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REVIEW

Food allergy in gastroenterologic diseases: Review of literature

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Abstract

Food allergy is a common and increasing problem worldwide. The newly-found knowledge might provide novel experimental strategies, especially for laboratory diagnosis. Approximately 20% of the population alters their diet for a perceived adverse reaction to food, but the application of double-blind placebo-controlled oral food challenge, the "gold standard" for diagnosis of food allergy, shows that questionnaire-based studies overestimate the prevalence of food allergies. The clinical disorders determined by adverse reactions to food can be classified on the basis of immunologic or nonimmunologic mechanisms and the organ system or systems affected. Diagnosis of food allergy is based on clinical history, skin prick tests, and laboratory tests to detect serum-food specific IgE, elimination diets and challenges. The primary therapy for food allergy is to avoid the responsible food. Antihistamines might partially relieve oral allergy syndrome and IgE-mediated skin symptoms, but they do not block systemic reactions. Systemic corticosteroids are generally effective in treating chronic IgE-mediated disorders. Epinephrine is the mainstay of treatment for anaphylaxis. Experimental therapies for IgE-mediated food allergy have been evaluated, such as humanized IgG anti-IgE antibodies and allergen specific immunotherapy.

Key words: Food intolerance; Food allergy; Skin prick test; Serum food-specific IgE; Oral food challenges

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INTRODUCTION

Food allergy is recognized as a common worldwide problem, and, like other atopic disorders, its incidence seems to increase. Moreover, food-related allergic disorders are the leading cause of anaphylactic reactions treated in the emergency departments in a number of countries, accounting for approximately 30 000 emergency department visits, and 150-200 deaths each year, and the public opinion has become increasingly aware of the problem[1,2]. In the past years, investigations of allergic food proteins and related immunological responses have moved to the molecular level, and the newly-found knowledge might provide novel experimental strategies for the laboratory diagnosis and the immuno-modulatory control of food-induced allergic reactions[1,3-5].

Recently, the European Academy of Allergy and Clinical Immunology task force published a revised nomenclature for allergy. Adverse food reactions, defined as "food hypersensitivities", include any abnormal reaction resulting from the ingestion of a food, and it might be the result of food intolerance, defined as "non-allergic food hypersensitivities", excluding immunologic mechanisms, or food allergy, defined as "allergic food hypersensitivities", including clear, or strongly suspected, immunologic mechanisms[6]. Our review focused on the food allergy.

EPIDEMIOLOGY AND PATHOGENESIS

Epidemiology

Approximately 20% of the population alters their diet for a perceived adverse reaction to food, but the application of double-blind placebo-controlled oral food challenge, considered as the gold standard for diagnosis of food allergy, shows that questionnaire-based studies overestimate the prevalence of food allergies and food intolerance[7-9].

In the United States, approximately 6% of infants and young children and 3.7% of adults have food allergy. In young children, the most common causal foods are cow's milk, egg, peanut, wheat, soy, tree nuts, fish, and shellfish. In adults, the most common causal foods are shellfish, peanut, tree nuts and fish[7,10-12]. Early childhood allergy to milk, egg, soy, and wheat are usually resolved by school age (approximately 80%), whereas peanut, tree nuts and

seafood allergies are generally considered permanent. In Europe, early childhood allergy to cow's milk has an incidence of approximately 2%. The relatively high prevalence of peanut allergy in British children (0.5%) ("Americanised" eating habit) is not reflected in the results from other European countries. Cow's milk, egg and orange seem to be the most common causes of allergy in European infants and children. As the children become adults, allergy to milk and eggs become less frequent. In adults, the allergies appear toward pollen-related food, i.e. *Compositae*-celery, birch-apple and birch-peaches. Adult European population presents a prevalence of food allergy/intolerance of approximately 5%[7,13].

