are also relatively easy to replace.[304]

For infants and children with CMPA, the nutritional risks are significant. In addition to nutritional deficiencies, a cow's milk protein elimination diet can cause eating disorders, changes in taste preferences, taste development, and food acceptance, with lifelong repercussions.[305,306] In such cases, special infant formulas are recommended, which will be detailed below, along with the dietary follow-up. Relactation should also be considered, including a cow's milk protein elimination diet for the nursing mother, if necessary.[177]

For children and adolescents with multiple FA, due to the important nutritional risk, rigorous systematic monitoring of their nutritional status is essential.[297]

Inclusion diet for patients with cow's milk protein allergy (infant formulas)

The use of special infant formulas for infants with CMPA should only be considered when breastfeeding (exclusive or supplemented) is not possible. Formulas for infants with CMPA must comply with 2 parameters: they must be hypoallergenic or non-allergenic, and they must meet the macro- and micronutrient nutritional needs of infants and children. In Brazil, the infant formulas currently available for children with CMPA are classified as:

– extensively hydrolyzed protein formula obtained from human milk, containing lactose, for children aged 0-36 months;
– extensively hydrolyzed protein formula obtained from human milk, lactose-free, for children aged 0-36 months;
– extensively hydrolyzed protein formula, obtained from human milk, lactose-free: hypercaloric for children aged < 1 year and normocaloric for children aged > 1 year;
– amino acid-based formula for children aged 0-36 months;
– amino acid-based formula for children aged 1-10 years;
– amino acid-based supplement for children aged > 1 year;
– soy protein-based formula for children aged 0-12 months;
– soy protein-based formula for children aged 1-3 years.

Extensively hydrolyzed formulas consist of amino acid peptides with a molecular weight < 3,000 Da, which are obtained by enzymatic and/or thermal hydrolysis or ultrafiltration, and are considered hypo-allergenic, rather than non-allergenic, since the peptides may contain residues of the allergen.[307,308] These products differ by protein source (whey protein and/or casein from cow's milk) and peptide size. The efficacy and safety of each hydrolyzed formula must be determined, since the manufacturer, protein source, and method and degree of hydrolysis may vary.[309]

The extensively hydrolyzed formulas that have already been tested appear to be well tolerated by most children with CMPA, although based on the published data, one formula cannot be considered superior to another for CMPA treatment.[310] According to the American Academy of Pediatrics, for a formula to be considered "hypoallergenic", it must be tolerated by ≥ 90% of infants with documented CMPA.[307] For all newly marketed hydrolysates, The European Food Safety Authority requires ≥ 1 randomized clinical trial demonstrating non-inferiority in child growth compared to a standard formula.[311]

Partially hydrolyzed formulas, which consist of oligopeptides with a molecular weight < 5,000 Da, are not recommended for CMPA treatment.[307] Amino acid formulas are considered non-allergenic and should be used in special situations in CMPA.[126]

The decision about which formula to use is based on the symptom types and severity, as well as the nutritional composition and residual allergenicity of the formula.[308] For non-breastfed infants with CMPA, extensively hydrolyzed formulas are the first choice, while amino acid formula is reserved for more severe cases and/or those with significant nutritional impact.[201] Cow's milk protein-derived extensively hydrolyzed formulas that have been tested in randomized controlled trials are preferable.[174] Formulas containing purified lactose are considered safe and effective for CMPA treatment and are more palatable to infants. However, if diarrhea and

diaper rash result from enteropathy, it might be due to secondary lactose intolerance. In such cases, lactose-free formulas are recommended, especially at the beginning of treatment.[126] In infants with CMPA, if complete symptom control or nutritional recovery does not occur with extensively hydrolyzed formula, switch to AAF.[283]

Soy-based infant formulas contain soy protein isolate, which has high protein quality. However, it also contains phytate, aluminum, and phytoestrogen isoflavones at levels not present in cow's milk-based formulas, although these levels have been significantly reduced in recent decades. Mothers who consume large amounts of soy have higher levels of aluminum and estrogens in their breast milk.[310] A global assessment of the impact of modern soy formulas on human development suggests that they are not harmful.[312]

The prevalence of soy sensitization decreases with age: 36.8% in the first year, 16.4% in the second year and 13.7% in the third year of life. The latest ESPGHAN consensus recommends soy-based infant formula for infants with CMPA if other elimination diets are impossible due to economic or cultural reasons, especially in IgE-mediated allergy, due to its lower association with CMPA compared to non-IgE-mediated allergy. One advantage of soy formulas is their palatability, which is considered better than that of extensively hydrolyzed formula.[126] For patients who are already using soy formula with good tolerance, regardless of IgE-mediated or non-IgE-mediated CMPA, it is unnecessary to switch to extensively hydrolyzed formula.

As a substitute for cow's milk, milk from other mammals (eg, sheep and goats), partially hydrolyzed formulas, and lactose-free polymeric formulas should not be prescribed, since they are not considered hypoallergenic and safe. Cow's milk modified with type A2 casein (containing only β-casein A2) is not considered hypoallergenic and should not be used as a food alternative in children with CMPA. Mare's and donkey's milk have less protein homology to cow's milk and may be tolerated by some individuals, despite not being nutritionally adapted.[313]

Soy, oat, nut, and other vegetable-based beverages are inappropriate substitutes for young infants with CMPA. For older children, these so-called vegetable milks can be used in recipes or consumed directly, bearing in mind that they are not nutritionally equivalent to cow's milk, especially in terms of protein, calories, or calcium. Thus, the daily diet will require adjustments to meet nutritional needs. Rice-based beverages are not recommended for children < 4.5 years of age due to their high arsenic levels.[314]

For older children with CMPA who do not achieve tolerance and are not receiving supplementation with infant formula, calcium and vitamin D supplementation is recommended during the elimination diet. The dose of elemental calcium can vary from 500 mg/day in childhood to 1,000 mg/day or more in adolescence.[305]

Applying all these concepts in clinical practice will ensure that children with CMPA receive adequate nutrition, which can guarantee adequate growth and development, similar to that of non-allergic children.[305]

Duration of the elimination diet

The duration of the food allergen elimination diet should be individualized, given that it depends on factors such as the allergen type, patient age at symptom onset, the immunological mechanisms involved in the allergy, and the different phenotypes of FA. For example, most children allergic to cow's milk through a non-IgE-mediated mechanism are expected to develop clinical tolerance within the first 3 years. Spontaneous clinical tolerance is rarer for peanuts, tree nuts, and shellfish, which usually persist throughout life in at least 70% of cases.[177]

For cases of non-IgE-mediated CMPA, a therapeutic elimination diet is generally recommended for ≥ 6 months or until 9-12 months of age (whichever comes first). A Brazilian study reported that 80% of infants with suspected proctocolitis tolerated cow's milk until a mean age of 6.3 months, suggesting that in the case of food protein-induced allergic proctocolitis, reintroduction attempts may be considered after 6 months of age.[315]

In cases of mild allergic proctocolitis, if the child is exclusively breastfed and is progressing

well after eliminating cow's milk and derivatives, after 3 months of an elimination diet, cow's milk protein may be reintroduced to the mother. Children with enteropathy and malnutrition may require a longer recovery time (until 1-2 years of age) as in FPIES, for which the minimum elimination diet is 12-18 months after the last reaction.[126,288] The relaxation of dietary restrictions should be guided by OPT results.

Oral tolerance status can be assessed by re-exposure under medical supervision or at home, depending on factors such as the type and severity of the reaction and the risk of conversion to an IgE-mediated reaction. Patients with IgE-mediated allergies, FPIES, and severe forms of non-IgE-mediated allergy should undergo OPT in a health care facility under medical supervision. However, patients with a non-IgE-mediated allergy (moderate/mild forms) may be reintroduced to the allergen at home, which should be individually guided. In all cases, the risk of allergic sensitization due to acquired IgE should be considered, especially for patients on a very long-term elimination diet, with moderate-to-severe atopic dermatitis, or FPIES. A large cohort study reported that allergic proctocolitis was associated with an increased risk of IgE-mediated CMPA (adjusted odds ratio 5.4 [95% CI: 1.4–20.8]).[273,316-318]

In mild-to-moderate non-IgE-mediated CMPA after the therapeutic elimination diet period, cow's milk can be reintroduced in small volumes, according to milk ladder recommendations.[192,319-322]

ESPGHAN considers that home-based introduction protocols are safe in non-IgE-mediated FA since, for example, heating alters the structure of the peptides and patients can tolerate cooked cow's milk. However, it warns that the concept of "baking" milk is questionable, given that boiling any liquid at 100°C usually means that the entire volume has reached that temperature. However, during baking, the core temperature of foods containing cow's milk, for example muffins, usually does not exceed 80°C. Thus, boiling cow's milk is more certain to alter the structure of the allergenic components than baking.[126]

Although reintroduction can be performed at home for mild-to-moderate non-IgE-mediated CMPA, caregiver supervision is mandatory. However, before this it is essential to review the patient's history to ensure that there are no immediate reactions, sensitization, or significant atopic dermatitis, which increase the risk of immediate reactions. If in doubt, a specific IgE test should be performed, especially if the child has atopic dermatitis. Home re-exposure is contraindicated if the patient has a severe dermatological condition, signs of IgE-mediated manifestations, FPIES, severe FA manifestations, or multiple FA.[83]

For non-IgE-mediated CMPA, reintroduction through a milk ladder (Figures 5 and 6) is a practical suggestion that can be performed in different ways and adapted to regional customs, in accordance with international interpretation of Milk Allergy in Primary Care) as reported in 2022 by the Brazilian Society of Pediatrics' Department of Pediatric Gastroenterology.[192,287,323]

