

Food Allergy: From Diagnosis to Treatment

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Key Words

Adverse food reactions · Food allergy · Hypersensitivity reactions · Toxic reactions · Allergen-specific/nonspecific therapies

Abstract

Adverse food reactions, an adverse health effect arising from an immune or nonimmune response that occurs reproducibly on the exposure to a given food, can be divided into toxic and hypersensitivity reactions. When an immunologic mechanism has been shown, hypersensitivity food reactions should be referred to as food allergy that may be IgE- or non-IgE-mediated. Food allergy diagnosis is mainly guided by a correct and accurate history and physical examination, thus leading to prick test and elimination diets. The treatment gold standard is still represented by an elimination diet together with antihistamines and corticosteroid usage in order to reduce the gastrointestinal and potentially life-threatening systemic symptoms. Other treatments are currently under investigation with promising results.

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Definition and Epidemiology

Adverse food reactions, defined as an adverse health effect arising from an immune or nonimmune response that occurs reproducibly on the exposure to a given

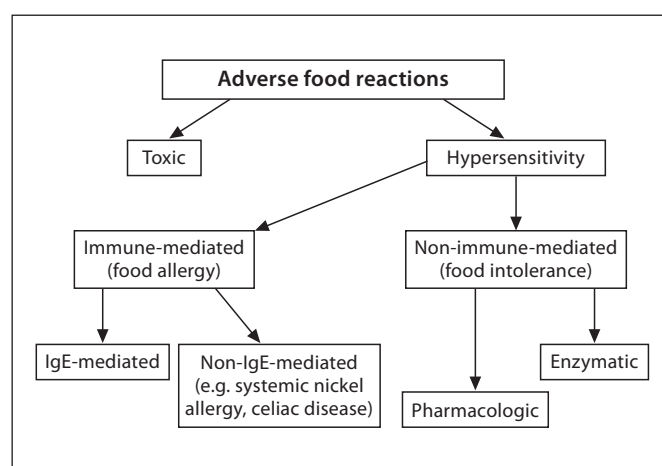


Fig. 1. Adverse food reactions classification.

food, can be divided into toxic and hypersensitivity reactions (HRs). When an immunological mechanism has been shown, hypersensitivity food reactions should be referred to as food allergy; if the role of IgE is highlighted, the exact term is IgE-mediated food allergy. All other reactions should be called nonallergic food hypersensitivity (pharmacological, enzymatic, undefined) [1] (fig. 1).

About 20% of people report an adverse food reaction, but true food allergy has a prevalence of only 0.5–3.8% in children and 0.1–1% in adults [1].

Clinical Features

Food allergy can cause a number of typical cutaneous, gastrointestinal, respiratory and systemic symptoms [2].

Acute urticaria (pruritus, hives, swelling) and angioedema are the most frequent cutaneous manifestations.

Gastrointestinal anaphylaxis usually presents with nausea, colicky abdominal pain, vomiting, or diarrhea and generally coincides with allergic manifestations in other organs. Allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis are characterized by eosinophilic infiltration of the esophagus, stomach, or intestinal wall and peripheral eosinophilia, leading to nausea, vomiting, dysphagia, epigastric and abdominal pains. Food protein-induced proctocolitis is a non-IgE-mediated disorder that typically affects infants in very early months of life, caused by food proteins contained in maternal breast milk or by milk or soy-based formulas. It is characterized by the presence of blood in the stool, and the eosinophilic infiltration of the distal large bowel. Food protein-induced enterocolitis is another non-IgE-mediated disorder usually caused also by milk or soy proteins presenting with prolonged vomiting appearing about 1–3 h after allergen ingestion. Dietary protein-induced enteropathy presents with diarrhea and poor weight gain, associated with villous atrophy and a mucosal mononuclear cell infiltrate with a few eosinophils.

Isolated rhinoconjunctivitis (periocular pruritus, tearing and conjunctival erythema, nasal congestion, sneezing and rhinorrhea) or asthma (wheezing, cough, dyspnea), frequently associated with other allergic manifestations, are the most common respiratory features of food allergies.

Food allergy is responsible for at least one third to one half of anaphylaxis cases seen in emergency wards. Food-dependent exercise-induced anaphylaxis is a rare condition which occurs only during exercise within 2–4 h of food ingestion. The pollen-food allergy syndrome (oral allergy syndrome) is caused by some plant proteins that cross-react with airborne allergens, especially birch, ragweed and mugwort. It starts typically with mild pruritus, tingling or angioedema of the lips, palate, tongue or oropharynx while systemic symptoms are rare [2, 3].