Unfortunately, data from many parts of Asia are still lacking. However, the prevalence of food allergy in Asia seems to be low, but is likely to increase with the global increase of allergy. Asia is unique because of the many different cultures and eating habits, with the existence of unique food allergens. Peanut and tree nuts are rarely the cause of allergic reactions in this area[14]. In a population-based study carried out in the United Kingdom establishing reported food problems and sensitization among 11- and 15-year-old children, the prevalence of food hypersensitivity was 1.4% and 2.1% for the 11- and 15-year-olds, respectively[15] on the basis of a combination of a clear history of previous reactions, a positive skin prick test response, a positive open food challenge result, and a positive double-blind placebo-controlled food challenge.

Pathogenesis

Food allergy represents an abnormal response of the mucosal immune system to antigens delivered through the oral route[6]. The healthy gastrointestinal mucosal immune system encounters enormous quantities of antigen on a daily basis and generally suppresses immune reactivity to harmless foreign antigens (food proteins and commensal bacteria), although it is fully capable of mounting a brisk protective response against dangerous pathogens. The process by which the gastrointestinal immune system avoids attacking harmless antigens is termed "oral tolerance"[16,17]. Food allergy might result from a failure in oral tolerance to food while they are being ingested (class 1 food allergy) or from a sensitization to allergens recognized instead during respiratory exposure (class 2 food allergy). Class 1 food allergy is typically related to food proteins, generally stable to digestion, which is encountered by infants or children at a presumed immunological immaturity. In contrast, class 2 food allergy is the result of a sensitization to protein susceptible to enzymatic degradation, encountered in the respiratory tract, such as pollens, resulting in an IgE antibody production that recognize homologous epitopes on food proteins of plant origin (i.e. pollen-food related syndrome)[10,11,18,19].

Gut barrier: The gastrointestinal mucosal barrier is a complex of physical (mucus, acid, enzymes, bile salts, and epithelial cell tight junctions) and immunologic structures-both "innate" (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, and toll-like receptors), and "adaptive" (intraepithelial and *lamina propria* lymphocytes, Peyer's patches, secretory immunoglobulin type A [sIgA], and cytokines)-which all serve to destroy antigens and to render antigens nonimmunogenic[16,20-22]. Alteration of the gut barrier might lead to food allergy. Developmental immaturity of components of the gut barrier (enzymatic activity and sIgA) might account for the increased prevalence of food allergy in infancy[23]. Despite the evolution of this barrier, about 2% of ingested food antigens, both particulate and soluble, are adsorbed by the follicle associated epithelium (M cells), overlying Peyer's patch and the intestinal epithelial cells, respectively, and transported throughout the normal mature gut, but they infrequently induce clinical symptoms, because tolerance develops in most individuals[24,25].

Oral tolerance induction: The immunologic mechanisms involved in oral tolerance induction have not been fully elucidated. Antigen-presenting cells, epithelial and dendritic cells, and regulatory T cells play a central role. Intestinal epithelial cells, as non-professional antigen-presenting cells, process luminal soluble dietary antigen and present it, on an MHC class Ⅱ complex, selectively to $CD8^+$ suppressor T cells, thus playing a role in local control and suppression of immune responses. Dendritic cells, residing within the *lamina propria*, are professional antigen presenting cells that secrete IL-4, a pro-inflammatory T_H2 cytokine, and IL-10, an anti-inflammatory cytokine. However, the specific role of these cells in directing the balance between active immunity and food tolerance in the intestine, depends on the cytokine microenvironment and the expression of costimulatory molecules. Five regulatory T cells have been identified in association with intestinal immunity: T_H3 cells, a population of $CD4^+$ cells that secrete transforming growth factor β (TGF-β), might play an important role in oral tolerance, inducing T cell suppression and promoting B-cell switching to sIgA production; T_R1 cells, $CD4^+$ cells that secrete IL-10 and suppresses the antigen-specific immune responses; $CD4^+CD25^+$ regulatory T cells, together with $CD8^+$ suppressor T cells, that are both capable of suppressing the effector T cells; and γδ T cells, whose role in oral food tolerance is still unclear[26,27]. Dose of dietary antigens, frequency of exposure, and chemophysical properties of food proteins, might also influence the tolerance induction. Particularly in mice, oral food tolerance has been induced after administration of either a single dose or repeated lower doses of antigen. These two forms of tolerance, termed high-dose and low-dose tolerance, respectively, might be mediated by different mechanisms: by the activation of regulatory T cells (T_H3, T_R1, and $CD4^+CD25^+$), with suppressor function, and by the anergy or delection of effector T cells. Anergy can occur through T-cell receptor activation in the absence of costimulatory signals provided by soluble cytokines or by interactions between costimulatory receptors on T cells and counter-receptors on antigen presenting cells. Delection occurs by means of FAS-mediated apoptosis of lymphocytes[28].