In IgE-mediated allergies, reintroduction to establish tolerance should be guided by symptom severity and specific serum IgE and/or skin prick test results, according to the World Allergy Organization Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines (2023).[273] The appropriate timing for reintroducing cow's milk after a therapeutic elimination diet remains debatable. It is important to emphasize that for moderate-to-severe IgE-mediated CMPA, this strategy poses a higher risk of reaction and should only be performed under close supervision/guidance of an allergist in a health care environment prepared for severe reactions.[273]

Introducing complementary feeding in allergic children

The introduction of complementary feeding in children with CMPA should follow the same principles recommended for children without allergies, beginning in the sixth month of life, according to developmental milestones, regardless of the diet received (breast milk, formula or both). It is important to emphasize that the introduction of foods containing potentially allergenic proteins (eg, well-cooked eggs, fish, meat in general, and oilseeds) should ideally occur within the first 12 months of life, preferably while still breastfeeding and respecting the family routine.[126,324,325]

For patients diagnosed with FPIES, current guidelines do not recommend delaying the introduction of complementary foods: fruits and vegetables, followed by red meat and cereals, can begin after 6 months of age. Several tables that classify foods according to the highest risk of FPIES-type reactions have already been published, but it is important to note that regional epidemiological differences should be considered. In general, most FPIES reactions are to a single food (65% to 80%), with the most common being cow's milk, soy, eggs, fish, and fruits, especially bananas. When the child already tolerates a food from one group, the risk of cross-reactivity to another food in that group is much lower (for example: in a patient with a FPIES reaction to soy who tolerates beans, the risk of FPIES to other legumes is minimal). FPIES may also develop long after introduction of the food, even in adulthood.[125,303,326-330]

In the event of a new FA diagnosis during the introduction of solid foods, it is important to seek medical advice and avoid delaying exposure to other foods, but be aware of the risk of new episodes with foods that are likely to cause cross-reactivity. Special attention should be given to IgE-mediated cases, especially those involving anaphylaxis, and those associated with foods with a high risk of cross-reactivity (such as cashew nuts and pistachios, or shrimp and other shellfish, or latex-fruit syndrome). The occurrence of multiple FA is rare, and fear of it should not delay the introduction of solid foods, which could even increase this risk, as previously discussed.[325,329-333]

General aspects of dietary monitoring

The greatest difficulties in implementing the diet are the complete exclusion of the allergen(s) and the need to provide adequate nutrition for satisfactory growth and development. Some studies have demonstrated the risk of diets that can compromise nutritional status and cause specific nutritional deficiencies, such as lower intake of calories, proteins, lipids, calcium, phosphorus, vitamin D, and other micronutrients, as well as their impact on food neophobia.[177]

Dietary counseling can significantly improve nutritional intake and prevent nutritional deficiencies and failure to thrive. Therefore, children with FA, especially those with multiple FA or allergies to staple foods such as egg and cow's milk, should be referred for nutritional counseling. Essential preventive measures include recommending alternative nutrient-rich foods at the time of diagnosis and ensuring that alternative foods are accepted and incorporated into the diet.[334-337]

Monitoring macro- and micronutrient intake, particularly vitamin D and calcium, is necessary in children on a cow's milk elimination diet, especially in those aged > 1 year. Nutritional risks are especially important in children with multiple allergies and should be systematically monitored. In practice, replacing cow's milk is not a simple task, as families often seek low-cost alternatives. However, plant-based "milks" have lower caloric-protein values and lower micronutrient values than hypoallergenic formulas.[338] For younger children, complementary feeding should be introduced at the same age as children without CMPA and should follow the same recommendations (except dairy products).[126]

A systematic review of 5 articles on the prevalence of feeding difficulties in children with FA found values ranging from 13.6% to 40%, with the highest prevalence associated with multiple FA.[339] Raitano et al. highlighted how children with CMPA may have feeding difficulties, and their occurrence should not be underestimated.[340] A multicenter Polish study found that 16% of children with CMPA had feeding difficulties and greater impairment in weight-for-length and body mass index z-scores and, thus, were at higher a risk of moderate malnutrition than children with CMPA who did not have feeding difficulties.[341] In Brazil, Rodrigues et al. compared children with CMPA who underwent an elimination diet with children without CMPA on an unrestricted diet, finding a higher frequency of picky eating and higher eating problem scores in the former group. Picky eaters had lower weight/age z-scores.[342] Thus, it is critical to regularly monitor the growth of these patients and advise them about the substitutions needed to prevent feeding difficulties.[343]

Such nutritional disorders reflect an inadequate nutritional approach, sometimes due to a multidisciplinary team not being involved in care, difficult family dynamics, a lack of access to formula, or the social and economic context. It is important for patients and their families to find a balance between adequate monitoring and the daily burden of an elimination diet. Although strategies to minimize the likelihood of accidental allergen ingestion should be implemented, over-caution can create an unnecessary burden for families. Health professionals must help patients and their families learn to deal with the perceived risks of FA to maintain a life as close to normal as possible and prevent negative long-term consequences, such as changes in body image, eating disorders, and difficulties in interpersonal relationships in later life.[177,344-346]

Emotional aspects

It is recognized that FA can induce post-traumatic stress symptoms, which is more common in children who have experienced anaphylaxis or anxiety due to unpredictable food exposure. Strict adherence to the diet is stressful for both children and their families. A higher incidence of bullying against children with FA has been reported.[347] In several international studies, more than 30% of children and adolescents reported having been bullied because of their FA, with multiple episodes in up to 26%.[348] Because it affects multiple facets of patients' lives, FA reduces quality of life for patients and their families. In addition to growth monitoring and nutritional counseling with specialist pediatricians and nutritionists, psychological support for anxiety and depression may be necessary.[348,349]

Summary of recommendations for infants with cow's milk protein allergy

– When eliminating cow's milk and its derivatives in children with CMPA, if suitable substitutes are not found significant harm can occur throughout life, with repercussions even in adulthood.
– Insist on the continuance of breastfeeding and provide support to nursing mothers. Formulas should only be recommended for infants who are not breastfed.
– To ensure the growth and development of infants with CMPA, hypoallergenic (ie, extensively hydrolyzed) or non-allergenic (amino acid) formulas are recommended, which are nutritionally adequate.
– For infants with CMPA, the first option is hypoallergenic formulas obtained from cow's milk proteins.
– AAF is reserved for the most severe cases and for those who had no or partial response to extensively hydrolyzed formula.
– Provided that diarrhea and diaper rash (which are indicative of enteropathy) do not occur, extensively hydrolyzed formula should preferably contain lactose. Although less studied, hydrolyzed rice formulas can be considered as an exception.
– Isolated soy protein formulas are a treatment option, especially for infants aged > 6 months with IgE-mediated CMPA. They can also be considered for economic, cultural, and/or palatability reasons.
– The duration of the treatment phase elimination diet for non-IgE-mediated CMPA is generally 6 months (or until the child reaches 9 to 12 months of age), but it varies according to FA phenotype, being shorter in allergic proctocolitis and longer in FPIES.
– Tolerance acquisition generally takes longer in IgE-mediated cases, and reintroduction should be individualized.

Vaccination and food allergy

Since some vaccines contain small amounts of food proteins, patients with FA should exercise caution when updating their vaccination records. In addition to food allergens, several other vaccine components can trigger allergic reactions, principally gelatin.

Type I hypersensitivity reactions rarely occur, but due to the potential severity they should be taken into consideration in vaccine prescription.[350] Reactions typically occur immediately or within 4 h of exposure to the allergen and can manifest with cutaneous or systemic symptoms (anaphylaxis).[351]

The main foods involved in immediate reactions to vaccines are hen egg and cow's milk. Yellow fever and rabies vaccines are produced in hen egg culture and contain a high quantity of egg protein (ovalbumin), while the measles, mumps, and rubella vaccine which is cultivated in chicken embryo fibroblasts, contains a small quantity of egg protein and is not contraindicated for people with egg allergy.[352,353]

Currently marketed influenza vaccines generally contain < 1.2 µg/mL of egg protein. Studies have shown good tolerance to the vaccine, even in individuals who have had an anaphylactic reaction to eggs. The current recommendation is that individuals with a history of severe allergy (anaphylaxis) to hen egg receive the influenza vaccine and remain under observation for 30-60 min. No additional precautions are needed during influenza vaccination for patients with mild allergic reactions to hen egg.[351]

The yellow fever vaccine contains high amounts of egg protein. In Brazil, 2 vaccines are available, and the amounts of ovalbumin can vary from 2.43-4.42 µg/mL depending on the batch. The vaccine is not heated at any point during production, so even patients who can tolerate boiled/fried eggs may have a reaction.[354]

In people with a history of other severe allergies who are about to receive the yellow fever vaccine, it is appropriate to ask about severe allergic reactions after contact with eggs. However, in children with no clinical history of egg allergy who are being introduced to complementary foods, no evidence supports the need for egg ingestion or IgE testing for egg allergy prior to yellow fever vaccination.[351]

If an allergist has diagnosed IgE-mediated egg allergy based on clinical and laboratory criteria, studies suggest that yellow fever vaccination is possible after skin and intradermal tests with the vaccine. For those with positive test results, desensitization or fractionation of the dose should be performed in an appropriate environment in case of anaphylaxis.[356] There are several protocols for determining yellow fever vaccine allergy and desensitization.[357] However, a recent Brazilian study concluded that it is safe to administer the vaccine in a single dose, dispensing with prior testing or dose fractionation, as long as vaccination occurs in an environment prepared for severe allergic reactions.[353] The authors recommended observing children with a history of anaphylactic reaction to eggs for at least 60 min after vaccination.[353]

Two rabies vaccines are available: a human diploid cell vaccine, which does not contain egg, and a purified chicken embryo cell vaccine, which contains traces of egg protein, including ovalbumin (Rabipur®, GlaxoSmithKline). Allergic reactions and anaphylaxis to the egg-cultured vaccine have been reported, thus it is relatively contraindicated in children who have had an anaphylactic reaction to egg. In such cases, the risks and benefits of the vaccine should be carefully evaluated. It should be noted that human rabies immune globulin does not contain egg protein.[357]

Some formulations of the anesthetic propofol contain egg lecithin, which derived from the yolk. However, due to its low rate of clinical reactivity, with no serious reactions having been reported, it is considered safe in adult and pediatric patients with egg allergy.[357]

Patients with CMPA should avoid the Serum Institute of India's measles, mumps, and rubella vaccine because it may contain alpha-lactalbumin.

