

Adverse Reactions to Foods

Anna Nowak-Wegrzyn, MD^{a,b},
Hugh A. Sampson, MD^{a,b,*}

^a*Division of Allergy and Immunology, Department of Pediatrics,
Mount Sinai School of Medicine, New York, NY, USA*

^b*Jaffe Food Allergy Institute, New York, NY, USA*

Over the past 20 years, food allergy has emerged as an important clinical problem in Westernized countries. Not only has food allergy prevalence almost doubled but its severity and scope have increased. Consequently, research focusing on characterization, mapping, and cloning of food allergens, as well as on deciphering the nature of immune responses to food allergens and the mechanisms of oral tolerance, has blossomed. It is hoped that this research will lead to the development of therapeutic modalities for food allergy in the near future. This article discusses the pathomechanism of food allergic reactions, classification and manifestations of clinical food allergic disorders, and an approach to diagnosis and management.

Definition

Food allergy is defined as an immune-mediated adverse reaction to foods. Food allergy must be distinguished from a variety of adverse reactions to foods that do not have an immune basis but may resemble it in clinical manifestations. Examples of such adverse food reactions are presented in [Table 1](#).

Prevalence

Food allergy affects about 6% to 8% of infants and young children and approximately 3.5% to 4% of adults [1,2]. Children with moderate to severe persistent atopic dermatitis have a higher prevalence of IgE-mediated food

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* Corresponding author. Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai Hospital, Box 1198, One G. Levy Place, New York, NY 10029.

E-mail address: hugh.sampson@mssm.edu (H.A. Sampson).

Table 1
Adverse reactions to foods mimicking food allergy

Condition	Symptoms	Mechanism
Lactose intolerance	Bloating, abdominal pain, diarrhea (dose-dependent)	Lactase deficiency
Fructose intolerance	Bloating, abdominal pain, diarrhea (dose-dependent)	Fructase deficiency
Pancreatic insufficiency	Malabsorption	Deficiency of pancreatic enzymes
Gallbladder/liver disease	Malabsorption	Deficiency of liver enzymes
Food poisoning	Pain, fever, nausea, emesis, diarrhea	Bacterial toxins in food
Scombroid fish poisoning	Flushing, angioedema, hives, abdominal pain	In spoiled fish histidine is metabolized to histamine
Caffeine	Tremors, cramps, diarrhea	Pharmacologic effects of caffeine in susceptible individuals
Thyramine	Migraine	Pharmacologic effects of thyramine in susceptible individuals
Auriculo-temporal syndrome (Freye syndrome)	Facial flush in trigeminal nerve distribution associated with spicy foods	Neurogenic reflex, frequently associated with birth trauma to trigeminal nerve (forceps delivery)
Gustatory rhinitis	Profuse watery rhinorrhea associated with spicy foods	Neurogenic reflex
Panic disorder	Subjective reactions, fainting upon smelling or seeing the food	Psychologic
Anorexia nervosa	Reactions to multiple foods, weight loss	Psychologic
Allergy to contaminants in foods	Hives, pruritus, angioedema, coughing, vomiting	IgE-mediated reactions to dust mites and molds contaminating flour, <i>Anisakis</i> parasite in fish

allergy, estimated at about 35% [3]. The most common food allergens in the pediatric population include cow's milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish, whereas peanuts, tree nuts, fish, and shellfish predominate in adults. Recent studies report doubling of peanut allergy in young children. A 5-year follow-up study of peanut and tree nut allergy using a random-digit dial telephone survey found that, in comparison with the 0.4% prevalence of peanut allergy in American children aged 5 years or younger in 1997, there was an increase to 0.8% in 2002 [4]. Similarly, results reported from the Isle of Wight in the United Kingdom indicate a doubling of clinical peanut allergy and a tripling of IgE peanut sensitization in young children over a period of 10 years [5].

Food allergy remains the leading single cause of anaphylaxis outside the hospital, and an increasing trend has been noted in recent years [6,7]. In

addition, there has been a significant increase in reports of eosinophilic gastroenteropathies, such as allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis, which are due to dietary food protein hypersensitivity in a subset of patients [8,9]. Finally, it has recently been appreciated that as many as 50% of episodes of gastroesophageal reflux in infants younger than 1 year are caused by hypersensitivity to dietary food proteins, primarily cow's milk and soybean [10].

The reasons for the increase in food allergy prevalence are not known, but, considering the short period over which the change occurred, environmental factors are clearly more relevant than genetic factors [11]. The hygiene hypothesis has been proposed as an explanation for the increase in prevalence of all allergic diseases and may also apply to food allergy. The hygiene hypothesis postulates that decreased early life-exposures to immunomodulatory factors, such as certain viral infections and endotoxins, may be responsible for the increasing prevalence of allergic disorders, including asthma, allergic rhinitis (AR), and food allergy [12]. It is likely that additional factors play an important role, such as early introduction of solid foods into infants' diets, diversification of diet to include a variety of tree nuts, seeds, and fish, propagation of peanut/peanut butter as a healthy nutritional supplement for pregnant and lactating women and young children, and alternative, non-ingestion routes of sensitization resulting from application of skin care products that contain food allergens (eg, peanut oil, milk protein) [1,13,14].

Recent reports demonstrate development of food-IgE antibodies and clinical reactivity in mice and in adult patients receiving medications that lower gastric pH [15,16]. These findings highlight a possibility that liberal use of antacids may contribute to development of hypersensitivity reactions to foods, because reduced protein digestion in the stomach results in increased food protein allergenicity, both in pediatric and adult patients.

Pathophysiology

Immaturity of the immune system and gastrointestinal tract predisposes young infants to food allergy. Compared with older children and adults, infants and young children have an immature glycocalyx, decreased gastric acidity, and decreased intestinal and pancreatic enzyme activity [17]. The intestinal permeability is increased, resulting in higher concentrations of intact food proteins in the circulation and most likely leading to stimulation of the immune system and development of IgE-sensitization [17]. The mucosal immune response is immature; surface secretory IgA concentration is lower, but T-lymphocyte reactivity to food proteins is increased. Early introduction of food allergens has been shown to stimulate IgE antibody production [18] and induce allergic conditions in predisposed infants [19]. Impaired mucosal gut barrier together with the resulting increased intestinal permeability has been proposed as an important factor contributing to the development

of food allergy in infants and young children. During the first 2 years of life, gradual maturation of the intestinal barrier corresponds to decreased prevalence of food allergy and may be associated with the process of outgrowing food allergy [17].

Even in the mature gut, about 2% of ingested food allergens are absorbed and transported throughout the body in an immunologically intact form [20,21]. However, in most individuals these food proteins do not cause clinical symptoms because of oral tolerance—the physiologic mucosal immune response to soluble antigens such as those in foods, resulting in a state of unresponsiveness. Oral tolerance is hypothesized to result from T-cell anergy or induction of regulatory T cells. Intestinal epithelial cells act as nonprofessional antigen-presenting cells and induce tolerance [22,23]. In addition, intestinal dendritic cells express interleukin (IL)-10 and IL-4, which favor the generation of tolerance *in vivo*. The regulatory T cells that are potent sources of tumor growth factor- β (TGF- β) are generated in mucosal lymphoid tissue in response to low-dose antigen. The gut flora are also believed to play a significant role in the induction of normal mucosal immunity, because animals raised in a germ-free environment fail to develop normal tolerance [24]. Childhood food allergy therefore may be viewed as a failure to develop oral tolerance in the setting of immature gastrointestinal and immune systems.