Food intolerances are non-immune-mediated adverse food reactions with aspecific gastrointestinal symptoms not associated with extraintestinal signs or symptoms such food allergy features. These adverse reactions include sugar and food additive intolerances; the most common among these is lactose intolerance, elicited in most

cases due to declining levels of intestinal lactase activity in later childhood and adult life (metabolic food intolerance), although rare congenital deficiencies can occur. Symptoms of lactase insufficiency are usually dose-related and include bloating, flatulence, and diarrhea.

Diagnostic Flowchart

The diagnostic approach to suspected food HRs is mainly based on medical history and clinical examination. The medical history should investigate (a) the food component that is responsible for the HR, (b) the time interval between food ingestion and development of symptoms, (c) whether other factors (e.g. exercise, alcohol or drug ingestion) can provoke symptoms, (d) the symptoms provoked by the responsible food, (e) the use of any medication (e.g. antihistamines, corticosteroids or epinephrine) and (f) whether the patient is suffering from other allergies. Moreover, foods may be contaminated with and contain hidden allergens (e.g. milk and soy proteins often added to increase protein content or enhance flavor).

The physical examination should focus on the cutaneous, gastrointestinal and respiratory systems, which are mostly involved in food allergy [4] (fig. 2).

Diagnostic Tests

Skin Prick Testing and IgE Dosage

Skin prick testing (SPT) provides a rapid method to screen patients with suspected food allergy. Glycerinated food (when available) extracts are applied by the prick or puncture technique. A wheal at least 3 mm larger than the negative control is considered positive. In case of negative SPTs with food extracts, SPTs with fresh foods (prick-by-prick method) should be performed. SPT has a high sensitivity and negative predictive value (>95%), but low specificity and positive predictive value (50–80%) [5, 6]. Negative SPT responses, together with the absence of food-specific IgE virtually exclude IgE-mediated reactions but do not exclude the diagnosis of food intolerance; a positive SPT, if it is not confirmed by the measurement of specific IgE and by a double-blind, placebo-controlled food challenge (DBPCFC), also does not confirm the diagnosis of food allergy. However, a positive SPT may be considered diagnostic in patients who experienced life-threatening reactions after ingestion of an isolated food [6] (fig. 2).