The diphtheria, pertussis, and tetanus vaccine may contain casein derivatives. Individual risk assessment is recommended, and for patients with severe allergy and a low reaction threshold, the vaccine should only be administered under medical supervision.[354]

Drug- and allergen-specific reactions

Action plan for adverse reactions

We know how difficult it is to avoid accidental exposure to food allergens, especially those frequently used in cooking. In mild cases, there may be spontaneous remission or resolution with antihistamines alone. However, some reactions will evolve into a serious form, anaphylaxis. The severity or clinical course of an allergic reaction cannot be predicted, since it can depend on potentializing cofactors, including medication use, infections, menstruation, and exercise.[358]

People with FA should have a written action plan with clear guidelines for the steps to be taken according to the severity of the reaction.[359] Five reasons to have a FA action plan are presented below.

1. Emergency preparedness: FA can lead to severe and potentially life-threatening reactions, such as anaphylaxis. Having an action plan ensures that everyone involved is prepared in the event of a reaction. It provides clear instructions on what actions to take, including emergency medications, such as epinephrine auto-injectors.
2. Standardized communication: an action plan serves as a communication tool between individuals with FA and their caregivers, teachers, school staff, and other relevant personnel. It provides vital information about the specific allergens, symptoms, and appropriate steps to take during an allergic reaction.
3. Early recognition and intervention: the action plan includes a list of potential allergy symptoms, allowing for early recognition of an allergic reaction. By promptly identifying symptoms, appropriate action can be taken, potentially preventing worsening.
4. Education: an action plan helps increase awareness and understanding among everyone involved. Education about FA is crucial to creating a safe environment and promoting empathy and support for individuals with allergies.
5. Consistent care: by having a documented action plan, individuals with FA can receive consistent care across different settings. The plan provides a reference for caregivers and ensures that appropriate precautions and interventions are followed.

The ICD-11 defines anaphylaxis as a severe, life-threatening systemic hypersensitivity reaction involving rapid onset of potentially fatal changes in the airways, breathing, or circulation that is usually associated with changes in the skin and mucous membranes.[360] Diagnosis is clinical, there are no definitive markers, and there is no pattern of symptom development. In 2019, the World Allergy Organization simplified the diagnostic criteria and included severe reactions not previously classified as anaphylaxis (Table 16).[360]

The only medication that can relieve all symptoms of anaphylaxis is adrenaline (epinephrine). However, despite the increasing use of epinephrine autoinjectors, deaths from anaphylaxis still persist.

Using an epinephrine autoinjector for cases of anaphylaxis can prevent fatalities. Even after using adrenaline, emergency room assessment may be necessary to continue treatment and observation for at least 4 h, since anaphylaxis can have a biphasic pathophysiology, with initial improvement followed by a recurrence of severe symptoms.[361] A recent review of practical recommendations in anaphylaxis suggests that if a rapid response to adrenaline occurs, there is no need to go to the emergency room, although this should be decided by the patient's doctor.[361]

Since no validated studies have determined when to prescribe epinephrine auto-injectors, recommendations are based solely on expert opinion. According to the EAACI, absolute recommendations include previous episodes of anaphylaxis to food and unstable asthma or moderate-to-severe persistent asthma in patients with systemic mastocytosis.[362] For lower-risk patients, a shared decision-making process has been suggested that considers access to emergency services and patient costs and preferences.

Intramuscular adrenaline is safe and effective, with no absolute contraindications to its use in anaphylaxis. The intravenous route requires greater care, as adverse cardiovascular and neurological reactions may occur when administered too quickly or in an incorrect dose. Thus, intramuscular is the safest route and it should be used as soon as possible after onset. Even in older adults and individuals with cardiovascular impairment, intramuscular adrenaline should be used immediately, mainly due to their higher risk of morbidity and mortality in severe allergic reactions.[363] Even in patients who use cardioselective beta blockers and angiotensin-converting enzyme inhibitors, intramuscular adrenaline should be used during anaphylaxis, despite the risk of reduced efficacy. Because anaphylaxis is a rapidly evolving and potentially fatal reaction, the risk/benefit ratio favors intramuscular adrenaline in all cases, regardless of underlying diseases or current medications.[364]

Although FA reactions can occur anywhere, they are most common at home, followed by schools (for children) and restaurants (for adults). Training programs for caregivers, school staff and restaurant staff are essential. Unfortunately, no health policies require airports, restaurants, or schools to stock adrenaline.[365]

It is essential to educate those involved in food preparation and in identifying food allergens on menus about the risks, as well as to provide guidance on how to manage reactions. Food is the leading cause of anaphylaxis on airplanes, and patients should bring their own food when traveling. In the USA, only 1 in 1,000-10,000 flights has an emergency adrenaline kit on board, and appropriate doses must be prepared using a needle and syringe, which can hamper and delay treatment. Thus, it is imperative for patients to carry their own epinephrine autoinjectors. Patients should notify the flight crew of any allergic reactions so that in-flight assistance and ground medical support can be mobilized if necessary.[366]

According to recent expert recommendations, epinephrine autoinjectors should be used in all cases of immediate systemic reaction to food and/or anaphylaxis.[361] Current recommendations also suggest that patients with moderate-to-severe asthma who have experienced food-triggered anaphylaxis should carry a second dose of self-injectable epinephrine.[361]

To date, no robust studies have defined the risk factors for multiple adrenaline doses. Most experts recommend that all patients have 2 doses available. Universal prescription of ≥ 2 devices allows for a second dose in case of persistent symptoms, symptom worsening, a biphasic reaction, or device malfunction or administration error.[366]

The increased cost of prescribing two devices is justified, since 10% of reactions require ≥ 2 doses during an anaphylaxis episode.[367] Furthermore, there is a risk of delayed access to medical care, such as in remote areas or during travel. If patients and caregivers forget to replace an expired auto-injector or are unable to do so for other reasons, it is preferable to use an expired device rather than none at all.

Recent studies have shown that expired auto-injectors contain adrenaline concentrations (80% to 90%) well beyond their expiration dates.

However, compared to adult doses, pediatric doses may degrade more quickly after the expiration

Table 16
Diagnostic criteria for anaphylaxis[360]

Anaphylaxis is highly likely when 1 of the following 2 criteria is met
1. Acute onset (a few minutes to a few hours) involving the skin, mucosa, or both (hives, pruritus, lip-tongue-uvula edema) and at least one of the following
a. Respiratory symptoms: dyspnea, bronchospasm, stridor, reduced peak flow, hypoxemia
b. Drop in blood pressure or symptoms of target organ dysfunction: hypotonia, syncope, fecal/urinary incontinence
c. Severe gastrointestinal symptoms: severe abdominal cramps, repetitive vomiting
2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen, even without skin symptoms, including one of the following:
a. Drop in systemic blood pressure
b. Bronchospasm
c. Laryngeal involvement

date.[368] Thus, to justify prescribing a single device, autoinjectors would need to be available in schools and other public settings, similar to community provision of cardiac defibrillators, which does not occur in practice in our environment.

The recommended adrenaline dose for anaphylaxis is 0.01 mg/kg of body weight of a 1:1000 (1 mg/mL) solution, with a maximum dose of 0.5 mg in adults and 0.3 mg in children. Intramuscular administration in the anterolateral thigh region is preferable and may be repeated every 5-15 minutes as necessary. Table 17 shows the recommended doses according to weight.[369]

When an additional dose of adrenaline is required after an initial dose of 0.3 mg, the subsequent dose should be 0.5 mg. The autoinjector technique is an essential factor, including the need to position the needle against the thigh and maintain pressure for a few seconds to ensure complete application of the medication.[369,370]

The literature indicates that 2% to 3% of severe anaphylactic reactions do not respond to 2 doses of adrenaline. Such case could be refractory anaphylaxis. However, certain aspects should be considered in these cases: (1) whether the injection occurred at the beginning of the reaction or later; (2) whether the epinephrine autoinjector was used correctly, including the injection site and sufficient skin pressure for the correct amount of time; (3) whether an adequate dose was applied; (4) whether the medication had not yet expired. Factors such as dosage, needle length, cost, accessibility, and patient treatment preferences should be considered when prescribing an autoinjector.[371]

In obese patients, for example, subcutaneous rather than intramuscular injection may be used to the size of the needle, which may be insufficient to reach the muscles. Furthermore, the fixed autoinjector dose may be insufficient, or an overdose may occur, especially in children. Nevertheless, for the vast majority of patients with anaphylaxis, autoinjectors are the safest and most effective option, and they should be encouraged by anyone at risk of new episodes.[371]

When adrenaline does not work, emergency medical treatment is required, including intravenous infusion of low-dose adrenaline, sufficient fluids, allowing the adrenaline to reach sufficient tissue levels. Another possibility would be refractoriness to beta-blockers, in which case adjunctive therapy with glucagon may be indicated.

Table 17
Adrenaline dosage recommendations according to weight

0.15 mg device	The 0.15 mg device is suitable for children weighing between 7.5 kg and 25-30 kg. This device provides a dosage suitable for younger children, ensuring treatment efficacy while minimizing the risk of overdose.
0.3 mg device	Recommended for children weighing 25-30 kg, adolescents, and adults. This dosage is suitable for most cases of anaphylaxis in individuals with higher body weight, providing an effective response.
0.5 mg device	Recommended for adolescents and adults. This dose is used in situations where higher doses are required due to body weight (obesity) or the severity of the anaphylactic reaction.