When immune tolerance fails, sensitization to ingested food allergens occurs. In genetically predisposed, atopic individuals, sensitization leads to the generation of allergic IgE antibodies that facilitate immediate reactions, such as food-induced anaphylaxis, urticaria, angioedema, bronchospasm, or gastrointestinal symptoms of emesis and diarrhea. In others, allergic sensitization affects primarily T lymphocytes without generation of IgE antibody. Such non-IgE, cell-mediated food allergic disorders are represented by allergic proctocolitis and food protein-induced enterocolitis syndrome. Atopic dermatitis and allergic eosinophilic gastroenteritis are examples of disorders with mixed mechanism, in which both IgE antibody and cell immunity may play a role [25].

Characterization of food allergens

In spite of the tremendous diversity of the human diet, a few foods account for the majority of food allergies. In the United States, milk, egg, peanut, wheat, and soybean are the most common culprits in children, whereas peanut, tree nuts, fish, and shellfish are the most common culprits in adults [25]. Raw fruits and vegetables are responsible for the oral allergy syndrome that affects approximately 50% of adults with rhinitis caused by birch pollen [26]. Modern diets that routinely include exotic foods as well as a variety of fresh fruits and vegetables have resulted in an increase in allergic reactions to fruits, such as kiwi and papaya, and seeds, such as sesame, poppy, mustard, and rape (canola).

Traditional or class 1 food allergens induce allergic sensitization by way of the gastrointestinal tract and are responsible for systemic reactions (traditional or class 1 food allergy). Type 1 food allergens are typically heat- and low pH-stable, water-soluble glycoproteins ranging in size from 10 to 70 kD. Type 2 food allergens are heat-labile and susceptible to digestion. Type 2 food allergens are highly homologous with proteins in pollens, and sensitization occurs in the respiratory tract as a consequence of sensitization to the cross-reactive pollen allergens (oral allergy syndrome or class 2 food allergy). Cooking can reduce the allergenicity of fruits and vegetables responsible for the oral allergy syndrome, or that of raw or undercooked egg and fish, by destroying heat-labile conformational allergenic epitopes. In contrast, high temperatures (eg, roasting) may increase allergenicity of certain allergens, such as peanut, through the induction of covalent binding that leads to new antigens or improved stability.

Clinical food allergic disorders

Food allergic disorders may be classified based on the role of IgE antibody as IgE-mediated, non-IgE, cell-mediated, or mixed, IgE- and cell-mediated (Table 2).

IgE-mediated food allergy reactions typically start within minutes to 1 hour (rarely past 2 hours) and may affect skin (urticaria, angioedema, morbilliform eruptions, flushing, pruritus), the respiratory tract (sneezing, rhinorrhea, congestion, cough, wheezing, difficulty breathing), and the gastrointestinal tract (oral allergy syndrome, nausea, vomiting, diarrhea, cramping abdominal pain). Generalized reactions involving the cardiovascular system (tachycardia, hypotension) are called anaphylactic shock. Mixed and cell-mediated mechanisms typically have delayed onset of symptoms (>2 hours) and a chronic, relapsing course.

Food-induced anaphylaxis

Anaphylaxis represents the most severe form of IgE-mediated food allergy and is clinically defined as a food-allergic reaction involving two or more organ systems [27]. In extremely sensitive individuals, reactions may be triggered by minute amounts of food proteins [28]. Symptoms start within seconds to 2 hours following allergen ingestion and include feelings of impending doom, throat tightness, coughing or wheezing, abdominal pain, vomiting, diarrhea, and loss of consciousness. Cutaneous symptoms of flushing, urticaria, and angioedema are present in most anaphylactic reactions; however, the most rapidly progressive anaphylaxis may involve no cutaneous manifestations.

Risk factors for fatal anaphylaxis in teenagers and young adults include allergy to peanut, asthma of any severity, and delayed administration of epinephrine [6]. Anaphylaxis may have a biphasic course in as many as 20% to

Table 2
Food allergy disorders

Disorder	IgE-mediated	Mixed mechanism: IgE- and cell-mediated	Non-IgE-mediated
Generalized	Anaphylactic shock, food-dependent exercise-induced anaphylaxis	—	—
Cutaneous	Urticaria, angioedema, flushing, morbilliform rash, acute contact urticaria	Atopic dermatitis, contact dermatitis	Dermatitis herpetiformis
Gastrointestinal	Oral allergy syndrome, immediate gastrointestinal food allergy	Allergic eosinophilic esophagitis, allergic eosinophilic gastroenteritis	Allergic proctocolitis, food protein-induced enterocolitis syndrome, celiac disease, infantile colic
Respiratory	Acute rhinoconjunctivitis, bronchospasm	Asthma	Pulmonary hemosiderosis (Heiner's syndrome)

25% of cases, with initial improvement with or without treatment followed by recurrence of severe symptoms within 1 to 2 hours. Severity of late symptoms cannot be predicted based on the early symptoms—for instance, mild early symptoms may be followed by anaphylactic shock. Given this potential for late-phase reactions, an observation period of at least 4 hours following a reaction is recommended. Rarely, anaphylaxis may have a protracted course, with symptoms lasting for days [28]. Peanut, tree nuts (eg, almond, cashew, hazelnut, pecan, and walnut), fish, and shellfish are most often responsible for food-induced anaphylaxis (Box 1).

Food-dependent, exercise-induced anaphylaxis (FDEIA) has been reported in young, athletic individuals (especially women in late teens to mid-30s) and occurs in two forms: anaphylaxis may occur when exercise follows the ingestion of a particular food to which IgE-sensitivity can be identified (eg, wheat, shellfish, fish, celery) or, less commonly, 2 to 4 hours after the ingestion of any food (postprandial anaphylaxis). Affected patients frequently identify hot and humid weather as an additional factor. Ingestion of the incriminated food or exercise alone does not provoke symptoms, although occasionally patients have a history of reacting to the food when they were younger. Patients generally (60%) have asthma and other atopic disorders. The pathogenesis of FDEIA is not known. In the case of wheat FDEIA, the putative mechanism may involve reduced splanchnic blood flow, resulting in transient intestinal ischemia and increased intestinal permeability, with subsequent activation of tissue transglutaminase and formation of high-molecular-weight complexes of ω -5 gliadin (an alcohol-soluble fraction of gluten) that have increased allergenicity. An alternative (or additional) pathway of tissue transglutaminase activation might involve exercise-

Box 1. Key points about food-induced anaphylaxis

- IgE-mediated massive release of mediators affecting two or more target organ systems
- Flushing, pruritus, generalized urticaria and angioedema, rhinitis, throat tightness/swelling, dyspnea, cough, wheezing, vomiting, cramping abdominal pain, uterine contractions, hypotension, shock, collapse, metallic taste in mouth, feeling of impending doom
- In approximately 20% to 30% of food-anaphylactic episodes, symptoms recur within 2 to 4 hours (biphasic anaphylaxis); rarely, prolonged reactions may last for a few days.
- An estimated 200 people die in the United States each year from food anaphylaxis; food anaphylaxis is responsible for an estimated 30,000 emergency room visits every year.
- Risk factors: asthma, age (late teen to young adult), peanut and tree nut allergy, no treatment or delayed treatment with epinephrine

induced generation of cytokines (IL-6, IL-1 β , tumor necrosis factor- α [TNF- α]), hormones (cortisol, growth hormone), reactive oxygen species, and catecholamines [29]. Management involves avoiding exercise or any intense physical activity for 4 to 6 hours following a meal of the incriminated food, carrying emergency medication (EpiPen, cetirizine, or diphenhydramine), exercising with a partner, wearing a Medic Alert bracelet, and avoiding exercise in hot and humid weather.