Commensal gut flora might also influence the mucosal immune response. Gut flora is largely established in the first 24 h. after birth and is dependent on maternal flora and local environment. Gut flora might enhance a T_H1 cytokine response, with secretion of interferon-γ (IFN-γ) that inhibits T_H2 responses. However, in adults, commensal gut flora seems to be less important in the regulation of mucosal immune response[29,30].

Table 1 Pathophysiologic classification of adverse reactions to food

Non allergic food hypersensitivities
Toxic
Pharmacologic
Metabolic disorders
Idiosyncratic responses
Allergic food hypersensitivities
Allergy
IgE-mediated
Non IgE-associated
Mixed IgE-mediated/non IgE-mediated

Table 2 Clinical classification of allergic disorders induced by food

Gastrointestinal food-induced allergic disorders
Pollen-food allergy syndrome
Allergic eosinophilic esophagitis
Allergic eosinophilic gastroenteritis
Food protein-induced enterocolitis, proctocolitis, and enteropathy
Celiac disease
Infantile colic
Gastrointestinal anaphylaxis
Cutaneous food-induced allergic disorders
Acute urticaria and angioedema
Atopic dermatitis
Dermatitis herpetiformis
Respiratory food-induced allergic disorders
Rhinoconjunctivitis
Bronchial asthma
Systemic food-induced allergic disorders
Generalized anaphylaxis
Food-associated exercise-induced anaphylaxis

Food allergens: The regional dietary habits and methods of food preparation clearly play a role in the prevalence of specific food allergies in various countries around the world[31].

The major food allergens identified as class 1 allergens are water-soluble glycoproteins, 10 to 60 kilo-Dalton in size, that are stable to heat, acid, and proteases. Cooking can reduce the allergenicity of certain food proteins; conversely, heating can increase the allergenicity of other food proteins, through the induction of covalent modifications that lead to new antigens or improved stability[11,32]. The class 2 food allergens are presumably comprised of conformational epitopes and therefore are highly heat-labile, susceptible to enzymatic degradation and difficult to isolate. An example of a class 2 allergens is the birch pollen Bet v 1, that can induce sensitization through the respiratory tract and results in oral symptoms of pruritus to homologous class 2 allergens in raw apple (Mal d 1) or carrot (Dau c 1)[19,33].

Genetic of the host: Studies examining potential associations of specific HLA antigens with allergies to different food show variable results. No difference was observed when HLA-A, HLA-B, and HLA-C locus antigen were compared between patients with food allergy and control subjects. However, when individuals with peanut allergy and unrelated control subjects were typed for the HLA-class Ⅱ genotypes, DRB1*08, DRB1*08/12tyr16, and DQB1*04 were found at higher frequency in those with peanut allergy than in control subjects. These findings indicate that allergic reactions to peanut are in part under genetic control. Additional genes might be involved in the overall expression of food allergy and are under investigations[34].

CLINICAL CLASSIFICATION

The clinical disorders determined by adverse reactions to food (or food hypersensitivity) can be classified on the basis of nonimmunologic or immunologic causes (Table 1), and the organ system or systems affected (Table 2)[6]. Food intolerance by toxic and pharmacologic reactions is due to toxic contaminants (histamine in scombroid fish poisoning, and bacterial food poisoning) or pharmacological substances within the food (tyramine in aged cheeses) which can affect most healthy individuals when given at appropriate doses. Food intolerance may also be attributed to some unique physiologic characteristics of the host, such as a metabolic disorder (lactase deficiency), or an idiosyncratic response. Instead, food allergy is defined as an adverse reaction to food that is immunologically mediated, and involves specific IgE or non-IgE (T cell-mediated) mechanisms or both[6].