Furthermore, the European Medicines Agency's Committee for Medicinal Products for Human Use recently recommended EU marketing authorization for Eurneffy (already approved in the USA), the first nasal epinephrine spray for anaphylaxis. Other laboratories are developing intranasal and sublingual formulations.

The action plan should detail clinical information, the names and phone numbers of emergency contacts, as well as instructions about the medication and course of action in the event of allergic reactions. The plan should be reviewed periodically by the physician and the patient and/or guardians during the consultation (Figure 7).

In the emergency room

As mentioned above, anaphylaxis is a severe, potentially fatal acute allergic reaction that requires immediate and appropriate treatment. For immediate intervention, emergency room physicians must be trained and instructed in the early recognition of signs and symptoms of anaphylaxis, thus preventing progression to a fatal outcome, remaining alert to the possibility of biphasic reaction.[362]

Due to the difficulty of conducting randomized clinical trials on anaphylaxis treatment, guidelines based on the best available research evidence, theory, and expert consensus are widely used.

A recently published article cites a list of materials and medications needed to treat anaphylaxis, which we present below due to its great usefulness in clinical practice. These materials and medications should be available in health units.[372]

1. A stethoscope, pulse oximeter, and equipment for continuous blood pressure and heart rate monitoring, and a watch.
2. Tourniquets, 1 mL, 10 mL, 20 mL syringes; needles (sizes 19, 21, 23 and 25) and catheters (gauges 14, 16, 18, 20 and 22).
3. Aqueous adrenaline (1 mg/mL or 1/1,000): doses of 0.01 mg/kg to a maximum of 0.5 mg (adult) and 0.3 mg (child).
4. An oxygen tank.
5. Equipment for intravenous fluid administration.
6. Intubation equipment: bag/valve/mask with reservoir (volume 700-1,000 mL [adult], 100-700 mL [child]) and disposable face masks; oropharyngeal airways: 6 cm, 7 cm, 8 cm, 9 cm, 10 cm; pocket masks, nasal cannula, and laryngeal masks.
7. Intravenous antihistamines (diphenhydramine: 25-50 mg in adults and 1 mg/kg, maximum 50 mg, in children).
8. Intravenous corticosteroids (hydrocortisone 200 mg in adults, maximum 100 mg in children or methylprednisolone 50-100 mg in adults and 1 mg/kg, maximum 50 mg in children).
9. Intravenous vasopressors (dopamine, norepinephrine).
10. Glucagon (1-5 mg in adults, and 20-30 µg/kg, maximum 1 mg, in children).
11. Defibrillator.
12. Inhaled beta-adrenergics: salbutamol solution 2.5 mg/3 mL or 5 mg/3 mL (adult); (2.5 mg/3 mL, child) administered by nebulizer and face mask; salbutamol spray, spacers and masks.
13. Other supplies: extension tubes, T-connectors, arm rests, written emergency protocol for anaphylaxis treatment, gloves and a flowchart for recording times and events.
14. Available oxygen.
15. Material for venous puncture.

Adrenaline

Intramuscular adrenaline is the first-line treatment for anaphylaxis. It should be administered into the vastus lateralis muscle of the thigh in the following doses: 0.01 mg/kg at a concentration of 1:1,000 (maximum of 0.3 mg in children) and 0.3 mg or 0.5 mg at a concentration of 1:1,000 in adults for any episode of anaphylaxis.[373] If necessary, depending on the response to the initial dose, it can be repeated in 5 to 15 minutes.[374]

Intravenous infusion, through a dedicated route and under careful ECG monitoring, should only be administered to patients who do not respond to intramuscular injection (after 3 attempts). When beta-blockers are used, adrenaline should always

Action Plan for Allergic Reactions

Name: _____ **Age:** _____

I am allergic to: _____

Asthmatic: ( ) **Yes** ( ) **No**

Current medications: _____

If the patient has only one of the symptoms below, take the prescribed medications (anti-allergy and corticosteroids) and go IMMEDIATELY to the NEAREST EMERGENCY ROOM. REMEMBER THAT SYMPTOMS CAN PROGRESS RAPIDLY.

- **Skin:** itching, tingling, lip swelling, redness, red patches.
- **Nose:** runny nose, itchy nose, and sneezing, in addition to itchy eyes.
- **Mouth:** itching and swelling of the lips and tongue.
- **Gastrointestinal tract:** nausea, cramping abdominal pain, vomiting, diarrhea.

For any symptom below, either alone or in association with the symptoms above, adrenaline should be administered immediately.

- **Throat:** itching, hoarseness, closing.
- **Lung:** cough, shortness of breath, chest tightness, wheezing.
- **Heart:** low blood pressure, weak pulse, fainting.

DO NOT HESITATE TO APPLY ADRENALINE TO THE LATERAL REGION OF THE THIGH ACCORDING TO THE DOSE BELOW. BEFORE APPLYING ADRENALINE, LIE DOWN AND CONTACT EMERGENCY SERVICES AND/OR YOUR CLOSEST RELATIVE.

Self-injectable adrenaline, intramuscularly in the lateral region of the thigh:

Manufacturer: _____

Purchase date: _____ / _____ / _____ Expiration date: _____ / _____ / _____

( ) 0.15 mg
( ) 0.3 mg
( ) 0.5 mg

Emergency contacts:

Public Health Emergency Service: _____

Emergency contact 1: Name: _____ Telephone: _____

Emergency contact 2: Name: _____ Telephone: _____

Emergency contact 3: Name: _____ Telephone: _____

Doctor's signature: _____

Guardian's signature (if the patient is <18 years of age): _____

Figure 7
Action plan for allergic reactions

be the first course of action and, if ineffective, glucagon should be used.[375]

Other routes of adrenaline administration are being studied, such as intranasal and orodispersible films (sublingual), the latter of which is still in phase III trial, although both have shown promising results.[376,377]

Position the patient

Correctly positioning the patient is essential when treating anaphylaxis. A horizontal position, with or without elevated legs, maximizes venous return. If this position is uncomfortable, usually due to airway or breathing problems, the patient can be placed in a semi-prone position with or without elevated legs.[378]

The posture should not be changed from supine to standing position, as there may be serious cardiovascular problems, collapse, or death during anaphylaxis due to reduced venous return and a consequent reduction in myocardial filling and perfusion.[379]

Volume

Current guidelines recommend early intravenous administration of the first dose of adrenaline in patients with cardiovascular involvement, since it may be effective in restoring circulatory volume. Normal saline 0.9% is preferred over other solutions in most situations, and adults should receive 1 to 2 liters of normal saline via large-bore intravenous catheter. Children should receive saline as a bolus of 10 to 20 mL/kg over 5-10 min, which can be repeated as needed. It may also be administered in severe cases of anaphylaxis with significant respiratory compromise and when a second dose of intramuscular epinephrine is necessary.[362]

Antihistamines

Due to their slow onset of action, antihistamines are never used as a first-line treatment for anaphylaxis. They are widely used to relieve skin reactions. They can be administered intravenously in emergency departments and may have an adjuvant effect on treatment, but can never replace intramuscular adrenaline.[380]

Corticosteroids

Despite their frequent use in anaphylaxis, there is a lack of data on the clinical benefit of glucocorticoids, and they should also be avoided as first-line treatment. No studies have clearly established their benefit, when combined with adrenaline and/or antihistamines, to prevent biphasic reactions.[381]

Inhaled beta-2 agonists

The use of this medication in anaphylaxis is extrapolated from its use in acute asthma. In patients with mild-to-moderate respiratory symptoms for whom oxygen therapy is not recommended, these medications can be administered through a metered-dose inhaler. If respiratory symptoms intensify or are already severe, beta-2 agonists should be administered through a nebulizer and with oxygen supplementation. The patient should be reassessed periodically to determine the severity of the condition and the need for adrenaline.[362]

Figure 8 describes the essential steps for proper anaphylaxis treatment.

Observation period

Although it has not yet been determined how long a patient with anaphylaxis should remain under observation in an emergency department, Dood et al. suggested the protocol below.[382]

Consider rapid discharge (within 2 h of resolution) if there is:

– good response (in 5-10 min) to a single dose of adrenaline administered within 30 min of reaction onset; AND
– complete resolution of symptoms; AND
– the patient has an unused adrenaline auto-injector and has been trained on how to use it; AND
– there is adequate supervision after administration.

Consider a minimum of 6 h of observation after resolution of symptoms if:

– 2 doses of intramuscular epinephrine were required to treat the reaction; OR
– there was a previous biphasic reaction.

Observe the patient for at least 12 h after symptom resolution for any of the following:

– a severe reaction requiring ≥ 2 doses of adrenaline;
– a patient with severe asthma or whose reaction involved severe respiratory impairment;
– the possibility of continuous allergen absorption, eg, slow-release medications;
– patients in regions where access to emergency care is difficult.

Considerations

When there is early suspicion of anaphylaxis by patients or health care professionals, they should be advised to begin immediate treatment.

Other important interventions to remember:

– identifying the trigger(s);
– maintaining routine appointments with an allergist-immunologist or a specialized health professional;
– reviewing the written action plan with the patient;
– instructing patients to always carry adrenaline autoinjectors, preferably 2, and provide training on correct usage;
– managing risk factors for fatal outcomes, such as poorly controlled asthma and cardiovascular disease;
– advising patients to carry some form of medical alert tag that identifies products to which you are allergic;
– promoting public health initiatives, eg, to improve food labeling.