*Cutaneous food allergic disorders**IgE-mediated cutaneous food allergy disorders*

Acute urticaria and angioedema are the most common manifestations of acute allergic reactions to ingested foods in children and adults. Onset of symptoms may be rapid, within minutes of ingesting the responsible food. Skin involvement may be isolated or associated with other organ systems in food anaphylaxis. Acute IgE-mediated urticaria can be induced by skin contact with cow's milk, raw egg white, raw meats, fish, vegetables, and fruits. Skin contact reactions are typically local in nature, but contact with oral mucous membranes (eg, kissing) or conjunctiva (eg, eye rubbing) may lead to generalized reactions [30,31]. Chronic urticaria (symptoms lasting longer than 6 weeks) is rarely caused by food allergy (Table 3).

Mixed IgE-mediated and cell-mediated cutaneous food allergy disorders

Food allergy is frequently seen in children with atopic dermatitis (AD) but infrequently in adults. AD is a chronic inflammatory disease of the

Table 3
Cutaneous food allergic disorders

Disorder	Age group	Characteristics	Diagnosis	Prognosis/course
<i>IgE-mediated</i>				
Acute urticaria and angioedema	Any	Pruritic, evanescent skin rash (hives) and swelling within minutes to 2 h after food ingestion; food identified as a culprit in 20%	History, positive PST, and/or serum food-IgE; confirmed by OFC if necessary	Variable, food-dependent; milk, soy, egg, and wheat typically outgrown; peanut, tree nuts, seeds, and shellfish typically persistent
Chronic urticaria and angioedema	Any	Hives and swelling on and for > 6 wk; only 2% caused by food	History, positive PST, and/or serum food-IgE; confirmed by OFC if necessary	Variable
<i>IgE and cell-mediated</i>				
Atopic dermatitis	Infant and child; 90% start < 5 y	Relapsing pruritic vesiculopapular rash; generalized in infants, localized to flexor areas in older children; food allergy in 35% of children with moderate-severe AD	History, PST, and/or serum food-IgE, elimination diet and OFC	60%–80% improve significantly or resolve by adolescence
<i>Cell-mediated</i>				
Contact dermatitis	Any; more common in adults	Relapsing pruritic eczematous rash, frequently on hands or face; often in occupational contact with food stuff	History, patch testing	Variable
Dermatitis herpetiformis	Any	Intensely pruritic vasicular rash on extensor surfaces and buttocks	Biopsy diagnostic: IgA granule deposits at the dermo-epidermal junction; resolves with dietary gluten avoidance	Life-long

skin characterized by marked pruritus and a remitting and relapsing course. The vesiculopapular rash of AD has a typical distribution, with generalized involvement in infants and young children and localization to flexural areas in older children. AD starts before age 5 years in more than 95% of patients. In a study of 63 children with moderate to severe AD referred to a pediatric dermatologist in a tertiary medical center who underwent 1613 double-blind, placebo-controlled food challenges, 37% of patients were allergic to at least one food [3]. In the presence of extensive chronic eczematous skin lesions, acute skin symptoms are not easily appreciated, and identification of the responsible food allergen is notoriously difficult, if not impossible. However, following a 2-week strict dietary elimination period, reintroduction of the causative food results in clear-cut, immediate cutaneous reactions. In some adults with birch pollen sensitivity, ingestion of birch pollen-related foods (eg, apple, carrot, celery) causes immediate or late eczematous reactions or both [32,33]. Strict elimination of the causative food allergen results in significant improvement in dermatitis (Box 2) [3,34].

Gastrointestinal food allergic disorders

IgE-mediated gastrointestinal food allergy

Gastrointestinal anaphylaxis (immediate gastrointestinal hypersensitivity) is an IgE-mediated gastrointestinal reaction that frequently accompanies

Box 2. Key points about food allergy in atopic dermatitis

- Approximately 35% to 40% of children with moderate–severe persistent AD refractory to medical treatment have food allergy; food allergy is uncommon in adult-onset AD.
- Egg is the single most common allergen in children with AD; egg, milk, and peanut account for about 80% of food allergy in children with AD; more than 30% of children are allergic to more than one food.
- Extremely pruritic papulo-vesicular rash that waxes and wanes
- Difficult to identify offending foods in chronic AD based on history
- Avoidance of the food for 2 weeks and reintroduction under supervision results in acute skin reactions that may be accompanied by respiratory and/or gastrointestinal symptoms.
- Removal of the offending foods from diet results in significant improvement of skin rash in most children with AD.
- Most children improve by teenage years; many grow into respiratory allergy: ~50% risk in children with AD and egg allergy

allergic manifestations in other target organs (eg, skin and lungs) and presents with a variety of symptoms, including oral pruritus, nausea, abdominal pain, colic, vomiting, and diarrhea (Table 4) [25].

Oral allergy syndrome

Oral allergy syndrome (OAS) is a form of contact allergy to raw fruits and vegetables that is confined to the oropharyngeal mucous membranes and affects subjects allergic to pollens such as birch (apple, cherry, peach, carrot), grass (tomato, kiwi), ragweed (melon, banana, tomato), and mugwort (carrot, celery) (Box 3) [35]. OAS affects approximately 50% of pollen-allergic adults and represents the most common adult food allergy. It results from the cross-reactivity between the allergenic proteins in the pollens and plant foods [26]. Local IgE-mediated mast cell activation provokes the rapid onset of pruritus, tingling, and angioedema of the lips, tongue, palate, and throat, occasionally accompanied by a sensation of pruritus in the ears, tightness in the throat, or both. These symptoms resolve promptly when the food is swallowed or removed. Patients typically tolerate cooked or baked forms of fruits and vegetables in which unstable allergens are destroyed by high temperature. Symptoms of OAS are typically mild, but in a small subset of patients, allergy to fruits and vegetables may progress to systemic reactions [36]. Risk factors for systemic reaction are not well delineated but may involve sensitization to heat-stable and protease-resistant lipid transfer proteins and storage proteins, such as globulins (7S and 11S) and albumins (2S). Other possible risk factors include lack of pollen allergy, peach hypersensitivity, positive allergy tests with commercial extracts (64% rate of systemic reaction versus 6%; $P < .001$), history of systemic reaction to one of the related foods, and reactions to cooked foods.

Mixed IgE- and cell-mediated gastrointestinal food allergy disorders

Allergic eosinophilic esophagitis (AEE) and gastroenteritis (AEG) are characterized by infiltration of the gastrointestinal tract with eosinophils, basal zone hyperplasia, papillary elongation, and absence of vasculitis. The eosinophilic infiltrates may involve the mucosal, vascular, or serosal layers of the esophagus, stomach, or small intestine. The underlying pathophysiology of these disorders is poorly understood, but both T-lymphocyte and food-specific IgE antibody are implicated. Clinical symptoms correlate with the extent of eosinophilic infiltration of the bowel wall [9]. AEE is seen most frequently in infants, children, and adolescents and presents with symptoms of gastroesophageal reflux, such as nausea, dysphagia, emesis, and epigastric pain, that fail to resolve with standard antireflux therapy. Patients typically have a negative pH probe; on esophageal biopsy, more than 10 to 20 eosinophils per 40 \times high-power field are seen [8]. AEG may occur at any age, including early infancy, and failure to thrive is common. In young infants, AEG may cause gastric outlet obstruction with pyloric

stenosis. Patients also present with abdominal pain, emesis, diarrhea, blood loss in the stool, anemia, and protein-losing gastroenteropathy [37].