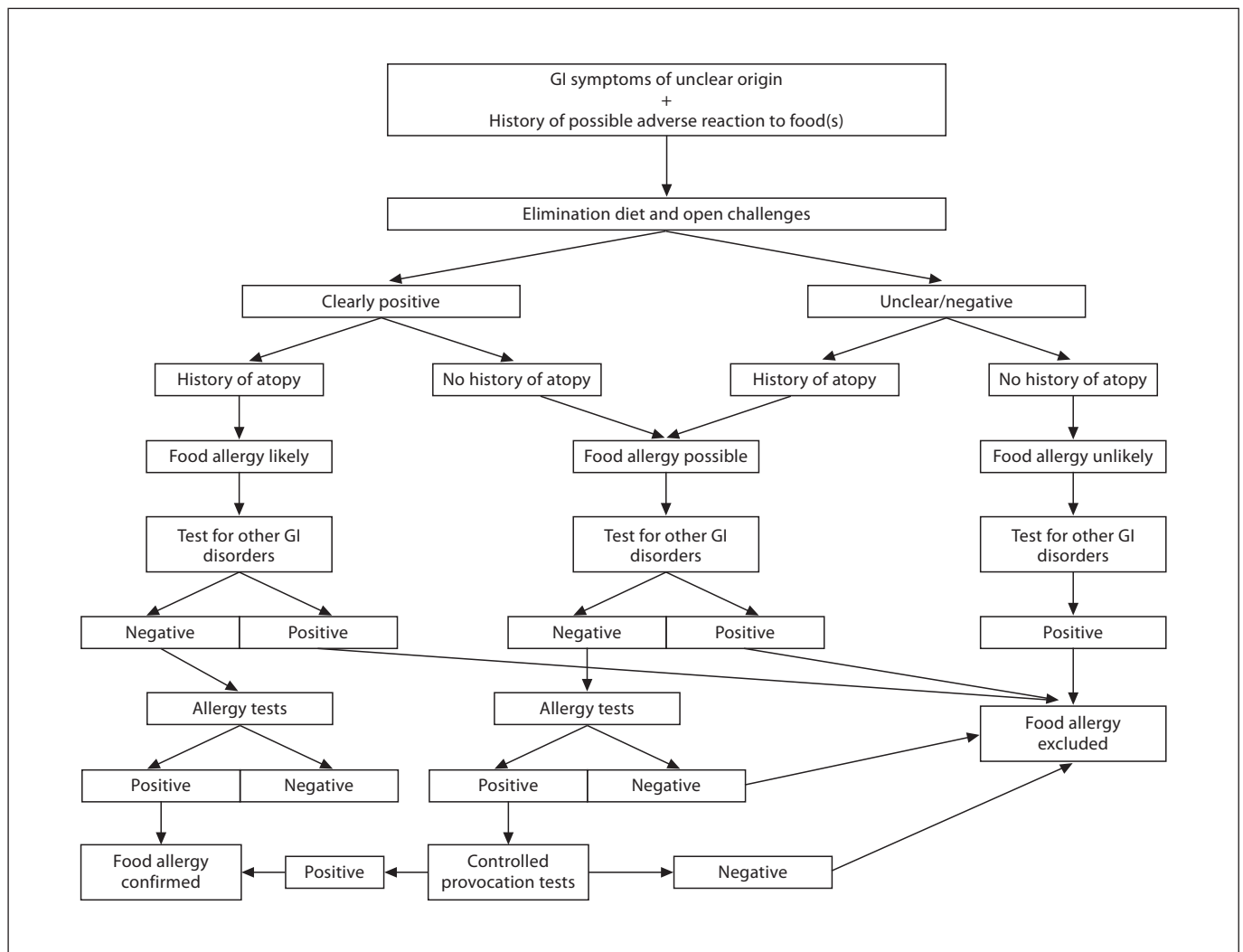


Fig. 2. Diagnostic food allergy flowchart. Adapted from Bischoff and Crowe [4].

Detection in the serum of an antigen-specific IgE is the second step after SPTs for the diagnosis of food allergy, although this should be considered as a first-line test in patients with significant dermatographism, with skin disease (e.g. atopic dermatitis or psoriasis), or in those having difficulties in discontinuing antihistamines. Detection of specific IgE is more time-consuming and more expensive than SPTs. Some authors determine food-specific IgE levels with a 95% positive predictive value and show that there is a direct correlation between the food-specific IgE level and the probability that a patient will react to a food if ingested, but this remains a controversial issue in the literature [7]. Some of these discrepancies may arise from the fact that different authors studied

different populations. Moreover, patients with food-specific IgE levels less than 0.35 kUA/l may still experience an allergic reaction and should be exposed to a food challenge to confirm the absence of clinical food allergy. It is important to remember that false-positive tests are common in patients who are sensitized to pollens or latex and in those with atopic eczema. Recently, multiplex variants for specific IgE analysis have become available allowing the testing for the most common allergens in a single analysis but very often without proper clinical advice or interpretation. Moreover, indiscriminate testing of this nature has insufficient clinical data to justify its place in the routine approach [7, 8].

Elimination Diets and Oral Provocation Tests

Once some specific foods, according to a detailed clinical history, are suspected to be responsible for an allergic disorder, an elimination diet is able to bring the patient's symptoms to an end, thereby confirming the diagnostic hypothesis (fig. 2). When symptoms, such as chronic urticaria or gastrointestinal disorders unrelated to enzymatic deficiencies or to small bowel bacterial overgrowth, do not seem to be related to a single food, the physician should consider a delayed-type allergy to nickel [9], chrome, cobalt or a latex-fruit syndrome [10]. In case of a positive patch test to nickel, chrome or cobalt, patients should avoid foods containing these metals (a positive response is usually seen at least after 4 weeks of the elimination diet). In case of a latex-fruit syndrome, the elimination of cross-reacting foods should promptly improve the clinical feature [10].

Elimination diets should be given on the basis of allergy testing results. In case of allergy to a single or a few foods, diets are based on its elimination with a prompt resolution of symptoms in a few days. When after testing it is not possible to identify a candidate food, the patient should undergo an elemental diet that very seldom causes sensitization for at least 4 weeks. If the symptoms disappear, the patient can introduce a single food every 4 days until the responsible food is identified by symptom recurrence. Foods may naturally contain active substances (such as tyramine, histamine, phenyl-ethylamine, sodium nitrate), or may provoke the release of histamine from mast cells (e.g. strawberries). Elimination diets usually cause a resolution of these food-related disorders, but should be followed for several weeks. Intolerance to food additives (mainly sulphites, glutamate, benzoates and p-oxybenzoates) may mimic food allergy. In this case, an exclusion diet is recommended.

