

Food Allergies

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DEFINITION

The term “allergy” is subject to a wide range of interpretations. Many conditions are labeled as allergic disorders; however, a clear immunologic basis for disease is not present. As a result, a clear definition is necessary before delving into the subject of food allergy.

Adverse reactions to food include food allergic and nonallergic reactions (see Figure 1). Immunologic interactions, through either IgE or non-IgE-mediated mechanisms, result in the development of food allergy. Nonallergic adverse food reactions include intolerances which result from host factors,¹ such as enzyme deficiencies, for example, lactase deficiency, which results in the bloating, abdominal pain, and occasionally diarrhea of lactose intolerance. Toxic food reactions represent a separate category, which result from inherent toxicities or properties of the food, for example, histamine-mediated symptoms due to scombroid fish poisoning.¹

PREVALENCE

Food allergy affects approximately 6 to 8% of children under age 3 years, although the public’s perception of food allergy prevalence is greater.² Investigators sought to determine the prevalence of food allergy in an unselected population of children and adults within families ($n = 1834$) and found that self-reported food allergy occurred in 16.6% of participants.³ A pivotal prevalence study, which followed a cohort of 480 children from birth, determined the prevalence of food reactions in their population. Twenty-eight percent of the cohort displayed adverse symptoms,

which either a physician or a family member attributed to food ingestion. Food challenges confirmed food reactions in 8% of the study cohort.² A more recent prevalence study of food allergy in adolescent patients revealed that two cohorts (11-year-old and 15-year-old children) reported adverse reaction to foods with frequencies of 11.6 and 12.4%, respectively. Prick skin testing to food allergens revealed sensitization rates of 5.1 and 4.9% for the 11- and 15-year-old cohorts. When supported by oral food challenges, the authors concluded that the prevalence of food hypersensitivity in both cohorts was 2.3%.⁴ This result is similar to the estimated 3.5 to 4% prevalence of food allergy in the general population.⁵

Cow’s milk allergy affects approximately 2.5 to 2.8% of infants in their first year of life.^{2,6,7} IgE-mediated processes account for approximately 60% of cases. Hypersensitivity to egg affects approximately 1.3% of children⁸ and peanut affects approximately 0.8% of children.⁹ Interestingly, over a 5-year period, the rate of peanut allergy in the United States appears to have doubled in young children.^{9,10} Similarly, a cohort of children from the Isle of Wight was compared with a previous cohort in terms of peanut clinical reactivity and sensitization, and a twofold increase in clinical reactivity and a threefold increase in peanut sensitization was reported.¹¹

The persistence of symptomatic food allergy varies depending upon the food. The majority of children outgrow milk and egg hypersensitivities, 85% by age 8.6 years for milk and 66% by age 5 for egg.^{12,13} Approximately, 20% of children become tolerant to peanut,^{14,15} and it has been recently shown that at least 9% of young children outgrow tree nut allergy.¹⁶

Pollen-food allergy syndrome (also known as oral allergy syndrome) is a common symptom complex, which usually provokes isolated oral symptoms following exposure to heat-labile proteins in uncooked fruits and vegetables. Pollen allergic individuals are at risk due to the homology between specific pollen proteins and proteins in certain foods. Of patients with allergic rhinitis, it has been estimated that 23 to 76% of patients experience oral symptoms to at least one food.¹⁷ The cooked version of the foods is typically tolerated due to disruption of the protein conformation or tertiary structure.

Food allergy commonly presents in patients with or who will develop other atopic diseases. Approximately, one-third of children and adolescents with moderate–severe atopic dermatitis have IgE-mediated food allergy,¹⁸ and some investigators have reported a correlation between the rise in the rate of food allergy with increasing severity of atopic dermatitis.¹⁹ The presence of food allergy increases the probability of developing allergic airway disease^{20,21} and has been shown to be an independent predictor of a persistent wheezing phenotype.²² Despite the concomitant existence of food allergy and asthma, asthma is rarely an isolated finding in a food allergic reaction. Positive food challenges in food allergic, asthmatic patients are rarely characterized by only asthmatic symptoms.²³

PATHOPHYSIOLOGY

Food allergy results from an atypical response of the mucosal immune system to orally consumed antigens. The gastrointestinal mucosa is an extensive structure responsible for digestion and absorption of nutrients as well as protection from pathogenic organisms. A nonspecific physical barrier works with immune and nonimmune cells and cytokines to maintain immunologic homeostasis.

The physical constituents of the gastrointestinal (GI) mucosa are composed of epithelial cells, the mucin glycoprotein lining, trefoil factors, proteolytic enzymes, and bile salts. The epithelial cells are attached by intercellular tight junctions. The mucin lining traps large particles due to its viscous nature and functions as a reservoir for secretory IgA, which entraps bacteria and viruses. Trefoil peptides maintain barrier function by restoring its integrity if defects occur. Proteolytic enzymes, bile salts, and exposures to wide ranges

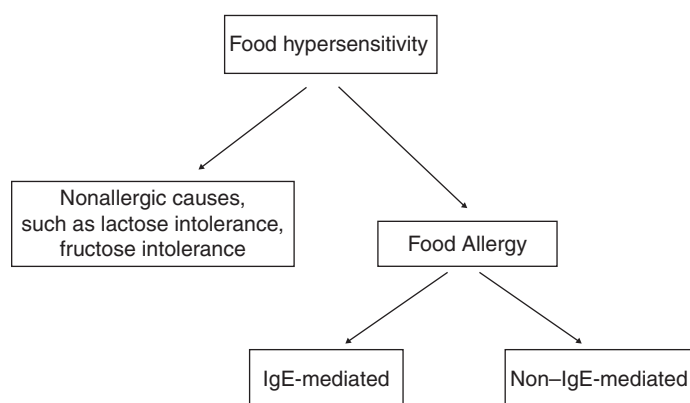


Figure 1 Classification of food hypersensitivities.