As many as 50% of patients with these eosinophilic disorders are atopic and have detectable IgE sensitization to food allergens (by prick skin test [PST] or radioallergosorbent test [RAST]). However, food-induced IgE-mediated immediate reactions are uncommon. Furthermore, results of PST and RAST correlate poorly with clinical response to elimination of the food and thus must be interpreted with caution. Resolution of symptoms typically occurs within 3 to 8 weeks following the elimination of the responsible food allergen (frequently multiple foods, most commonly cow's milk, soy, wheat, and egg). Because patients who have AEE and AEG may be sensitive to trace amounts of the offending foods in the diet, and testing may fail to identify all relevant food allergens, an elemental diet based on an amino acid formula may be needed to achieve improvement (Box 4) [38–40].

Non-IgE-mediated gastrointestinal food allergy disorders

Allergic proctocolitis typically starts in the first few months of life, with blood-streaked stools in otherwise healthy-looking infants, and is considered a major cause of colitis before age 1 year; more than 50% of infants in published reports are exclusively breastfed [41]. Food protein-induced proctocolitis typically presents in the first 4 months of life, usually at 1 to 4 weeks of age, with intermittent blood-streaked normal to moderately loose stools. Pathologic findings are limited to the colon and include focal acute inflammation with epithelial erosions and eosinophilic infiltration of the lamina propria, the epithelium, and lamina muscularis. After 9 to 12 months of age, the infants typically tolerate an unrestricted diet.

Food protein-induced enterocolitis syndrome (FPIES) is most frequently seen in young infants who present with irritability, protracted vomiting, and diarrhea [42,43]. Twenty percent of cases may result in shock, presumably due to intense intestinal inflammation leading to third-spacing and intravascular volume depletion. Vomiting generally occurs 1 to 3 hours after feeding, but continued exposure may result in bloody diarrhea, anemia, abdominal distention, and failure to thrive. FPIES is most frequently due to cow's milk and soy, but other foods, such as grains (rice, oat), meats (turkey, chicken), and vegetables (pea), have also been reported [44,45]. Breast-feeding appears to have a protective effect [45]. The pathophysiology of FPIES may involve depressed TGF- β expression in intestinal mucosa and increased secretion of TNF- α by circulating milk-specific T cells, resulting in increased intestinal permeability [46–48].

Celiac disease (CD) is a dietary protein enteropathy characterized by an extensive loss of absorptive villi and hyperplasia of the crypts; it leads to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive [49]. Oral ulcers and a linear papular, intensely pruritic rash of dermatitis herpetiformis may occur, occasionally in the absence of gastrointestinal symptoms. Patients who

Table 4
Gastrointestinal food allergic disorders

Disorder	Age group	Characteristics	Diagnosis	Prognosis/course
<i>IgE-mediated</i>				
Gastrointestinal anaphylaxis	Any	Onset: minutes to 2 h; nausea, abdominal pain, emesis, diarrhea; typically in concert with cutaneous and/or respiratory manifestations	History, positive PST and/or serum food-IgE; confirmatory OFC	Variable, food-dependent; milk, soy, egg, and wheat typically outgrown; peanut, tree nuts, seeds, and shellfish typically persistent
Oral allergy syndrome (pollen-food allergy syndrome)	Any; most common in young adults (50% of birch pollen adults)	Immediate symptoms on contact of the raw fruit with oral mucosa: pruritus, tingling, erythema or angioedema of the lips, tongue, oropharynx, throat itching/tightness	History, positive prick-prick skin test with raw fruits and vegetables; OFC positive with raw fruit, negative with cooked	Severity of symptoms may vary with pollen season; may be treated with pollen immunotherapy in a subset of patients
<i>IgE and/or cell-mediated</i>				
Allergic eosinophilic esophagitis	Infants, children, adolescents	Chronic/intermittent symptoms of gastroesophageal reflux, emesis, dysphagia, abdominal pain, irritability	History; positive PST and/or food-IgE in 50%, but poor correlation with clinical symptoms; patch testing may be of value; elimination diet and OFC; endoscopy, biopsy provides conclusive diagnosis	Variable, not well-established, improvement with elimination diet within 6–8 wk; elemental diet may be required
Allergic eosinophilic gastroenteritis	Any	Chronic/intermittent abdominal pain, emesis, irritability, poor appetite, failure to thrive, weight loss, anemia, protein-losing gastroenteropathy	History, positive PST and/or food-IgE in 50%, but poor correlation with clinical symptoms, elimination diet and OFC; endoscopy, biopsy provides conclusive diagnosis	Variable, not well-established, improvement with elimination diet within 6–8 wk; elemental diet may be required

Cell-mediated

Allergic proctocolitis	Young infants (< 6 mo), frequently breast-fed	Blood-streaked stools, otherwise healthy-appearing	History; prompt response (resolution of gross blood in 48 h) to elimination of milk or soy or switching to casein hydrolysate formula; biopsy conclusive but not necessary in vast majority	Majority able to tolerate milk/soy by first year of age
Food protein-induced enterocolitis syndrome	Young infants	Chronic emesis, diarrhea, failure to thrive on chronic exposure; upon re-exposure following a period of elimination: subacute, repetitive emesis, dehydration (15% shock), diarrhea; breast-feeding protective	History; response to dietary restriction; OFC	Most resolve in 1–3 y
Celiac disease (gluten-sensitive enteropathy)	Any	Chronic diarrhea, malabsorption, abdominal distension, flatulence, failure to thrive or weight loss, may be associated with oral ulcers and/or dermatitis herpetiformis	Biopsy diagnostic: villus atrophy; screening with serum IgA antibodies against tissue transglutaminase and gliadin; resolution of symptoms with gluten avoidance and relapse on oral challenge	Life-long

Box 3. Patterns of pollen–fruit and vegetable cross-reactivity*Birch*

Apple, peach, plum, nectarine, cherry, almond, hazelnut,
and carrot
Celery
Hazelnut

Ragweed

Melons (watermelon, cantaloupe, and honeydew)
Banana
Tomato

Grasses

Tomato
Melons
Kiwi

Mugwort (weed)

Carrot
Celery
Spices

Box 4. Key points about food-allergy allergic eosinophilic gastrointestinal disorders

- Diagnosis of AEE and AEG is established by endoscopy and biopsy.
- Food allergy affects > 50% of patients; > 50% of patients are atopic.
- Food PST and RAST correlate poorly with clinical response to elimination diet; relevant foods may be negative.
- Most common foods implicated in AEE and AEG are milk, soy, egg, and wheat.
- Elimination of the offending food(s) results in improvement in 3 to 6 weeks; repeat biopsy helpful in confirming resolution of eosinophilic inflammation
- Elemental diet based on an amino-acid formula may be necessary for initial improvement, with subsequent gradual introduction of foods, one food every 2 weeks, starting with fruits and vegetables.

have CD are permanently sensitive to gliadin, the alcohol-soluble portion of gluten found in wheat, rye, and barley. Symptoms of CD resolve completely with exclusion of gluten from the diet but recur when gluten is reintroduced. CD is associated with human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 and affects as many as 1% of some white populations. CD is diagnosed by intestinal biopsy showing classic villus atrophy; serologic ELISA tests detecting IgA antibodies to tissue transglutaminase have a sensitivity of 92% to 98% and are a useful screening tool. Biopsy and serologic tests may be falsely negative when taken during gluten elimination; hence testing for CD is only conclusive when the patient ingests gluten on a regular basis for at least several weeks [2–4].