Immunotherapy

FA imposes a substantial burden on patients and their families, who experience considerable anxiety related to the risk of accidental exposure. This may require significant lifestyle changes, including dietary restrictions, constant vigilance in food selection, and limiting social activities. This psychological impact of this can be profound, affecting the mental health and lives of both patients and caregivers. Patients who have experienced a severe reaction also live in fear of a potentially fatal reaction.[383,384]

The standard treatment for FA has traditionally been strict avoidance of the allergen and treating emergency reactions. However, dietary restriction can be very challenging and it does not change the natural course of the allergy.

Immunotherapy has emerged as a promising treatment that could modify the course of the disease, provide long-lasting protection, and ultimately improve the quality of life of individuals with IgE-mediated FA. By gradually introducing small, controlled amounts of the allergen, immunotherapy aims to desensitize the immune system, thereby reducing the severity of allergic reactions and, in some cases, inducing long-term tolerance.[385,386]

The concept of immunotherapy dates back more than a century, originally developed for inhalant allergens such as pollen. Over the years, immunotherapy has evolved to include allergies to Hymenoptera venom and food allergens.[387]

Immunotherapy for FA is a more recent development. Early studies focused on oral immunotherapy (OIT), and subsequent research has explored sublingual IT and epicutaneous IT. Advances in understanding the immunological basis of allergies and improved clinical protocols have significantly increased the safety and efficacy of these treatments.[387]

How immunotherapy works

Immunotherapy works by introducing the allergen into the immune system in a controlled manner, gradually altering the immune response. This process begins with extremely small doses of the allergen, which are gradually increased over time. The initial low doses aim to minimize adverse reactions while stimulating the immune system to begin the desensitization process.

Desensitization and tolerance

Desensitization refers to the temporary state achieved during immunotherapy where the individual can tolerate larger amounts of the allergen without experiencing an allergic reaction.

Steps 4, 5 and 6 must be performed simultaneously and quickly

In addition

1. **Follow an "Action Plan"** for recognizing and treating anaphylaxis, which should be reviewed regularly.
2. **If possible, remove the allergen,** eg, discontinue the therapeutic agent that appears responsible for the condition.
3. **Assess the patient's Airway/Breathing/Circulation (ABC), mental status, and skin and estimate the patient's weight.**
4. **Call for help:** a resuscitation team (hospital) or emergency medical services, if available.
5. **Inject adrenaline** intramuscularly into the anterolateral region of the middle thigh: 0.01 mg/kg of adrenaline 1:1,000 (1 mg/mL), solution, maximum 0.5 mg (adults) or 0.3 mg (children). **Record the time of the dose and repeat every 5-15 minutes, if necessary.** Most patients respond to 1 or 2 doses.
6. **Place the patient in the supine position** or a comfortable position if there is respiratory distress and/or vomiting; **elevate the lower extremities.** Death can occur within seconds if the patient stands or sits up suddenly.
7. **When indicated, provide high-flow supplemental oxygen** (6-8 L/minute), via face mask or laryngeal mask airway.
8. **Establish intravenous access** access using large-bore (14-16 gauge) cannula or catheters. **Consider giving 1-2 liters of 0.9% (isotonic) saline** rapidly (eg, 5-10 mL/kg in the first 5-10 minutes for an adult or 10 mL/kg for a child).
9. **If ndicated, perform cardiopulmonary resuscitation at any time** with continuous chest compression.
10. **At frequent, regular intervals, monitor the patient's blood pressure, heart rate, respiratory rate, and oxygenation** (continuously, if possible).

Figure 8
Step-by-step approach to anaphylaxis
Source: modified from Cardona et al.[360]

It requires continued exposure to the allergen to maintain. Tolerance, however, is a more stable and long-lasting state where the individual can safely consume the allergen even after regular exposure has ceased, which is the ultimate goal of immunotherapy.[388]

The mechanism of action of immunotherapy for food allergy

Generally speaking, immunotherapy involves gradually introducing a specific allergen into the patient's diet in controlled and increasing amounts to desensitize the immune system and reduce the severity of allergic reactions. Its ultimate goal is not only to control symptoms, but to induce long-term tolerance to the allergen. It is considered an effective method for treating IgE-mediated FA.[389]

The mechanisms involved in tolerance induction and immune modulation during immunotherapy for FA are not fully understood. Immune tolerance induction and alterations in T and B cell response have been found in patients during immunotherapy.[390,391] A shift in immune response from Th2 to Th1 cell polarization with increased interferon-γ and decreased Th2-related cytokines (IL-4, IL-13) was observed. During immunotherapy, exposure to continuous high doses of food allergens leads to Th2 anergy and/or deletion and an increase in Tregs, resulting in suppressed allergic response. Immunotherapy incompletely targets type-2-cell mediated response, which is a transient change.[392] Studies have also shown that the function and number of Treg cells increase.[390,393] In peripheral tolerance induction, Treg cells play a critical role, including the activation of specific cell subpopulations, such as inducible Treg cells, natural Treg cells and Tr1 cells and Th3 cells producing TGF-β.[394] However, the impact of immunotherapy on the differentiation of Treg subsets is poorly understood. Certain studies have found an association between increased Tregs and improved immunotherapy outcomes,[395,396] while others have not.[392,397]

Significant suppression of follicular Th cells and transformation of follicular Treg cells were observed after food immunotherapy. Follicular Th cells may play an important role in immune tolerance induction, resulting in a significant decrease in Th2 response. Modifying Th2-mediated immune response appears to be essential for tolerance induction to a specific food allergen, ie, in predicting the efficacy of immunotherapy.[398] In egg immunotherapy, high baseline levels of specific CD4+ Th2 cells was found to strongly predict treatment failure.[399] In a study on peanut immunotherapy, failure to suppress Th2 response was also associated with treatment failure.[392]

Every form of dietary immunotherapy (oral, sublingual, and epicutaneous) is characterized by decreased basophil and mast cell activation[400,401] during the desensitization phase, as measured by suppressed allergen-specific skin test reactivity and basophil activation testing.[402] Peanut OIT and milk sublingual IT have shown early but transient reductions in basophil activation with loss of tolerance after immunotherapy is discontinued.[403,404]

During the dose-escalation phase of immunotherapy, there is an initial increase in allergen-specific IgE levels, which is a consequence of the proliferation of antigen-specific memory B cells, followed by a gradual decrease in allergen-specific IgE at the end of therapy.[405] Changes in humoral response during food immunotherapy are manifested by an increase in food protein-specific IgG, subclass 4 (IgG4) and IgA.[406,407] Increased food-specific IgA may play a role in tolerance induction.[388] Increased levels of specific IgG4 are thought to facilitate desensitization through binding with inhibitory IgG receptor FcγRIIb,[408] thus suppressing IgE signaling pathways.[409,410] The induction of allergen-specific IgG4 during immunotherapy appears to be a result of producing IL-10 regulatory T or B lymphocyte subpopulations in desensitized patients.[390,411]

Modulating CD8+ T cell response could also predict OIT response. In the POISED study, baseline levels of naive CD8+ T cells and peanut- and Ara h 2-specific IgE were positively correlated with peanut OIT efficacy.[412]

Mechanisms related to immune response modulation and tolerance induction during food IT are described independently of the method of allergen exposure. There are certain differences in the initial immune response depending on whether

the allergen is introduced orally, sublingually, or epicutaneously.

Basic knowledge about the mechanisms of sublingual IT has been published in research on grass pollen IT in patients with allergic rhinitis.[413] Allergens delivered by sublingual IT are presented by oral Langerhans cells or myeloid DCs in the oral mucosa, which migrate to oral draining lymph nodes, where they promote FOXP3-positive Treg cells and the production of tolerogenic cytokines, including IL-10 and TGF-β, and downregulate Th2-related cytokines (IL-4, IL-13).[414]

During epicutaneous application, allergens pass through the epidermis and are absorbed by epidermal Langerhans cells, or allergens may be taken up directly by dermal DCs. Epidermal Langerhans cells or dermal DCs migrate to the lymph nodes, draining the skin, where they can activate T cells and other cells of adaptive immunity to induce Th2/Th1 switching and immune tolerance.[415]

Although there have been numerous recent studies on food IT's mechanisms of action, it has not yet been clarified which immune response changes are related to treatment efficacy. Additional research is needed to identify biomarkers that can predict the treatment success or failure.[416]

Types of immunotherapy for food allergies

Oral immunotherapy (OIT)

OIT involves oral administration of gradually increasing doses of the food to desensitize the patient to the allergen until a predetermined maintenance dose is reached.

Efficacy and results

Studies have shown that OIT can achieve significant desensitization in a substantial proportion of individuals, allowing them to tolerate larger amounts of the allergen without severe reactions. Some patients may achieve a state of sustained nonresponsiveness, a form of tolerance in which they can safely consume the allergen even after a period of abstinence. OIT efficacy varies depending on the allergen and the individual, but success rates (desensitization) in clinical trials range from 60% to 80%.[417-419]

Adverse effects and management

The most common adverse effects of OIT include gastrointestinal symptoms (eg, abdominal pain, nausea) and itchy mouth and throat, but systemic reactions such as anaphylaxis can also occur. To manage these risks, OIT should be performed in a controlled medical environment, especially during dose escalation phases. Medications such as antihistamines are often prescribed to mitigate mild reactions, and patients should carry epinephrine autoinjectors for emergency use if needed.[417-419]

Sublingual immunotherapy

In sublingual IT, small doses of the food allergen extract are placed under the tongue, where it is absorbed through the oral mucosa. Like OIT, the dosage begins at very low levels and is gradually increased until a maintenance dose is reached. Sublingual IT is typically administered daily and can be performed at home after the initial dose, which is administered under medical supervision. In some protocols, an initial period of sublingual IT is followed by a transition to OIT.[420,421]

Efficacy and results

It has been demonstrated that sublingual IT is effective in desensitizing individuals to a variety of food allergens, including peanut and hazelnut. Although desensitization in sublingual IT is generally slower than OIT, it has a favorable safety profile and may increase the threshold of allergen tolerance. Clinical trials have reported varying degrees of efficacy, often slightly lower than OIT, but it still provides significant protection against accidental exposure.[414]