Elimination diets have some drawbacks [11]: the responsible food(s) may be an essential component of the diet (such as milk or egg) for children, elderly or pregnant women, or it may be contained in various foods; also, the diets may be expensive.

The DBPCFC is the gold standard for the diagnosis of food hypersensitivity [12] (fig. 2). It must not be performed in the case of a clinical history of anaphylaxis to a well-known food, if the patient is suffering from a systemic acute illness, if the patient is taking drugs that may diminish (antihistamines, corticosteroids) or amplify (ACE inhibitors, etc.) the reaction or drugs that diminish the efficacy of epinephrine (beta-blockers). For these reasons, DBPCFCs should be conducted in a clinic or hospital setting, and with trained personnel and equip-

ment immediately available for the treatment of anaphylaxis.

Although DBPCFCs are considered the gold-standard in the diagnosis of food-related symptoms, false-negative and false-positive results are possible: false-negative results may be obtained because of drug use during challenges; augmentation factors such as physical exercise, drugs (e.g. aspirin), alcohol, hormonal factors (e.g. menstruation), respiratory or gastrointestinal infections, systemic mastocytosis or psychogenic factors may compromise the reproducibility of the DBPCFC when these factors are absent. Such factors may also be responsible for positive reactions during a previously negative challenge [11, 12].

Not Recommended Tests: IgG Dosage and Basophil Activation and Leukotriene Release Assays

With the single exception of celiac disease, IgG-specific tests are of no proven value. In fact, there are some celiac disease patients who are positive for IgG anti-gliadin and negative for IgA anti-gliadin and hence doing both improves the sensitivity of screening. Nevertheless, IgA anti-gliadin antibody is more specific than IgG anti-gliadin. Otherwise, IgG class anti-food antibody has no proven value, either in the context of IgE-mediated allergies or in 'food intolerance'. Poor specificity is the major issue. In fact, depending on the assay cutoff, IgG anti-gliadin is found in up to 15% of healthy blood donors [13]. The presence of these antibodies might therefore be over-interpreted. For example, IgG anti-gliadin antibodies are found in some patients with ataxia. While some have interpreted this as a new disease 'gluten ataxia', others have seen this as a result of the common finding of IgG anti-gliadin (and other food antibodies) in the general population [14]. A recent publication focusing on irritable bowel syndrome has once again brought IgG class antibodies into attention. Based on differences in outcome for IgG antibody-based diets versus random diets, the authors suggest that these may play a role in food hypersensitivity, but it should be remembered, as noted above, that the specificity of such assays is very low, and in this particular study the composition of standard and exclusion diets were significantly different [15].

Several months after starting subcutaneous allergy desensitization regimens (e.g. for pollen allergy), levels of allergen-specific IgG4 increase during successful treatment. This has been attributed to 'blocking antibodies' which interfere with the binding of allergen to specific IgE. Recently, it has been shown that high-dose sublingual allergen exposure may also induce blocking anti-

bodies. Hence, in the limited context of laboratory support for clinics involved in allergen desensitization, a case may be made for checking allergen-specific IgG4. However, these comments are largely irrelevant in the context of food allergy where desensitization treatments are in their infancy. Specific IgG4 has been shown to be elevated in some patients with atopic dermatitis in several studies, but clinical utility is very limited. Specific IgG4 has not otherwise been shown to be helpful in either diagnosis or monitoring of therapy [16].

Basophils may be activated in vitro by allergen-specific IgE, leading to expression of CD63 and release of leukotriene C4. Assays have been developed and have been demonstrated to correlate with clinically proven food allergy. However, the sensitivity of the basophil activation test is only in the order of 60–80%. The sensitivity of the leukotriene release assay is in the order of 65%. The leukotriene release assay may also detect activation through nonimmune mechanisms. Moreover, both are time-consuming assays, requiring specialist facilities and have not yet found general utility in the routine investigation of food hypersensitivity [17].

A number of other tests have been advocated for allergy investigation but with at least a dubious scientific basis: applied kinesiology, the leukocytotoxic test, electrodermal testing and hair analysis [18].

Treatment

The gold standard in treating food allergies consists of identifying the responsible food allergen and educating patients on how to avoid ingesting the food unknowingly and how to recognize and treat early signs of an allergic reaction in case of accidental ingestion. Given the increasing prevalence of food allergy and associated hospitalizations, this approach is clearly not optimal, and there is a strong need to develop effective therapies. Several allergen-specific and allergen-nonspecific strategies are currently available or under investigation.