Respiratory food allergic disorders

Upper respiratory symptoms (allergic rhinoconjunctivitis) and lower respiratory symptoms (bronchospasm and asthma) have been frequently reported in blinded food challenges, but isolated respiratory symptoms without any cutaneous or gastrointestinal symptoms appear rare [50]. Acute bronchospasm is a feature of severe food-induced anaphylaxis, but airway hyperreactivity and worsening of asthma have been documented in children undergoing oral food challenge and exhibiting milder reactions [51]. Food allergy has been identified as a risk factor for severe asthma requiring intubation in children and adolescents [52]. Inhalation of food particles may induce asthmatic reactions: reactions to exposures to peanut dust on an airplane and vapors or steam from cooking fish have been well documented, as have reactions to occupational exposure to grains and aerosolized egg white in bakery workers [53–56]. In highly allergic individuals, inhalation of trace amounts of food particles may lead to systemic reactions (Table 5) [57].

Food allergic disorders in adults

Adult food allergy may represent persistence from childhood (as commonly seen with peanut or tree nuts) or de novo development at an older age. New onset of food allergy has been reported in the setting of heavy occupational exposure by skin contact or inhalation in bakers (wheat, egg), crab processing workers, and harbor workers unloading soybean. In many individuals, reactions are limited to asthma caused by inhalation of food particles, but in some subsequent systemic reactions to ingestion of egg ensue (so-called “egg-egg” syndrome) [58]. Increasingly, adult food allergy is recognized as a consequence of cross-reactivity between respiratory and food allergens. The implicated panallergens are typically highly conserved proteins, such as pathogenesis-related proteins, structural proteins (profilin, tropomyosin), and albumins. Examples include OAS to fresh fruits and vegetables in as many as 50% of pollen-allergic adults, OAS and rare systemic reactions to soy, peanut, and hazelnut in birch pollen-allergic adults, and

Table 5
Respiratory food allergic disorders

Disorder	Age group	Characteristics	Diagnosis	Prognosis/course
<i>IgE-mediated</i>				
Allergic rhinoconjunctivitis	Any	Ocular pruritis, conjunctival injection and watery discharge, nasal pruritis, congestion, rhinorrhea, sneezing within minutes to 2 h following food ingestion or inhalation; often associated with cutaneous and gastrointestinal manifestations	History, PST, and/or serum food-IgE; OFC	Variable
Acute bronchospasm	Any	Cough, wheezing, dyspnea upon ingestion or inhalation of food; may be a risk factor for severe anaphylaxis	History, PST, and/or serum food-IgE; OFC	Variable
<i>IgE- and cell-mediated</i>				
Asthma	Any	Chronic cough, wheezing, dyspnea; food allergy is a risk factor for intubation in children who have asthma	History, PST, and/or serum food-IgE; OFC	Variable
<i>IgG-/cell-mediated (presumed)</i>				
Pulmonary hemosiderosis (Heiner's syndrome)	Infants, children (rare)	Chronic cough, hemoptysis, lung infiltrates, wheezing, anemia; described in cow's milk and buckwheat-allergic infants	History, PST, and serum food-IgE-negative, but milk and buckwheat IgG precipitins positive; lung biopsy with deposits of IgG and IgA	Unknown

allergy to egg in people exposed to birds (so-called "bird-egg" syndrome) [58]. Immunologic cross-reactivity is also the basis of the allergy to fruits and vegetables (avocado, chestnut, banana, kiwi, papaya, fig, melon, passion fruit, pineapple, peach, and tomato) affecting 35% to 50% of latex-

allergic individuals. Exercise and ingestion of alcohol or aspirin have been reported to trigger food allergic reactions in some individuals who otherwise can ingest problematic foods without reactions [59]. Most of these patients are atopic, and some have distant history of a childhood food allergy. Adults receiving antacid medications have been reported to develop IgE-sensitization and clinical reactions to ingestion of hazelnut [15,16].

Allergic eosinophilic gastroenteropathies such as AEE and AEG are being diagnosed more frequently, in part as a result of increased awareness among adult gastroenterologists that significant mucosal inflammation may occur in the absence of visual endoscopic findings and of the increased frequency with which biopsies are obtained. AEE in particular has become widely accepted as a significant cause of dysphagia in adolescents and adults and should be considered in all patients who present with symptoms of gastroesophageal reflux symptoms unresponsive to antacids. AEE should also be suspected in any patient with dysphagia and esophageal strictures that are recognized as complications of the long-term eosinophilic allergic inflammation. **Box 5** summarizes the key points about food allergy in adults.

Diagnosis of food allergic disorders

Taking a careful medical history is the first step to establishing food allergy diagnosis. However, history needs to be validated by laboratory tests

Box 5. Key points about food allergy in adulthood

- Estimated prevalence: 2% to 4%
- Most common food allergens: peanut, tree nuts, shellfish, fish, fruits, and vegetables
- Factors predisposing to development of food allergy: heavy occupational exposure, latex allergy, birch pollen allergy; in selected patients, concurrent ingestion of alcohol or aspirin or exercise within 2 to 4 hours following a meal
- Management relies on avoidance; in case of multiple food restrictions, elemental formulas may be necessary.
- Young adults with IgE-mediated allergy to peanut and tree nuts are at high risk for severe anaphylaxis.
- Special considerations in patients with cardiovascular conditions: judicious use of epinephrine of utmost importance because of high risk for stroke or myocardial infarction; diminished efficacy of epinephrine seen in patients treated with β -blockers.
- AEE should be suspected in individuals with gastroesophageal reflux unresponsive to acid blockade and those with dysphagia and esophageal strictures.

and oral food challenges, especially in chronic disorders such as atopic dermatitis and AEG, in which symptoms wax and wane. In such remitting and relapsing disorders, accurate identification of the offending food is particularly difficult and sometimes impossible [3]. A food intake diary may be helpful in tracing the reactions and foods that might have caused them. Dietary elimination of the suspected foods may be helpful. However, it should be followed by reintroduction of the food, because in some patients symptoms improve with dietary restriction and do not recur on reintroduction of the suspected food. A general approach to food allergy diagnosis and management is presented in Fig. 1.

Prick skin tests

Well-standardized diagnostic tests are available for IgE-mediated food allergy disorders. PST is a bioassay in which a minuscule amount of food allergen is introduced into the skin by gently disrupting the integrity of the outer skin by scratching, puncturing, or pricking with a special bifurcated needle or lancet or multiprong plastic device. Intradermal skin testing should not be used for diagnosis of food allergy because of the risk of systemic reaction and high rate of false-positive results. In a sensitized individual, food allergen binds to specific IgE antibody present on the surface of the mast cells in the skin and causes degranulation of mast cells. Histamine released from mast cells leads to a flare (erythema) and wheal response within 10 to 15 minutes. PST with commercial food allergen extract has a high negative predictive value (>95%), whereas a positive skin test has only a 30% to 40% positive predictive value. However, in infants and young children, a large PST wheal (mean size 8 to 10 mm) is associated with greater than 95% likelihood of clinical reactivity to cow's milk, egg, and peanut [60]. In patients with OAS caused by raw fruits and vegetables, testing with raw fruit is typically more sensitive than testing with the commercial extract of fruit, because the responsible allergens are very unstable and disintegrate during the allergen extraction process. Prick-prick method involves puncturing the fruit through the peel and then puncturing the skin. PST will become more sophisticated and accurate with the availability of recombinant food allergens. Recombinant allergens of high purity offer superior safety and specificity in allergy testing, although diagnostic sensitivity is generally lower than that of allergen extracts. Recombinant allergens may be of special value in diagnosing allergy to plant foods in subjects who have allergy to pollens.