Adverse effects and management

Sublingual IT is generally well tolerated, with most adverse reactions being mild and localized. These include oral pruritus, local edema, and mild gastrointestinal symptoms. Systemic reactions are rare. Because of its favorable safety profile, sublingual IT has been studied in children and

individuals at high risk of severe reactions. Regular follow-up with an allergist is recommended to monitor progress and assess the threshold for clinical response.[414]

Epicutaneous immunotherapy

Epicutaneous immunotherapy uses a patch to administer a small amount of the allergen, usually to the upper arm or back. The allergen is absorbed through the skin, which modulates the immune response over time. Patches are usually worn for a specific period of time each day and are replaced daily or every few days, according to the treatment protocol.[422]

Efficacy and results

Epicutaneous IT has shown promise in clinical trials, particularly for peanut allergies, offering an alternative route of allergen exposure that is less reactive than oral ingestion. Some studies have demonstrated significant desensitization and increased protection against accidental exposure in children and adults. Although the desensitization levels may not be as high as those achieved with OIT, epicutaneous IT may be more convenient and potentially safer for certain patients.[422]

Adverse effects and management

The most common adverse effects of epicutaneous IT are localized skin reactions, such as pruritus, erythema, and mild eczema at the patch site. These reactions are generally mild and manageable. Systemic reactions are rare, making epicutaneous IT a very safe option. Regular monitoring and follow-up with an allergist is essential to ensure the efficacy and safety of the therapy.[422]

Approaches to multiallergen immunotherapy

Research has increasingly focused on multiallergen immunotherapy, in which patients are simultaneously desensitized to multiple food allergens. This approach is particularly beneficial for individuals with multiple FA. Preliminary studies suggest that multiallergen OIT may be effective, but it requires careful monitoring and individualized protocols due to the increased risk of adverse reactions.[423,424] The concomitant use of biologics, notably omalizumab, has allowed for more robust and safer results.[425,426]

Long-term results of immunotherapy for food allergy

Sustainability of desensitization

Sustainable desensitization is a critical factor in assessing the long-term success of immunotherapy. Although findings on lasting tolerance vary, many studies suggest that ongoing maintenance doses of the allergen are needed to maintain desensitization. For example, in OIT trials, some patients had sustained tolerance after a period of food restriction, while others required continued exposure to maintain their tolerance level.[427,428]

Long-term safety data

Long-term safety data are important risk-benefit ratio assessment for FA immunotherapy.[429] Most adverse reactions occur during the induction (ie, dose escalation) phase, with a significant decline in incidence once maintenance doses have been established. Long-term follow-up has indicated that serious adverse events are rare, highlighting the relative safety of immunotherapy for IgE-mediated FA when conducted under medical supervision.[424,429,430]

Improved quality of life

Improved quality of life is a significant measure of IT success. Studies consistently show that successful desensitization through IT can provide substantial psychological and practical benefits for patients and their families. These benefits include reduced anxiety about accidental exposure, increased dietary freedom, and improved social interactions. Parents of children who successfully undergo immunotherapy report reduced stress and improved overall family quality of life.[431]

Scientific guidelines for immunotherapy for food allergy

Recommendations on allergen-specific IT (mainly OIT) for IgE-mediated FA have been proposed in different countries.[158,419,432-434]

Recent European guidelines on allergen-specific immunotherapy for IgE-mediated FA have been developed using the Grading of Recommendations, Assessment, Development and Evaluations approach based on meta-analysis results[435] and worldwide expert consensus (Table 18).[4]

OIT is generally considered an effective means of inducing desensitization, ie, increasing the reactivity threshold to the allergen. OIT can also induce prolonged tolerance to the allergen through 2 different outcomes, "sustained unresponsiveness" and oral tolerance. Sustained unresponsiveness is the lack of a clinical reaction to a food allergen after active therapy has been discontinued, although some level of continued exposure to the allergen is necessary to maintain this state. Oral tolerance, however, describes a complete lack of reactivity without the need for continued exposure. Nevertheless, the data are still very limited and heterogeneous on this subject, with most studies reporting sustained unresponsiveness rather than oral tolerance.[432-434] The guidelines do not provide specific criteria for which patients should be offered OIT. The notion of FA severity appears inadequate for determining OIT eligibility because the risk and severity of reactions are unpredictable and do not correlate with the psychosocial impact of FA on patients and their families.[434] The guidelines emphasize the importance of shared decision-making with the patient/family prior to and during IT. OIT should be a personalized treatment, tailored to the context, wishes, goals, dietary habits, experience, and motivation of the patient.[436,437]

OIT involves restrictions and risks, so it requires commitment and strong adherence, with maintenance required for an "indefinite" period. The recommendations specify that centers which provide OIT must be experienced in this type of care and possess appropriate infrastructure for regular and personalized patient monitoring, oral provocation tests, and anaphylactic reaction management. They also recommend that each dose increase should be performed under medical supervision. The guidelines also agree on the contraindications to OIT, especially uncontrolled asthma, active EoE, pregnancy, and active neoplasia.[438,439]

Best practice recommendations for food allergy immunotherapy[440]

– Individualized treatment plan: develop personalized treatment plans based on the patient's specific allergies, medical history, and overall health.
– Informed consent: thoroughly discuss the potential benefits, risks, and expectations of IT with patients and their caregivers. Obtain informed consent before starting treatment.
– Controlled environment: perform initial dose escalation (induction) and any high-risk procedures in a controlled medical environment equipped to manage anaphylaxis and other serious reactions.
– Regular monitoring: maintain regular follow-up to monitor progress, adjust doses, and manage adverse effects. Provide patients with clear guidance on what to do at home if they experience a reaction.
– Education and support: educate the patient and their family about the recognition and management of allergic reactions. Offer psychological support.

Patient selection for food allergy immunotherapy

Selection criteria[440]

Confirmed allergy: for all candidates, diagnosis of IgE-mediated FA must be confirmed through a combination of clinical history, specific IgE testing, skin testing, and OPT.

Age considerations: immunotherapy may be appropriate for both children and adults, but better outcomes and lower rates of adverse reactions have been observed in pediatric populations. Most guidelines recommend beginning at 4 years of age.[441]

Previous reactions: the severity and nature of previous allergic reactions must be assessed. Immunotherapy may be more appropriate for patients with a history of severe reactions, but caution is needed.

Motivation and adherence: the patient's and the family's willingness and ability to adhere to the

schedule and strict protocols required for IT must be assessed.

Contraindications and precautions[440]

Severe uncontrolled asthma: patients with poorly controlled asthma are at increased risk of severe reactions and should be stabilized before starting IT.

Active EoE: since therapy may exacerbate the condition, active EoE is a contraindication to OIT.

Autoimmune diseases and neoplasms: patients with active autoimmune diseases or neoplasms

Table 18
European Academy of Allergy and Clinical Immunology recommendations for allergen-specific food immunotherapy[4]

Recommendation	Certainty of evidence	Strength of recommendation
In eligible patients with IgE-mediated FA, allergen-specific IT should be administered by a team specialized in food IT and in managing adverse effects and anaphylaxis.	Low	Strong
For children and adolescents with IgE-mediated peanut allergy, peanut OIT is recommended for desensitization.	High	Strong
In children and adolescents with IgE-mediated peanut allergy, when available, peanut epicutaneous IT is suggested for desensitization.	High	Conditional, since only clinical research data are available
In children and adolescents with IgE-mediated peanut allergy, peanut sublingual IT is suggested for desensitization.	Moderate	Conditional. The most recent publication raises the level of certainty, but no regulated product is commercially available
For children (usually > 4 years of age) and adolescents with IgE-mediated egg allergy, egg OIT is suggested for desensitization.	Low	Conditional due to low quality evidence for children aged ≥ 4 years
For children (usually > 4 years of age) and adolescents with IgE-mediated milk allergy milk OIT is suggested for desensitization.	Low	Conditional due to low quality evidence

IgE = immunoglobulin E; FA = food allergy; IT = immunotherapy; OIT = oral IT.

require a more complete evaluation before undergoing IT.

Pregnancy: Immunotherapy is generally not initiated during pregnancy. However, maintenance therapy may be continued with caution.

Adherence issues: individuals who may have difficulty with the adherence necessary for successful therapy, such as those with significant psychological disorders, should be carefully assessed.

Biological issues

Allergen-specific OIT is an immunomodulatory treatment to increase the patient's tolerance threshold and reduce the risk of reactions in the event of accidental ingestion of the allergenic food. However, in addition to being laborious and prolonged, this procedure is associated with the risk of allergic reactions, which can be severe; which prevents recommending it for general practice.[442]

One strategy that has been studied to increase the safety and, consequently, the efficacy of OIT, is the concomitant use of biologics, of which omalizumab has been the most successful. Omalizumab is a humanized monoclonal antibody that targets IgE and has been approved for use in asthma refractory to inhaled corticosteroids and chronic spontaneous urticaria.