Gastrointestinal food-induced allergic disorders

Various gastrointestinal food-induced allergic disorders share the same symptoms, such as vomiting, abdominal distension and pain, and diarrhoea, but they can be differentiated by patterns of illness and diagnostic tests.

Pollen-food allergy syndrome: Pollen-food allergy syndrome (or oral allergy syndrome): is an IgE-mediated food adverse reaction, elicited by a variety of plant-derived food proteins, especially concentrated in the peel, which cross-react with airborne allergens, including birch, ragweed, and mugwort pollens. It is characterized by mild pruritus, tingling, and/or angioedema of the lips, tongue, palate or oropharynx, occasional sensation of tightness in the throat, and rarely systemic symptoms, because the allergens responsible for these reactions are easily broken down by heat or gastric enzymes, and thus are not absorbed by the gastrointestinal mucosa. Reactions to all related food are rare, but sensitivity to more than one is common. Diagnosis is based on clinical history, positive skin prick test responses to fresh food and relevant airborne proteins, and, if necessary, on an oral challenge, positive with fresh food and negative with cooked food (see above)[35-37].

Allergic eosinophilic esophagitis: Allergic eosinophilic esophagitis is an IgE- or non-IgE-mediated, or both, food adverse reactions, seen most frequently during infancy through adolescence, characterized by gastroesophageal reflux, excessive spitting-up or emesis, dysphagia, intermittent abdominal pain, failure to respond to conventional reflux medications, and peripheral blood eosinophilia. Diagnosis is based on clinical history, skin prick tests, endoscopy with biopsy,

elimination diet and challenge. Patients who are not appropriately treated might develop fibrosis, with subsequent esophageal stricture, and Barrett's esophagitis[38,39].

Allergic eosinophilic gastroenteritis: Allergic eosinophilic gastroenteritis is an IgE- or non-IgE-mediated, or both, food adverse reactions, being diagnosed more frequently in adults, characterized by early satiety, intermittent vomiting, recurrent abdominal pain, blood loss in the stools, iron-deficiency anemia, and protein-losing enteropathy, with a peripheral blood eosinophilia. Clinical history, skin prick tests, endoscopy with biopsy, and elimination diet and challenge, are required[40,41] for the diagnosis.

Food protein-induced enterocolitis, proctocolitis, and enteropathy: Food protein-induced enterocolitis, proctocolitis, and enteropathy is a non-IgE-mediated (T cell-mediated) disorders, most commonly seen in infants before 3 mo of age, provoked by food proteins in maternal breast or cow's milk or soy protein-based formulas, characterized by nausea, protracted projectile vomiting, that begins about 1-3 h. after allergen ingestion, abdominal distension, flatulence, diarrhoea (steatorrhoea), sometimes with dehydratation, acidemia, methemoglobinemia, weight loss and gross or occult blood in stool mixed with mucus. In these patients, skin prick test responses are negative. Endoscopy and biopsy are often required. In patients affected by food protein-induced enteropathy, biopsy reveals a patchy villous atrophy, a prominent mononuclear round cell infiltrate, and few eosinophils. Elimination of food proteins leads to the clearing of symptoms in 24-72 h. Challenge induces recurrent vomiting or bleeding within 72 h.[42-46].

Celiac disease: Celiac disease (or gluten-sensitive enteropathy) is a more extensive enteropathy leading to malabsorption, associated with sensitivity to gliadin, found in wheat, rye and barley. Diagnosis is based on celiac IgA, anti-gliadin and anti-transglutaminase antibodies detection, endoscopy and biopsy, elimination diet, with resolution of symptoms and food challenge, if necessary[47,48].

Infantile colic: Infantile colic is due to food hypersensitivity in a minority of infants presenting with this disorder characterized by paroxysmal fussiness with inconsolable agonized crying, it generally develops in the first 2-4 wk of life, and persists through the third to fourth month of life. Diagnosis is based on the implementation of several brief trials of hypoallergenic formula[49,50].