Laboratory immune assays for detection of food-IgE antibody

A number of laboratory immune assays (CAP RAST system) have been developed for the detection of free allergen-specific IgE antibody circulating in the bloodstream. These assays have similar performance to skin tests, in that a negative test (specific IgE antibody < 0.35 kIU/L measured by

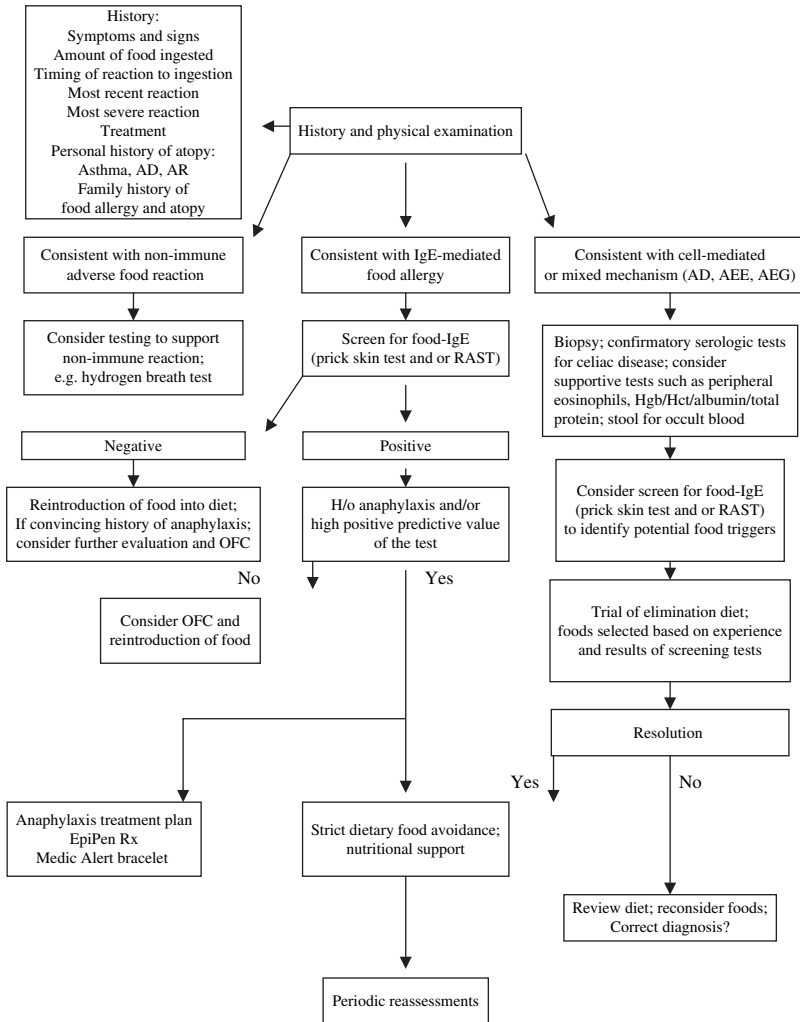


Fig. 1. Schematic approach to diagnosis and management of food allergy. Hgb/Hct, hemoglobin/hematocrit; H/o, history of.

Pharmacia CAP system) has a high negative predictive value ($> 95\%$). The positive predictive value of the CAP system has been evaluated in children undergoing oral food challenges [61,62]. Clinical decision points indicating greater than 95% likelihood of reaction were established for the most common food allergens, including milk, egg, peanut, tree nuts, and fish (Table 6). A child older than 2 years with milk-IgE antibody level of at least 15 kIU/L is highly ($> 95\%$) likely to react during an oral milk challenge, and milk challenge should be deferred unless there is compelling evidence that the child tolerated a significant amount of milk without a reaction. Food-specific IgE

Table 6
Food allergin-specific IgE antibody thresholds of clinical reactivity

Food	Serum food-IgE (kIU/L)	PPV (%)
Milk	15	95
	5 if \leq 1 y	> 95
Eggs	7	> 95
	2 if \leq 2 y	> 95
Peanuts	14	> 95
Fish	20	> 95
Tree nuts	\sim 15	> 95

Abbreviation: PPV, positive predictive value.

antibody levels below the decision points indicate decreasing likelihood of reaction that needs to be determined with oral food challenge.

Prediction of tolerance development

Currently available diagnostic methods for food allergy, such as PST and serum food allergen-specific IgE levels, do not distinguish between individuals who will achieve food tolerance and those who will have persistent food allergy. Previous studies aimed at identification of tolerance markers showed that children with long-lasting milk allergy have higher levels of total and milk-specific IgE. Recently, analysis of differences in recognition of allergenic epitopes in peanut-, cow's milk-, and egg-allergic subjects provided new insights into the development of tolerance to these foods. IgE antibodies may be directed at contiguous epitopes composed of sequential amino acids or conformational epitopes composed of amino acid residues from different regions of the allergen brought together by folding of the protein in its native state. Because food allergens are subjected to extensive chemical and proteolytic digestion before absorption and uptake by the cells of the gut-associated lymphoid tissue, it has been suggested that food allergenic epitopes are predominantly sequential in nature. However, it has recently been shown that subjects with transient egg allergy had IgE antibodies predominantly against conformational epitopes of the major egg white allergen, ovomucoid, whereas subjects with persistent allergy developed IgE antibodies against linearized (sequential, reduced, and alkylated) ovomucoid epitopes [63]. Furthermore, cow's milk-, egg-, and peanut-allergic subjects who lacked IgE antibodies against certain sequential epitopes of the major allergens were found to be more likely to achieve tolerance to these foods than subjects whose IgE antibodies were directed against those epitopes. The differences detected in specificity of IgE responses between patients with transient and persistent food allergy may reflect differences in digestion, absorption, or processing of food allergens. Further research focusing on epitope recognition patterns will use microarray technology that allows for automated, cost-effective, and rapid measurements of antibody specificity against multiple epitopes using microliters of patients' sera. The development of markers of persistent

food allergy is of tremendous importance because, when therapy for food allergy becomes available, the selection of subjects for therapeutic interventions will be crucial.

Diagnostic tests for cell-mediated food allergy

PST and measurement of serum food-IgE antibody concentration are not helpful in food allergic disorders with non-IgE, cell-mediated mechanism, such as FPIES, and have limited usefulness in disorders with mixed mechanism, such as AEE and AEG. Recently, patch testing for the diagnosis of food allergy in children who have AD and AEE has been investigated in a number of studies. Patch testing is typically used for diagnosis of delayed contact hypersensitivity reactions in which T cells play a prominent role and involves prolonged contact of the allergenic extract with intact skin under occlusion for 48 hours. The results are evaluated 20 minutes and 72 hours after removing the patch. A positive reaction to patch tests consists of erythema and induration. In children with challenge-proven milk allergy, PST was positive in 67% of cases with acute-onset reactions (under 2 hours) to milk challenge, whereas patch tests tended to be negative [64]. Patch tests were positive in 89% of children with delayed-onset reactions (25–44 hours), although PST was frequently negative. In another study of children with AD, the combination of a positive patch test with evidence of specific IgE or with positive PST had the highest positive predictive value [65]. These results indicate that a combination of patch testing and detection of IgE could enhance the accuracy of diagnosis of food allergy and eliminate the need for oral food challenges. However, before physicians incorporate atopy patch testing into clinical practice, standardization of the reagents, the timing of the results reading, and the scoring system for the interpretation of the results is necessary.