The association of omalizumab and OIT was first reported in 2011, when Nadeu demonstrated success in desensitizing 9 of 11 patients with CMPA in 7-11 weeks, which was faster and safer than conventional protocols.[443] Recent studies have shown that omalizumab and other anti-IgE therapies increase the reactivity threshold, whether administered alone or in combination with OIT. In this case, they can reduce the incidence and severity of adverse events and decrease the time required for dose escalation.[405,442-445]

Mechanism of action

Omalizumab binds to IgE antibodies, forming IgE/anti-IgE immune complexes, which prevent interaction of these antibodies with FcεRI receptors on mast cells and basophils, thus inhibiting their degranulation and the release of allergic response mediators. Blocking the actions of circulating IgE also induces a downregulation of FcεRI expression, further limiting the possibility of their activation.[442,446]

In addition to basophils and mast cells, FcεRI is also expressed by DCs, where it is believed to play a role in allergen presentation to T cells. It is speculated that omalizumab also negatively modulates FcεRI expression on DCs, hence negatively modulating allergen presentation by DCs and decreasing TH2 function, leading to further reduction in allergic response.[442,446]

In OIT, exposure to continuous high doses of food allergens causes anergy and/or Th2 deletion and an increase in Tregs, which leads to a suppression of subsequent allergic response.[390] However, the humoral response during food IT is manifested by a gradual decrease in specific IgE[405] and an increase in specific IgG4 to food proteins, as well as an increase in specific IgA.[406,407] It is postulated that treatment with anti-IgE + OIT may induce allergen desensitization through downregulation of FcεRI expression in basophils and mast cells, reducing specific IgE levels and increasing IgG4 levels.[442]

Evidence

Several studies have reported on associating omalizumab and OIT, some with robust evidence, although few studies have investigated other biologicals, ie, only a single publication each on etokimab and talizumab, in addition to the following ongoing trials: ligelizumab for peanut allergy (clinical trials.org: NTC04984876, and NTC05678959) and dupilumab (clinical trials.org: NTC03682770, and NTC04148352) for peanut and CMPA, respectively. There is evidence of omalizumab's effectiveness, both as an isolated agent for increasing the response threshold and reducing FA symptoms, and as an adjuvant to food OIT.

What is the evidence for current use in the OIT for food?

1. Clinical trials on omalizumab + OIT for desensitization to milk, peanut, egg, and multiple foods.

A recent systematic review and meta-analysis evaluated the efficacy and safety of omalizumab or omalizumab + OIT in patients with FA. The review included 36 good quality studies, of which 9 were randomized clinical trials, 19 were controlled clinical trials, and 8 were observational studies. These 36 methodologically consistent studies involved allergies to milk, egg, peanut, and multiple foods.[442]

2. Systematic reviews and meta-analyses of studies involving omalizumab + OIT.

   Two systematic reviews and meta-analyses involving biologics and OIT have been published recently. The first, cited above, analyzed the effect of omalizumab as monotherapy and as an adjuvant to OIT. As monotherapy, meta-analyses comparing the effect of omalizumab use with the sample's baseline condition showed that omalizumab increased the tolerance threshold for cow's milk, egg, wheat, peanut, and baked milk in patients allergic to these foods, in addition to increasing the tolerated dose of multiple foods in patients with multiple allergies and improving quality of life.[442]

   When combined with OIT, omalizumab increased the tolerated dose of multiple foods, increased the doses achieved in desensitization, helped maintain OIT, increased specific IgG4 levels for the target foods, and improved quality of life, compared to baseline. However, combining omalizumab with OIT has shown no advantages regarding safety and adverse effects.[442]

   A meta-analysis compared omalizumab + OIT vs placebo + OIT for both the primary outcome (desensitization rate) and the secondary outcome (sustained unresponsiveness/remission or higher dose). Omalizumab + OIT had a highly significant positive effect on desensitization (relative risk 2.17 [1.22, 3.85]). However, the results were less precise for the long-term effect (sustained unresponsiveness/remission): relative risk 2.42 [0.90, 6.50].[444]

3. Omalizumab increases the efficacy of OIT to multiple foods and enables faster and safer desensitization.

   A pioneering study involving 48 patients allergic to multiple foods (2-5 per patient) who were randomized 3:1 to receive omalizumab + OIT for multiple foods (36 patients) or placebo + OIT for multiple foods (12 patients). The primary objective was to pass a double-blind placebo-controlled OPT for 2 g of the foods to which they were allergic after 36 weeks. In the active group (omalizumab + OIT), 80% of patients passed their OPTs, compared with approximately 30% in the omalizumab + placebo group.[425]

4. As a single desensitizing agent, omalizumab increases the threshold for allergic reaction to foods.

   The recent OUtMATCH study analyzed 177 children and adolescents who were allergic to ≥ 2 foods (one of which was peanut). Randomized in a 2:1 ratio to receive omalizumab or placebo for 16 to 20 weeks, the patients underwent OPT with 600 mg of peanut (primary outcome) and OPT with the remaining foods to which they were allergic (secondary outcome) at the end of the study. Of those who received omalizumab, 67% passed the OPT with peanut, compared with only 7% of those who received placebo ($P < 0.001$). The results for the secondary outcomes were also consistent: milk (66% vs. 10%), egg (68% vs. 0%), and cashew (41% vs. 3%)($P < 0.001$ for all comparisons). This study demonstrated that omalizumab monotherapy effectively increases the reaction threshold for common food allergens.[426]

   Based on this study, the U.S. Food and Drug Administration approved omalizumab as a treatment option to reduce the risk of severe allergic reactions in children and adults with severe multiple food allergies.[447]

   OUtMATCH includes 3 phases, but only the first is reported here. The second phase will compare long-term treatment (52 weeks) with omalizumab + OIT for multiple FA, while the third phase will evaluate the introduction of allergenic foods into the diet for continuous consumption (minimum 52 weeks) at home after treatment discontinuation.[426]

Based on the evidence described above and that of several other recent studies, omalizumab has been recommended as an adjuvant to OIT by some guides and expert groups, highlighting the

important role it can play in drug and allergen-specific management of FA.[444,448]

Prebiotics, probiotics, synbiotics, and vitamins

Although FA treatment is still primarily based on allergen restriction and symptom management, other interventions for restoring oral tolerance, such as prebiotics, probiotics, and vitamins, have also been studied. These approaches can play an auxiliary role in modulating immune response and preventing allergic diseases.[5]

The role of the gut microbiome

Recent studies have indicated that the composition and diversity of the intestinal microbiome play a fundamental role in regulating immune response, being a critical interface between the environment and the immune system. Intestinal dysbiosis (imbalance in the microbial community that results in dysfunction) has been associated with an increased incidence of FA, which suggests that modulating this environment through biotic and vitamin supplementation could be an effective strategy.[449]

A recent Canadian birth cohort study (CHILD) followed 1,115 children from birth to 5 years of age, performing clinical and laboratory analyses (specific IgE and fecal microbiota). It demonstrated that children who had developed allergies by 5 years of age, including FA (n=136; 12%), had dysfunctional microbiota in the first year of life, probably due to greater use of antibiotics.[450]

Probiotics and immune modulation

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host, especially through immune system modulation. Some bacteria, such as strains of *Lactobacillus* and *Bifidobacterium*, including *Bifidobacterium breve M-16*, have been found efficacious for the prevention and treatment of allergic diseases by promoting the induction of Tregs, which are essential for continued oral tolerance. Probiotics also have a role in the production of secretory IgA, the stabilization of mast cells, and in reduced release of pro-inflammatory cytokines, such as IL-4 and IL-5, which are essential factors in allergic reactions.[450]

In the context of FA, some studies have found that probiotic supplementation in high-risk pregnant and lactating women, as well as in newborns, can significantly reduce the prevalence of allergic diseases, such as atopic dermatitis and CMPA. A classic example is Kalliomäki et al., who demonstrated reductions of up to 50% in atopic eczema prevalence among children whose mothers received probiotics during pregnancy and lactation.[451]

Despite these studies, which recommend probiotics for allergy prevention (especially atopic eczema) and allergy treatment in general, the results are less substantial. Some better-designed studies have found that specific probiotic strains may be effective for a subgroup of patients with atopic eczema, especially when FA is associated, such as CMPA. Fiocchi et al. demonstrated that adding a probiotic (*Lactobacillus rhamnosus GG*) to extensively hydrolyzed infant formula for 1 month was sufficient to reduce symptoms, from 26 to 15 in the group that received the probiotic directly, and from 26 to 11 in the group that received it indirectly, via breast milk. However, neither group improved regarding CMPA-related gastrointestinal symptoms. Continuation of these studies using an association of *Lactobacillus rhamnosus GG* and *Bifidobacterium lactis Bb-12* revealed CMPA-related eczema improvement, although other specific CMPA symptoms persisted.[452]

Both the pathogenesis of FA and the physiology of oral tolerance mechanisms are complex and not yet fully understood, but *Lactobacillus rhamnosus GG* favored oral tolerance induction in children with CMPA on an elimination diet. Tolerance induction through *Lactobacillus rhamnosus GG* added to extensively hydrolyzed infant formula was found to be significantly faster than AAF, soy formulas, and hydrolyzed rice formulas.[399] This suggests that, as part of the diet, *Lactobacillus rhamnosus GG* reduces the time needed to control CMPA symptoms and stimulates natural tolerance induction. *Bifidobacterium breve M-16* has been associated with a reduced allergic response in some studies and with microbiota modulation.[453-456]

Prebiotics and immune health

Prebiotics are non-digestible dietary compounds that benefit the host's health by promoting selective growth of beneficial bacteria in the intestine, such as *Lactobacillaceae* and *Bifidobacterium spp.* They are essential for maintaining a healthy intestinal environment, facilitating the production of short-chain fatty acids, such as butyrate, whose anti-inflammatory action contributes to the integrity of the intestinal barrier.[451]

Fructooligosaccharides, glucooligosaccharides, galactooligosaccharides, inulin, and isomalto-oligosaccharides are examples of prebiotics that stimulate the growth of intestinal probiotics, such as *Lactobacillaceae* and *Bifidobacterium spp.* Fructooligosaccharides, prebiotic supplements that can improve the host's immune response and activate mucosal immunity by regulating the gastrointestinal microbiota, have therapeutic potential for allergic diseases.[475]

Research shows that preventive measures involving prebiotics can reduce the incidence of allergic manifestations by up to 6, if the prevention protocol is started in the 5 years of life.[457]