Gastrointestinal anaphylaxis: Gastrointestinal anaphylaxis is an IgE-mediated reaction, food associated, not exercise-induced, characterized by rapid onset of nausea, vomiting, cramps, abdominal pain, and diarrhoea, often involving other target organs such as skin and respiratory tract. Diagnosis is established according to the clinical history, positive skin prick test or radioallergosorbent test (RAST) responses, and if necessary, based on an oral challenge[11,51].

Cutaneous and respiratory food-induced allergic disorders

IgE-, non-IgE- and mixed IgE- and non-IgE-mediated adverse reactions to food can induce a variety of cutaneous disorders. The most common cutaneous disorder of food-induced allergic reactions is "acute" urticaria and angioedema (symptoms lasting < 6 wk), whereas, food allergy causes infrequently "chronic" urticaria and angioedema (symptoms lasting > 6 wk)[52,53].

Atopic dermatitis: Atopic dermatitis is a form of eczema that generally begins in early infancy, characterized by typical distribution, extreme pruritus, and a chronically relapsing course. In about 35% of children with moderate-to-severe disease, food allergens specific serum IgE antibodies against cow's milk, egg, soya and wheat are demonstrable, and the ingestion of specific food might evoke a marked worsening of cutaneous lesions[54,55].

Dermatitis herpetiformis: Dermatitis herpetiformis is a rare chronic skin disorder, associated with gluten-sensitive enteropathy, characterized by a chronic, intensely pruritic, papulovesicular rash, symmetrically distributed over the extensor surfaces and buttocks. It can be clearly distinguished from the other subepidermal blistering eruptions by gastrointestinal, immunologic and histologic criteria. Both enteropathy and the dermatologic findings disappear with a gluten-free diet, therefore, dermatitis herpetiformis is thought to be the specific dermatologic finding of celiac disease[56].

Food allergy can also induce a number of disorders in the respiratory tract. Acute respiratory symptoms, caused by food allergy generally represent isolated IgE-mediated reactions, whereas chronic respiratory symptoms represent a mix of IgE- and non-IgE-mediated reactions. Isolated rhinoconjunctivitis and bronchial asthma are rarely the result of food-induced allergic reactions, although they frequently occur in association with other food allergy symptoms. However, food allergy was found to be a major risk factor for severe life-threatening asthma. Food-induced asthmatic symptoms should be suspected in patients with refractory asthma and a history of atopic dermatitis, gastroesophageal reflux, food allergy or a history of positive skin prick test responses to a kind of food[10,57-59].

Systemic food-induced allergic disorders

IgE-, non-IgE- and mixed IgE- and non-IgE-mediated adverse reactions to food can also induce systemic disorders.

Generalized anaphylaxis: Generalized anaphylaxis is an IgE-mediated food adverse reaction, accounting for at least one third to one half of anaphylaxis cases seen in hospital emergency departments. In addition to variable expression of cutaneous (itching, flushing and urticaria), respiratory (asthma) and gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea) symptoms, patients might have cardiovascular symptoms, such as hypotension, cyanosis, vascular collapse and cardiac dysrhythmias. Most of fatal food-induced anaphylaxis were adolescents or young adults, with previous histories of reacting to the implicated food (usually not life-threatening), and all were affected by underlying asthma. Peanuts, tree nuts and seafood were responsible for the vast majority of the fatalities in the United States. Aspirin, exercise and alcohol can increase the risk[60-62].

Food-associated and exercise-induced anaphylaxis: Food-associated and exercise-induced anaphylaxis is a form of anaphylaxis that occurs only when the patient (generally women aged 15-30 years) exercises within 2-4 h. of ingesting food. Crustaceans and wheat are the two commonest but other food can be implicated. In the absence of exercise, the patient can ingest the food without any apparent reaction. It might account for up to one

half of the cases of exercise-induced anaphylaxis. Diagnosis is based on patient history and the demonstration of food-specific serum IgE antibodies. Food dependent and exercise-induced anaphylaxis should be considered in young children with exercise-induced anaphylaxis of unknown origin[63,64].