Allergen-Specific Therapies

Allergen Immunotherapy

Immunotherapy entails gradually increasing exposure to allergens with progressive *desensitization* (temporary loss of responsiveness due to continuous exposure) and/or promoting *tolerance* (permanent immunologic non-response). Immunotherapy is widely used to treat respiratory allergies, and with the success of subcutaneous immunotherapy (SCIT) for asthma and allergic rhinitis,

food-specific immunotherapy is a possible treatment for food allergy. Although early attempts at using SCIT for food allergies resulted in unacceptably high rates of severe adverse reactions [19], oral immunotherapy (OIT) appears to be the most promising option. In the first randomized trial with OIT, children received daily milk OIT in 3 phases. Double-blind, placebo-controlled oral food challenges were performed before and after 13 weeks of OIT to establish thresholds of reactivity to milk. Following treatment, the threshold dose for reactions to milk increased more than 50- to 100-fold for all children on active OIT but remained unchanged in the placebo group. All children in the active OIT group experienced multiple adverse reactions, mostly mild. There was no significant change in milk-specific IgE levels or SPT results, but a significant increase in milk-specific IgG and IgG4 in the active treatment group. Importantly, the majority of participants experienced reactions during the post-OIT food challenge, indicating that complete protection from allergic reactions was not achieved. Furthermore, all successfully desensitized participants continued daily consumption of milk; therefore, it is unclear whether any OIT participants developed tolerance rather than desensitization [20]. In an uncontrolled open-label peanut OIT study [21], desensitization appeared successful in 93% of patients after 4–22 months of maintenance therapy. The increased tolerance was accompanied by decreased IgE levels at 12–18 months and significantly increased IgG4 levels. Adverse reactions during OIT are fairly common: nearly half of the active doses are associated with symptoms ranging from mild localized to systemic reactions requiring epinephrine.

Sublingual immunotherapy (SLIT) is another potential route of antigen administration which has been investigated for hazelnut [22] and peach allergy [23]. Both studies demonstrated increased tolerance after 5–6 months of treatment. Patients receiving SLIT frequently experience mainly mild, localized adverse symptoms. Like OIT, SLIT appears to desensitize patients, but whether it will lead to permanent tolerance remains to be established.

Clinical studies investigating tolerance to extensively heated (baked) milk and egg in allergic children demonstrated that administration of this ‘heat-denatured’ allergen in tolerant children resulted in virtually no adverse symptoms and was associated with decreased milk- and egg-specific SPT sizes and increased IgG4 levels. Furthermore, heated milk-tolerant children had a higher frequency of milk allergen-specific Treg cells [24], suppressed IgE-mediated basophil responses to milk aller-

gen stimulation, and decreased IgE epitope diversity and lower affinity binding on peptide microarray immunoassays as compared with milk-allergic children who could not tolerate baked products. These immunological changes are similar to many of the changes seen with OIT, suggesting that ingestion of heat-denatured milk or egg may present a more natural and safer form of immunotherapy [25].

In conclusion, immunotherapy appears to be a promising option for the treatment of food allergy, although adverse reactions with OIT may be problematic. Additional randomized, placebo-controlled trials are necessary to determine the true efficacy and safety of these methods, to standardize extracts, protocols, and durations of treatment, and to determine whether these forms of therapy can induce lasting oral tolerance, rather than simply desensitization, which necessitates continuous, almost daily treatment.

In order to decrease adverse effects of immunotherapy due to activation of mast cells and basophils, modified recombinant food proteins have been engineered to decrease IgE-binding capacity while retaining the protein's ability to stimulate T cells. Modified peanut allergens (Arah 1, 2, 3) can stimulate T cells from peanut-allergic individuals to proliferate, but have greatly reduced IgE-binding capacity as compared with wild-type peanut protein [26]. Heat-killed *E. coli* producing recombinant peanut proteins showed protective effects in a murine model of peanut anaphylaxis. The hypothesized underlying mechanisms include activation of T regulatory cells and downregulation of Th2 cells, and reduction of mast cell mediator release on reexposure to antigen [27].