From a prebiotic perspective, we cannot forget the fundamental role of human milk oligosaccharides, which are ideal nutritional components for infants, since they can increase immunomodulatory capacity. Human milk oligosaccharides can intervene in the development of allergies by modifying the intestinal microbiota and increasing specific levels of short-chain fatty acids. Human milk oligosaccharides can also improve intestinal permeability and directly or indirectly regulate the balance between helper T cells and Tregs by intensifying inflammatory signaling pathways to combat FA.[458,459]

The role of vitamins in food allergy prevention

CMPA is one of the most common types of childhood FA, especially in the first years of life. Although standard treatment involves eliminating cow's milk from the diet, the role of vitamins in CMPA prevention and treatment has been increasingly investigated, given that certain micronutrients, such as vitamins, are fundamental in immune system modulation.[459,460]

Vitamin D

Vitamin D is widely recognized for its role in bone health, but it also plays an important role in the immune system. Studies suggest that vitamin D deficiency may be associated with an increased risk of allergic diseases, including CMPA, due to its immunomodulatory functions, which affect both innate and adaptive immunity. Vitamin D deficiency may contribute to immune imbalances that facilitate FA. Vitamin D may also prevent the intestinal immune system from allergen exposure by maintaining the integrity of the mucosal barrier.[330,461]

Evidence suggests that adequate vitamin D supplementation during pregnancy and early life may reduce the risk of FA. An observational study found that mothers with sufficient vitamin D levels during pregnancy were less likely to have children with FA, including CMPA.[462,463] However, a systematic review was unable to confirm this.[155]

However, data in the literature are contradictory: some studies suggest that low sunlight exposure is associated with adverse events, while others suggest that high levels of vitamin D may increase allergic sensitization. Therefore, further randomized clinical trials are needed to clarify vitamin D's role in allergy prevention.[464,465]

Future perspectives and current recommendations

Although some clinical and experimental studies on FA have found that probiotics and prebiotics provide benefits, some issues still need clarification, such as the most effective strains, doses, and treatment duration. In addition, new therapies, such as postbiotics (inanimate microorganisms and/or their components that benefit the host) and fecal microbiota transplantation, are being investigated to restore microbial balance and prevent or treat FA, especially the most severe forms.

Although it is essential to maintain adequate vitamin levels through adequate diet, there is no conclusive evidence that vitamin supplementation alone can prevent or treat FA. As of yet, the prescription of pro-, pre-, and synbiotics, vitamins, and other supplements are not systematically recommended for FA treatment and prevention.[156,466,467]

Care at school for children with food allergies

The school is an ecosystem in which families, students, and the school community converge and interact with multiple functions. Allergic conditions must be reported at enrollment so that prevention, protection, and inclusion measures can be organized, since allergic diseases compromise quality of life and expose children to risks. Students with allergic conditions need food that is appropriate for their needs, whether in the public or private school system.

Children and adolescents with FA can and should attend school. Safety in the school environment depends on families working together with the school to accommodate them. The better the support for those with FA, the lower the risk of feelings of exclusion or embarrassing situations, such as bullying. Thus, the school must be notified, and the student must be followed up by a pediatrician, allergist, gastroenterologist, or attending physician and bring a biannual follow-up certificate. The school must make the necessary adjustments to the menu after a meeting between the family, the coordinator, and teachers. The patient's classmates should also be informed. Dietary changes should be made carefully, with the approval of the attending physician, and it is important to consider the risk of cross-contact. As with other diseases, the family with must provide the school with a minimum supply of prescribed medications for use in case of an emergency and must keep the telephone numbers of ambulance and emergency services at hand.[468]

School is an environment rich in opportunities for socialization, opinion formation, and critical thinking. It should value inclusion, and FA and the precautions that should be taken should be discussed collectively, developing educational activities that encourage care, generosity, and cooperation. Cooking classes supervised by a nutritionist and learning to read and interpret food labels can make this task easier.[469] Special attention should be paid to celebrations and birthdays, including that of the patient, since the risk of accidental allergen contact is greater in collective environments. The foods most commonly associated with FA are cow's milk, eggs, wheat, soy, shrimp, peanuts, nuts, fish, and seafood.[470]

Several laws addressing FA have been passed in Brazil, which are described below.

Law No. 12,982 of May 28, 2014[471]

School meals for students with special dietary needs.

This law requires adequate school meals to be provided to students with specific health conditions, such as FA, diabetes, celiac disease, lactose intolerance, and other specific conditions. This law ratifies and strengthens the National School Feeding Program guidelines determined in Law No. 11,947/2009.

Resolution No. 26 of July 2, 2015[472]

Mandatory labeling of the most common allergenic foods.

This resolution provides for mandatory labeling requirements for the main foods that cause FA. If the product contains an allergen listed in this resolution's appendix, the following warning must be stated: "PEOPLE WITH ALLERGIES: THIS PRODUCT CONTAINS (COMMON NAME OF THE ALLERGEN)". When the marketed product contains an allergenic food derivative (eg, wheat flour, yogurt, soy extract, casein), the following warning must be displayed: "PEOPLE WITH ALLERGIES: THIS PRODUCT CONTAINS DERIVATIVES OF (COMMON NAME OF THE ALLERGEN). For products that contain both the allergenic food and its derivatives, the following warning must be displayed: "PEOPLE WITH ALLERGIES: THIS PRODUCT CONTAINS (COMMON NAME OF THE ALLERGEN) AND ITS DERIVATIVES. When it cannot be guaranteed that cross-contact has not occurred between allergens and the other ingredients, food additives, or processing aids, the statement "PEOPLE WITH ALLERGIES: THIS PRODUCT MAY CONTAIN (COMMON NAME OF THE ALLERGEN)" must appear on the label.

Law No. 13,722, of October 4, 2018: "Lucas Law"[473]

First aid training for school staff.

This law mandates annual basic first aid training for the teachers and staff of all public and private

elementary schools and children's recreation establishments. All staff who deal directly with children must know what to do in emergencies, especially in cases of severe allergies and anaphylaxis.

Table 19 presents suggested patient safety measures.

Children with FA should be aware of their health and behavior. Their parents, in collaboration with the school and community, need to develop resources that promote good performance and self-esteem, always under the supervision and guidance of their physicians. It is recommended that children and adolescents always carry a medical alert tag or device that identifies foods or medications to which they are allergic.

Reassessment of allergic status

Resolving FA is a complex and individualized process that varies according to the allergen, the mechanism of the reaction, and the specific characteristics of each patient. The tolerance induction process is still not fully understood and probably involves multiple factors.

In IgE-mediated reactions, a drop in food-specific IgE levels is considered the best predictor of clinical tolerance.[477,478] However, it is important to note that some patients may develop tolerance even with elevated specific IgE and positive skin prick test results.

A crucial aspect in assessing patients with FA is investigating accidental exposure to the food, its different presentations, and any resulting reactions. This information provides valuable data on tolerance induction.

Reassessment of patients with FA should include:

– *in vitro* testing (specific IgE);
– skin prick testing; and
– detailed anamnesis, including information on accidental exposure.

Annual reassessment is generally recommended, although the frequency can be adjusted as appropriate, as shown in the examples below.[186]

– Young children with fruit allergy should be reassessed every 6 months;
– older children with persistent allergies (eg, to peanut) and high allergy test results should be reassessed at longer intervals.

It is important to emphasize that neither the skin prick test nor specific IgE are infallible methods for determining tolerance to a food:[479,480]

– negative test results do not guarantee allergy resolution;
– positive test results may persist even after tolerance has developed.

Provocation testing under medical supervision is indicated in severe cases of IgE-mediated allergy and non-IgE-mediated forms of FPIES in an environment equipped emergency material and medications.

Monitoring FA requires a multifaceted approach, combining clinical evaluation and, when necessary, laboratory tests and OPT. Careful interpretation of these data is essential to determine tolerance induction and adjust treatment, which should always be on an individual basis.

Table 19
Suggested measures to ensure greater safety for those with special dietary needs[474,475]

Health documents	For the school to better deal with food allergies, the family should ideally provide a detailed medical report with: – the child's data; – the food(s) the child is allergic to and the reaction types that usually occur; – an action plan for what to do in cases of allergic reactions, including the medications, dosage, and/or form of application.
How to prevent allergic reactions at school	Before the school year begins, the family, the administration, and teachers must meet to discuss the necessary precautions. It is essential for the school to make the necessary adaptations to the school menu. All school staff must be informed about the child's condition and restrictions, in addition to, if possible, the parents of the child's classmates. Take the necessary precautions to avoid cross-contamination (eg, collective snack tables).
First aid	The family must provide the school with a list of medications to be administered and their dosages. In the event that the child must be taken to the hospital, the school must be provided with information on health insurance and hospital preference. The school must have the parents'/guardians' phone numbers on hand in case of emergency.
The inclusion of children with food allergies	The child's classmates should receive instruction on the care required for someone with a food allergy. Educational activities should be developed that encourage care, generosity, and cooperation. Never isolate a child with a food allergy during meals. In any cooking classes, the recipe's ingredients should be adapted so that every child can participate. For celebrations, such as birthday parties, the school should inform the family in advance so that meals can be planned and organized to avoid excluding the child. When gifts or souvenirs involving food are distributed, provide guidance and underscore the importance making sure that children with allergies are not left out.
School meals	If the school provides meals, it is important to talk to the administration and the nutritionist responsible for the menu.
School trips	For school trips and outings, determine whether each student is to bring their own meal from home, whether it will be prepared by the school, or whether it will be prepared by third parties on site. It is important to talk to whoever will be preparing the meal to confirm which foods will be offered and look for safe solutions. Whenever there is an outing, the school must bring a copy of the medical report and the action plan and must ensure that there are at least 2 staff members who can identify reactions and know what to do in case of an emergency.

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Corresponding author:
Dirceu Solé
E-mail: alergiaimunoreumatounifesp@gmail.com