DIAGNOSIS

The evaluation of a patient with a possible allergic food reaction begins through clinical history and a complete physical examination to consider a potentially broad differential diagnosis between food-induced allergic clinical disorders and other gastrointestinal disease, such as food intolerance (toxic and pharmacological effects or metabolic disorders), infections (viral, bacterial and parasitic), celiac disease, inflammatory bowel diseases, bowel ischaemia, gallbladder disease, pancreatic insufficiency, and gastrointestinal neoplasms[7,10,11]. The medical history continues to be a mainstay in the diagnostic process, and might determine the possible causal food, quantity ingested, time course of reaction, ancillary factors (aspirin, exercise and alcohol) and reaction characteristics. However, the identification of suspected food is difficult because food is ingested throughout the day and symptoms that arise soon after an ingestion might be wrongly attributed to food allergy, or attributed to the wrong food. Diet records and symptom diaries can be a useful supplement to a medical history, especially in chronic disorders. From a diagnostic point of view, it is helpful to categorize food hypersensitivity disorders by the mechanism of response and the predominant target organ. IgE-mediated reactions are typically rapid in onset, whereas non-IgE-mediated disorders become evident after allergen ingestion. Some disorders might involve both IgE- and non-IgE-mediated mechanisms and vary in their time of onset. In other words, acute symptoms, such as acute urticaria after ingestion of a food, are likely caused by food allergy, whereas chronic symptoms (chronic urticaria and asthma) are less likely attributable solely to food allergy. Certain disorders are commonly associated with food allergy, such as moderate-to-severe atopic dermatitis. For other disorders such as chronic urticaria, suspicions about particular food are notoriously inaccurate, and are only verified in about 30% of cases. In some cases, confirmation of a diagnosis of allergic food reaction requires invasive tests, such as endoscopy, but usually the diagnosis relies on food-specific IgE determination (or confirmations of its absence), results of elimination diets, and responses to oral food challenges[7,10,11].

Skin prick test

For IgE-mediated disorders, skin prick tests provide a rapid mean to detect sensitization. This almost painless procedure allows the tested protein to interact with food-specific IgE on the surface of skin mast cells. If the antibody is present, mast cells degranulate and release mediators that rapidly cause localised vasodilation, angioedema and wheal and flare. While the patient discontinued antihistamines for an appropriate length of time, a device, such as a lancet, plastic probe or tip of a small gauge needle, is pressed through a commercial extract of food and a positive (histamine) and negative (saline-glycerine) controls into the epidermis. Allergens eliciting within 15 min a wheal at least 3 mm larger than that produced by the negative control are considered positive, indicating the possibility that the patients have symptomatic reactivity to the specific food, with strongly positive results implying a greater likelihood of clinical reactivity. On the other hand, negative skin prick test responses essentially confirm the absence of IgE-mediated allergic reactivity. To maximize the utility of skin prick test results, clinical history and disease pathophysiology are required. For example, a positive skin prick test response may be considered confirmatory for the diagnosis when combined with a recent and clear-cut history of a food-induced allergic reaction to the tested food[65-69].

When evaluating allergy to fruits and vegetables, commercially prepared extracts are often inadequate because they are prone to degradation, and therefore the fresh food might be used for prick-by-prick test[70]. A number of investigators have examined the use of the "atopy patch test" in addition to skin prick test for the diagnosis of non-IgE-mediated food allergy, with delayed reactions to food, but at this time, there are no standardized reagents or methods of application and interpretation. Thus, its diagnostic accuracy remains still controversial, especially in older children[71].

Detection of serum food-specific IgE

Laboratory tests to determine serum food-specific IgE antibodies (RAST or, more recently, the CAP System FEIA, or UniCAP [Pharmacia and Upjohn Diagnostics, Uppsala, Sweden], and others) provide another modality to evaluate IgE-mediated food allergy. Manufactures and substrates vary, and results can be classified into class one to six, or arbitrary units of concentration (kU$_A$/L). Increasingly higher concentrations of food-specific IgE correlate with an increasing likelihood of clinical reaction[72-74]. No conclusive studies indicate that determination of specific IgE-binding epitopes on an allergen might provide increased diagnostic utility. Further analysis revealed that determining epitope-specific binding might correlate with clinical reactivity better than quantitative IgE values to the whole protein. Moreover, evaluating the number of allergenic epitopes bound by the IgE antibodies might be useful for predicting the clinical severity of food-induced allergic reaction[75,76].