Other Allergen-Specific Therapies

Several other strategies currently under investigation include immunotherapy with peptides representing T cell epitopes of major food allergens [28], immunostimulatory sequence-conjugated protein immunotherapy [29], and plasmid DNA immunotherapy [30]. Preliminary results from murine models seem promising, but questions remain as to whether these approaches will be effective in humans. In fact, plasmid DNA had beneficial effects in one mouse strain but worsened symptoms in another.

Allergen-Nonspecific Therapies

Pharmacological Treatment

Anti-H1 antihistaminic drugs are useful for the treatment of the oral, cutaneous and upper airway symptoms, while they have less efficacy on lower respiratory airways (e.g. asthma) and gastrointestinal symptoms and anaphy-

laxis. Oral corticosteroids can be used for the treatment of chronic IgE-mediated disorders, but they have unacceptable side effects. Although the available evidence is limited, it seems that sodium cromoglycate can be used for the treatment of food IgE-mediated disorders, and for the prevention or reduction of the severity of adverse reactions during oral-specific desensitization treatment. Intramuscular epinephrine (0.3–1 mg for adults and 0.1–0.5 mg for children) is the treatment of choice for anaphylaxis, together with antihistaminic drugs and parenteral corticosteroids, which the patient should always carry as 'first aid kit' [7].

Anti-IgE Treatment

Recombinant monoclonal humanized anti-IgE treatment is currently being used for the treatment of allergic asthma, and has been investigated as a possible treatment for food allergy. In 2003, a double-blind, randomized, dose-ranging trial was carried out in 84 peanut-allergic patients [31] receiving either Hu-901 (humanized IgG1 monoclonal antibody against IgE) or placebo for 4 months. Patients receiving the highest dose experienced significant decreases in symptoms with peanut challenge as compared with the placebo. Although 25% of patients had markedly improved tolerance after treatment, 25% had no change in their threshold of reactivity, indicating that the treatment response is variable. Investigation of another anti-IgE preparation, omalizumab, for the treatment of peanut allergy was initiated, but discontinued for safety concerns related to the pretreatment oral peanut challenge [32]. In summary, anti-IgE therapy is a life-lasting treatment since IgE levels increase after treatment interruption; it is a very expensive treatment for the health system, and it can cause anaphylactic reaction by itself.

Combination therapy of anti-IgE and allergen immunotherapy is being investigated as a method to decrease adverse reactions to immunotherapy and decrease antigen-facilitated presentation by IgE-bearing antigen-presenting cells, which promotes Th2 responsiveness, in order to increase the safety and efficacy of this method [33]. No data from controlled clinical trials are currently available regarding the effectiveness of this strategy.

The role of anti-leukotrienes in the treatment of food allergy requires further studies. There are studies that report some efficacy of the treatment of atopic dermatitis [34] and of chronic urticaria related to food additive intolerance [35], and it has been suggested that anti-leukotrienes may prevent or reduce the severity of adverse reactions during oral-specific desensitization with foods.

Probiotics

Probiotics have also been evaluated in the prevention or treatment of food allergies. In a placebo-controlled randomized study *Lactobacillus* GG (*Lactobacillus rhamnosus*) or placebo were given to pregnant women during the last 4 weeks of pregnancy and during subsequent breastfeeding until infants were 3 months of age. A benefit was observed in the group of mothers/infants treated with the probiotic: allergic eczema occurred in 47% of offspring randomized to the placebo group, while only 15% of children whose mothers were receiving probiotics [36]. Similar benefit was observed in another randomized double-blind study in which *Lactobacillus* GG was administered to pregnant women and during breastfeeding for 6 months [37]. Other studies suggest that probiotics may also be beneficial in ameliorating the severity of allergic responses in established food allergy [38]. The use of *Lactobacillus* GG in conjunction with extensively hydrolyzed formula was shown to provide benefit over an extensively hydrolyzed formula alone in infants with atopic dermatitis and GI symptoms. However, in young adults and teenagers

with oral allergy syndrome to birch pollen and apples who were treated orally with *Lactobacillus* GG, no beneficial effect in terms of symptom occurrence and use of medications was observed [39]. Normal enteric flora established shortly after birth provides counter-regulatory signals against a sustained Th2-skewed immune response. Hence, it is not surprising that the greater benefits of probiotics use seems to occur in very young infants and/or as prophylaxis during pregnancy.

Conclusions

Despite substantial progress in understanding the pathophysiology of food allergies, many questions in the field of their management remain to be answered. The emerging lines of evidence of the role of the innate immune system and of its interaction with the gut microflora have opened new options such as the use of recombinant allergens and probiotics in therapy and prevention of the allergic features.

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