For gastrointestinal food allergy disorders such as AEE and AEG, ultimate diagnosis is established by obtaining a biopsy of the mucosa and finding increased numbers of eosinophils. Noninvasive diagnostic tests are highly desirable, but currently available laboratory techniques offer limited insight into these conditions. Peripheral blood eosinophil numbers may be followed in approximately 50% of subjects with AEE/AEG. Testing stool samples for occult blood may be useful in a subset of patients in whom gastrointestinal inflammation results in microscopic bleeding. Patients who have AEG and protein-losing gastroenteropathy may be followed with serial evaluations of serum albumin, total protein, and immunoglobulins (low IgG with preserved IgM and IgA). Measurements of stool α 1-antitrypsin may be used to approximate gastrointestinal protein loss.

Oral food challenges

Oral food challenges (OFC) remain the most accurate method for diagnosing food allergy. OFC may be used for diagnosing IgE-mediated as well as non-IgE-mediated food allergy. OFC may be done to confirm whether

the suspected food is indeed causing problems or to determine whether a person with known food allergy might have lost reactivity to food (outgrown food allergy). OFC are particularly useful because IgE antibodies persist after clinical reactivity has cleared. During an oral food challenge for an IgE-mediated food allergy, a premeasured amount of food (typically 8–10 g of dry food or 80–100 mL of liquid food) mixed with a masking food that is well tolerated by the patient is administered in small increments every 10 to 15 minutes over 90 minutes. OFC may be open (ie, both patient and person administering the challenge know which food is administered) or blinded and placebo controlled. In a placebo-controlled challenge, two 90-minute sessions (one with real food, one with placebo food) may be separated by a 90-minute break and completed on a single day, or each session may be done on a separate day. In a single-blind, placebo-controlled food challenge, only the patient is unaware when the real food is administered; in a double-blind, placebo-controlled food challenge, neither the patient nor the person conducting the challenge knows the sequence of real food and placebo. The double-blind, placebo-controlled food challenge is considered the gold standard for diagnosis of food allergy and is preferred in research settings or in patients in whom anxiety may interfere with interpretation of symptoms. Placebo-controlled OFC in which the patient tolerated both sessions without a reaction are always followed by an open challenge, during which a regular portion of food is ingested by the patient over a 30-minute period. OFC are stopped at the first sign of an objective reaction, such as hives, rhinorrhea, sneezing, coughing, or vomiting. Patients are observed for at least 2 hours following completion of an open challenge. In patients who have FPIES, the quantity of food for challenge is calculated as 0.15 to 0.3 g protein per kilogram of body weight (not to exceed 3 g of protein or 10 g of whole food) and administered gradually in three feedings over 45 minutes. If the patient remains symptom-free for 4 hours, a second dose is given, generally a serving amount followed by 2 to 3 hours' observation. OFC are always conducted under physician supervision in a controlled environment with emergency medications (epinephrine, diphenhydramine, methylprednisolone, and volume expanders) immediately available to treat an allergic reaction. Patients who have asthma or a history of severe reactions or who are at higher risk for a positive challenge and all patients with FPIES must have an intravenous line in place before starting a challenge, for immediate vascular access in case of hypotension. Double-blind, placebo-controlled food challenges can be completed during 1 day, or sessions may be conducted on separate days. Patients with AEE or AEG whose food-induced symptoms are delayed and more insidious may require prolonged challenges over several days.

Management of food allergy

Management of food allergy currently focuses on dietary avoidance of the offending foods, prompt recognition and treatment of food allergic

reactions, and nutritional support. Educating patients about how to read food labels is important, because common foods may be labeled using non-intuitive terms. For example, the presence of milk may be indicated as *casein* or *whey*, whereas wheat may be indicated as spelt, bran, farina, or gluten. In addition, *natural flavors* could refer to peanuts, tree nuts, milk, or any other food. Patients commonly make mistakes and are unable correctly to identify the food allergens in store-bought foods; in a recent study, only 7% of parents of children with milk allergy were able correctly to identify products that contained milk, and 22% of parents of children with soy allergy were able correctly to identify products that contained soy [66]. Another impediment faced by food-allergic patients is undisclosed contamination with trace amounts of food resulting from sharing of equipment. Current industry cleaning standards, although stringent, are not sufficient to prevent contamination with trace amounts of food allergens that may trigger severe reactions in highly sensitive food-allergic individuals [67]. This situation is expected to change with the new Food Allergen Labeling and Consumer Protection Law, effective January 1, 2006. The bill requires food manufacturers clearly to state if a product contains any of the eight major food allergens responsible for more than 90% of all allergic reactions: namely, milk, eggs, peanuts, tree nuts, fish, shellfish, wheat, and soy. The new law also requires that the Food and Drug Administration conduct inspections and issue a report within 18 months to ensure that the food manufacturers comply with practices to reduce or eliminate cross-contact of a food with any major food allergens that are not intentional ingredients of the food.

Families of patients with food allergies need information on how to cook foods safely at home and how to handle school, travel, and social situations such as parties and dining. An excellent resource is the Food Allergy and Anaphylaxis Network (www.foodallergy.org), which provides practical advice on dietary avoidance, survival strategies for school, restaurants, and camps, manufacturers' updates, and special support programs for teenagers. The American Partnership for Eosinophilic Disorders Web site (www.apfed.org) contains useful information for patients with eosinophilic gastroenteropathies.

Children who have food allergy, particularly those with multiple food allergies, are at risk for nutritional deficiencies as a result of restricted diets. Nutritional support may be limited to calcium supplementation in children avoiding dairy or may be extensive in children on severely restricted diets. Children allergic to multiple major food allergens are at risk for protein and calorie deficiency and may require a hypoallergenic formula to meet their needs. Hypoallergenic formulas available in the United States are either based on extensively hydrolyzed casein derived from cow's milk (Pregestimil, Nutramigen, Mead Johnson, Alimentum, Ross) or on a mixture of single amino acids (Neocate, SHS, Elecare, Ross). Hypoallergenic formulas are well tolerated by children with IgE-mediated and cell-mediated food allergy [38,40].

In spite of strict avoidance, accidental ingestions and exposures occur, and every food-allergic patient must always be prepared to recognize symptoms and treat food allergic reaction. In children with peanut allergy, 50% reported reactions to peanuts despite avoidance over a 2-year period [68]. Individuals with a history of immediate allergic reactions or anaphylaxis, those with asthma, and those with allergy to foods typically associated with severe reactions (eg, peanut, tree nuts, fish, shellfish) should be prescribed an epinephrine self-injector (EpiPen or EpiPen Jr; Dey, Napa, California). A clear emergency treatment plan indicating symptoms that require treatment with oral antihistamine or epinephrine or both must be provided to the patient by an allergist or primary physician. Templates of anaphylaxis emergency treatment plans may be downloaded from the www.foodallergy.org or www.foodallergyinitiative.org Web sites. Administration of the EpiPen should be demonstrated to the patient and the technique reviewed periodically. A single demonstration is not sufficient for most patients [69]. Patients frequently forget to carry their EpiPen with them and to check the expiration date. These issues should be reviewed regularly during follow-up visits. Patients must be instructed to seek evaluation in the emergency room following the use of an EpiPen. Given the approximately 20% risk of recurrence of allergic symptoms following initial improvement with or without treatment (so-called *biphasic anaphylaxis*), a minimum 4-hour observation period is recommended. Medic Alert bracelets indicating food allergy and specifying the treatment needed in case of a sudden reaction are helpful for older children and adults.