Other laboratory tests

When evaluating patients with gastrointestinal symptoms, suspecting a food hypersensitivities, a number of other standard laboratory studies might be useful. Patients with allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis have peripheral eosinophilia, and patients with severe allergic eosinophilic gastroenteritis might have anemia, blood in the stool, and decreased serum protein, albumin and IgG levels (with preservation of IgM and IgA)[77-79]. Endoscopy and biopsy are the most definitive approaches for diagnosing many of the gastrointestinal food hypersensitivities and might help the differential diagnoses. Greater than 10-20 eosinophils per 40 × high-power field in the esophagus is diagnostic of allergic eosi-

nophilic esophagitis, especially if the pH probe is normal and there is lack of responses to antireflux medication. Eosinophils are normally present in the gastric and intestinal mucosa, and therefore eosinophil number must be greater to make the diagnosis of allergic eosinophilic gastroenteritis. In these cases, diagnosis requires elimination of alternative diagnostic possibilities (parasites, inflammatory bowel disease)[77-79]. No conclusive studies suggest the possible usefulness of analyzing intestinal permeability by determining the 5-h. urinary excretion of [51Cr] EDTA, and inflammation markers, including histamine, eosinophilic cationic protein, tryptase, and calprotectin in gut lavage fluid[80].

Oral food challenge

Skin prick tests with food allergens and determination of serum food-specific IgE can detect "sensitization" (that is the presence of food-specific IgE), but because sensitization can exist without allergic clinical reactions (esophagitis, gastroenteritis, rhinitis and asthma), these tests generally cannot be used alone to diagnose food allergy. In this setting, it is important to consider also the clinical history and the results of oral food challenges. Skin prick tests and RAST are most valuable when they are negative, since their high sensitivity makes them about 95% accurate for discounting IgE-mediated reactions. The double-blind, placebo-controlled oral food challenge (DBPCFC) with gradually increasing amounts of the suspected food under observation over hours or days, is considered the "gold standard" test for the diagnosis of food allergy. The clinical history results, skin prick tests (RASTs) or both, indicate which food should be evaluated by DBPCFCs. Patients with histories of life-threatening anaphylaxis should be challenged only when the history and laboratory tests cannot conclusively determine the causative food. To increase the likelihood of a nonequivocal food challenge result, suspected food should be eliminated for 7-14 d before challenge and longer in some non-IgE-mediated gastrointestinal disorders (non-IgE mediated allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis). Medications that could interfere with the evaluation of food-induced symptoms (antihistamines and adrenergic bronchodilators) must be discontinued. The length of the observation period depends on the type of reaction suspected. Hypotension might occur in about 15% of these challenges, especially in patients affected by acute IgE-mediated reactions, enterocolitis syndrome, and severe atopic dermatitis, and therefore intravenous hydration therapy and supplies for resuscitation should be immediately available. The false negative rate of DBPCFC is about 3%, so negative challenges should always be followed by a supervised open or a single-blind oral food challenge[8,66,81].

MANAGEMENT

The primary therapy for food allergy is to avoid the causal food. In most countries, shortcomings on manufacturers and labelling, make it very difficult to identify allergens in commercial food products. Cross contamination, errors in packaged food shop, and restaurants are additional obstacles. Therefore, new food-labelling laws require simple terms to indicate the presence of major food allergens ("milk" instead of "casein"). Patients and care providers should be encouraged to obtain medical identification bracelets, taught to recognize symptoms, and instructed on using self-injectable epinephrine and activating emergency services. Clinical tolerance develops to most food allergens over time, except for peanuts, nuts and seafood. Periodic reintroduction of food allergens under physician supervision is warrant to determine whether clinical tolerance has develop[7,10-12].

There is a relationship between the decrease in serum food-specific IgE concentrations and the likelihood of developing tolerance. A greater decrease in serum food-specific IgE levels over a shorter period of time might be indicative of a greater likelihood of developing tolerance. The confirmation of this model and subsequent application in clinical practice would aid clinicians in the timing of food challenges and in providing prognostic information for patients and their families[82].

Medications

Various medications can provide relief for certain aspect of food-induced disorders[7,10-12].

Antihistamines might partially relieve symptoms of oral allergy syndrome and IgE-mediated skin symptoms, i.e. itching and rash, but do not block systemic reactions. Systemic corticosteroids are generally effective in treating chronic IgE-mediated disorders (atopic dermatitis). A course of corticosteroids can be used to reverse severe inflammatory symptoms, but the side effects of protracted use are unacceptable. Epinephrine is the mainstay of treatment for anaphylaxis. Intramuscolar injection allows more efficient absorption than the subcutaneous route[83].

Novel therapies for IgE-mediated food allergy have been evaluated. Subcutaneous injections of humanized IgG anti-IgE antibodies (TNX-901), that recognize and mask an epitope in the CH3 region of IgE responsible for the binding to the high affinity Fc epsilon receptor I (FCεRI) on basophils and mast cells, for the treatment of patients affected by peanut allergy, showed a long-term increase in the average amount of peanut tolerated, but 25% of subjects showed no improvement[84].

Another anti-IgE preparation (Omalizumab) has been approved for the treatment of persistent allergic asthma in patients who are poorly controlled with inhaled corticosteroids, but has not yet been evaluated for its efficacy in treating patients with peanut allergy. Theoretically, anti-IgE antibody therapy should be protective against multiple food allergens, although it would have to be administered indefinitely to maintain its protective effects[85].

No conclusive studies indicate that standard allergen specific immunotherapy for birch- or ragweed pollen-induced rhinitis might improve pollen-food allergy syndrome. The risk/benefit ratio of traditional immunotherapy for the treatment of peanut allergy was considered unacceptable, because the injection of food protein results in anaphylaxis. To address this problem, engineered proteins are altered to remove IgE-binging epitopes that trigger anaphylaxis, while T-cell epitopes that could induce toler-

ance to specific food allergen, are preserved[86,87]. Other immunotherapeutic strategies include use of engineered proteins lacking IgE-binding sites, immunomodulatory sequences being effective in reversing IgE-mediated sensitization, and engineered chimeric molecules forming complexes with allergen-specific IgE bound to mast cells and basophils, inhibiting their functions.

Some recent studies suggested that probiotics, commonly defined as live microorganisms (bacteria from the genera *Lactobacillus, Bifidobacterium*, *Escherichia*, *Enterococcus*, *Bacillus* and *Saccharomyces*), administered in adequate amounts, which confer a beneficial health effect on the host, might be useful in the treatment and prevention of food allergy. They might provide maturational signals for the gut-associated lymphoid tissue, balance the generation of pro- and anti-inflammatory cytokines, reduce the dietary antigen load by degrading and modifying macromolecules, reverse the increased intestinal permeability, characteristic of children with food allergy, normalization of the gut microecology, and enhance specific sIgA responses frequently defective in children with food allergy[5,88-92].

Prevention

Approaches to delay or prevent allergy through dietary manipulation have been considered. Some studies suggest a beneficial role for exclusive breast-feeding of infants at high risk for atopic diseases in the first 3-12 mo of life and avoidance of supplementation with cow's milk or soy formulas in favour of hypoallergenic formulas if breast-feeding is not possible[93].

Maternally ingested food can pass in immunologically intact form into breast milk and might induce reactions in infants. No conclusive studies indicate that manipulation of mother's diet during pregnancy or breast-feeding or the restriction of allergenic food from the infant's diet will prevent the development of food allergy[94]. The American Academy of Pediatrics recommends that high-risk infants (both parents and siblings atopic) be exclusively breast-fed, that lactating mothers avoid peanuts and nuts to avoid sensitization through breast milk, that the introduction of solid be delayed until 6 mo of age, and major allergens, such as peanuts, nuts and seafood, be introduced after 3 years of age[95].

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