Future therapy for food allergy

Conventional subcutaneous allergen immunotherapy has been attempted for peanut allergy. In a double-blind, placebo-controlled trial of rush (rapidly increasing doses) peanut immunotherapy, increased tolerance to oral feeding with peanut was observed in four of six patients receiving the active immunotherapy (although two of four could not tolerate maintenance dose) and in none of the six control patients [70]. However, the rate of serious adverse reactions was unacceptably high, even during the maintenance phase of immunotherapy (39%). Birch pollen immunotherapy has been reported to result in resolution or significant diminishment of oral symptoms caused by raw Golden Delicious apple in 49 adult birch-allergic patients in a prospective, nonrandomized, nonblinded clinical trial [71]. Subjects received birch immunotherapy for 12, 24, or 36 months. Forty-one patients (84%) compared with no controls (0%) reported a significant reduction (50% to 95%) or a total clearance (100%) of apple allergy symptoms after immunotherapy ($P < .001$). In a follow-up study, the duration of the effect of birch immunotherapy was evaluated in 30 birch pollen-allergic patients who experienced resolution of apple allergy and loss of skin-test reactivity to fresh apple [72]. More than 50% of patients were still able to tolerate eating apples

at the 30-month follow-up visit, although the majority showed evidence of re-sensitization to apple by PST. These studies strongly suggest that, in a subset of patients with birch pollen AR and oral allergy to apple, birch pollen immunotherapy may produce a long-lasting improvement in OAS.

Recently, a monoclonal IgG antibody against IgE (TNX-901) was tested in subjects older than 12 years who had severe peanut allergy [73]. Following subcutaneous injections of TNX-901, the subjects tolerated significantly greater amounts of peanut protein than those that had provoked symptoms before treatment. Currently, a similar monoclonal anti-IgE antibody, omalizumab, is being evaluated for treatment of peanut anaphylaxis in subjects 6 years and older in a controlled clinical trial. Anti-IgE antibody is the first novel therapy for food allergy undergoing clinical trials in human subjects. Anti-IgE therapy will not cure peanut allergy, but it could protect subjects with extreme peanut allergy who are at risk following the unknowing ingestion of traces of peanut. Other selected approaches to treatment of food allergy are summarized in [Table 7](#).

Natural history of food allergy

Food allergy to cow's milk and egg is outgrown by most children. Eighty-five percent of milk-allergic children and 66% of egg-allergic children become food tolerant by age 5 years. In contrast, approximately 20% of all children with peanut allergy become peanut tolerant [74]. However, children with peanut-IgE antibody level less than or equal to 5 kIU/L have at least a 50% chance of tolerating peanut [75]. Periodic evaluation should be offered to children with peanut allergy and OFC to peanut should be considered in patients who have not had reactions in the past 1 to 2 years and who have peanut IgE level of less than 5.0 kIU/L. Unlike milk and egg allergy, peanut allergy can recur in children who outgrew it [76]. Risk of recurrence appears to be approximately 10% in children who refuse to eat peanut on a regular basis, compared with no recurrences in children eating peanut regularly [77]. The authors recommend that the possibility of peanut allergy recurrence be discussed before offering OFC to peanut and that patients ingest peanut frequently following a negative OFC. Epipen should be carried until the patient has proved tolerance to multiple ingestions of regular servings of peanut and peanut-containing foods. It appears that tree nuts, seeds, fish, and shellfish are generally not outgrown, similar to peanut. Information regarding the course of food allergy in adults is scarce. In one study, 10 adults with double-blind placebo-controlled food challenge (DBPCFC)-confirmed allergy to 13 foods were followed for 1 to 2 years. On rechallenge, 38% of 13 foods were well tolerated, including milk in two patients and wheat, egg, and tomato in one patient each. The two patients with nut allergy, two patients with milk allergy, and one patient each with potato, garlic, and rice allergy remained reactive [78].

Table 7
Selected promising potential immunomodulatory therapies for food allergy

Therapy	Mechanism of action	Effects	Comments
Monoclonal anti-IgE antibody	Binds to circulating IgE and prevents IgE deposition on mast cells (blocks mast-cell degranulation and release of the mediators)	Improves symptoms of asthma and allergic rhinitis; possibly protects against food anaphylaxis	Subcutaneous injections at monthly intervals indefinitely; long-term consequences of IgE elimination
Anti-IL-5	Neutralizing antibody against IL-5	Lowers blood and sputum-eosinophil levels; may lower mucosal eosinophils in EE	In a clinical trial [82] in patients with hypereosinophilic syndrome, anti-IL-5 caused a 10-fold reduction in esophageal eosinophil counts and remarkable clinical improvement in one patient with severe eosinophilic esophagitis
Modified peanut immunotherapy	Binding to mast cells eliminated; altered T-cell responses as a result of altering peanut allergenic epitopes by way of site-directed mutagenesis	Protects against peanut anaphylaxis in mice	Improved safety profile compared with conventional immunotherapy; requires identification of IgE binding sites; awaiting FDA approval for studies in humans
Probiotics	Unknown; possibly increased IgA, IL-10, suppression of TNF- α , and inhibition of T-cell activation	Improve severity of atopic dermatitis in infants with milk allergy; prevent development of atopy in at-risk infants	Oral dietary supplement; generally safe and well-tolerated; inexpensive
Traditional Chinese medicine	Downregulations of Th2 cytokines (IL-4, IL-5), upregulation of Th1 cytokines (IFN- γ , IL-12), decreased allergen-IgE	Reverses allergic inflammation in the airways, protects mice from peanut anaphylaxis	Oral; generally safe and well-tolerated; inexpensive

Abbreviations: FDA, US Food and Drug Administration; IFN- γ , interferon-gamma; IL, interleukin; Th, T-helper cells; TNF- α , tumor necrosis factor- α .

Food allergy may be viewed as a marker of an atopic predisposition. In many children, food allergy coexists with other atopic conditions, such as AD, asthma, and AR. Sensitization to egg white in children with atopic dermatitis is associated with a 70% risk for respiratory allergic disease (asthma or AR) at age 5 years [79]. Therefore, subjects with past and current food allergy should be considered at high risk for asthma and environmental allergy.

Prevention of food allergy

Strategies for primary prevention of food allergy have been investigated in a number of studies. Exclusive breastfeeding and introduction of solid foods after 4 to 6 months of age have been associated with decreased risk of AD and cow's milk allergy in infants with an atopic background. If breastfeeding is impossible, formulas with reduced allergenicity, such as extensively hydrolyzed casein formulas or partially hydrolyzed whey formulas, may prevent atopic disease and food allergy [80]. Avoidance of highly allergenic foods (eg, peanut) during pregnancy and breastfeeding has not been shown to have a consistent protective effect. At this time, the American Academy of Pediatrics recommends that in high-risk infants (those with two close relatives—both parents or a parent and a sibling—with atopic disease), breastfeeding or hypoallergenic formula be preferred in the first year of life, solid foods be introduced at age 6 months, and highly allergenic foods, such as peanuts, tree nuts, fish, and shellfish, be delayed until 3 to 4 years of age [81]. Breastfeeding mothers should avoid peanuts and tree nuts in their diets.

Summary

Food allergy encompasses a variety of immune-mediated adverse reactions to foods. IgE-mediated, cell-mediated, and mixed-mechanism food allergy disorders are recognized. Over the past 2 decades, the prevalence of food allergy doubled and its phenotypic expression increased in Westernized societies. Major food allergens have been identified for many common foods. Laboratory diagnosis of food allergy relies heavily on the detection of food-specific IgE antibodies, but novel approaches include tests for T-cell-mediated disorders and tests for prediction of tolerance. OFC remains the diagnostic standard for food allergy. Management of food allergy focuses on avoidance of the offending foods, nutritional support, and prompt recognition and treatment of acute food allergic reactions. Anti-IgE monoclonal antibody is the first potential therapy for food allergy that is undergoing testing in clinical trials.

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