of pH gradients work to eliminate pathogenic organisms and modify the immunogenicity of proteins due to proteolysis and emulsification.²⁴

Furthermore, the mucosal immune system provides an active line of defense through both the innate and adaptive arms. Peyer's patches (organized lymphoid structures of the small intestine and rectum), sIgA, dendritic cells, antigen-presenting macrophages, major histocompatibility complex (MHC) class I and II bearing T lymphocytes, intestinal epithelia cells, as well as other cytokine-producing cells allow for immunologic responsiveness.²⁵ Despite the complex interplay of the mucosal system, approximately 2% of intact food proteins are absorbed through the mature GI tract and reach the lymphatic and portal circulation.^{26,27} The intestinal permeability is increased during infancy, and young children's vulnerability is further augmented by the nature of their immature mucosal barrier, which has decreased gastric acid production and reduced pancreatic and intestinal enzymatic activity.²⁸ Consequently, there is increased absorption of intact food proteins which may cause stimulation of the immune system and generation of IgE antibody.²⁸

Oral tolerance allows individuals to encounter immense quantities of dietary protein and commensal bacteria without inciting a dynamic immune response. Antigenic factors and host factors are involved in the generation of oral tolerance (see Table 1). Antigenic factors, which influence oral tolerance, include the form and the dose of the antigen. Soluble antigens are more tolerogenic than particulate antigens.²⁹ Antigenic dose is also a key component to tolerance development. Experiments in mice have shown that oral tolerance can be induced by the administration of a single high dose of allergen or repeated low doses.³⁰ High-dose oral tolerance may occur through Fas-mediated apoptosis³¹ or through the generation of anergy. Anergy occurs when T cells encounter antigens in the absence of costimulatory signaling.³² Low-dose tolerance develops as a result of regulatory T-cell activation. The best categorized regulatory T cells are CD4+ cells (Th3 via TGF- β , TR1 via IL-10, CD4+CD25+ cells possibly via surface-bound TGF- β), CD8+ suppressor cells, and NK1.1+T cells.^{25,33}

Table 1 Factors Influencing the Development of Oral Tolerance

Antigenic factors

- Form—Soluble antigens are more tolerogenic than particulate antigens
- Dose—Tolerance is induced by single high dose or repeated low doses

Host factors

- Age—Ability to generate oral tolerance increases with age
- Genetics—Genetic composition influences oral tolerance
- Gut flora—Contributes to the development of oral tolerance

Host factors involved in the generation of oral tolerance include age, genetics, and GI flora. The ability to become tolerant to food antigens appears to become more effective with age. Neonates develop a stronger immunologic response to dietary proteins in their first few months of life, as demonstrated by rapid increases in circulating antibodies when fed milk or soy formulas.³⁴ Host genetic composition influences the development of oral tolerance or food hypersensitivity, as demonstrated in murine models and human disease. Induction of oral tolerance in mice differs depending upon the strain of mouse.^{35,36} In humans, a higher frequency of three HLA class II genotypes has been found in peanut allergic patients.³⁷ Additionally, monozygotic twins have been shown to have a high concordance rate of peanut allergy,³⁸ supporting the interplay of genetic influence on oral tolerance and food hypersensitivity.

Commensal gut flora takes residence in the GI tract within 24 hours after birth at a concentration that has been estimated to be between 10^{12} and 10^{14} bacteria per gram of colon tissue.²⁴ The impact of gut flora on oral tolerance is supported by the finding that mice raised in germ-free environments following birth are unable to develop tolerance to orally administered ovalbumin (OVA).³⁹ Furthermore, both mice with toll-like receptor 4 (TLR) 4 deficiency plus normal GI flora and mice with intact TLR 4 signaling but are raised in germ-free conditions are susceptible to the induction of allergy,⁴⁰ suggesting that cooperation between the innate immune system and the gut flora is essential for oral tolerance induction. The effects of administering probiotics (supplemental microbes) on the downregulation of allergic disease have generated great interest. Recent publications suggest that the ingestion of probiotics by lactating mothers and their infants may be beneficial in the prevention of atopic disease, specifically atopic dermatitis.^{41,42}

FOOD ALLERGENS

Despite the wide range of foods that humans consume, surprisingly few foods account for the vast majority of food allergies. Milk, egg, peanut, wheat, and soy are responsible for most food-induced reactions in American children, while peanut, tree nuts, fish, and shellfish cause most reactions in adults.¹

Two forms of IgE-mediated food allergy have been proposed. Class 1 food allergy results from sensitization through the GI tract.⁴³ The class 1 food allergens are generally 10 to 70 kDa in size and highly stable when subjected to heat, acid, or proteases.²⁸ Examples of class 1 food allergens include milk (caseins), peanut (vicillins), egg (ovomucoid), and nonspecific lipid transfer proteins.⁴⁴

Class 2 food allergy results from sensitization to inhaled allergens that are partially homologous to proteins in certain fruits and vegetables, and principally occurs in adolescents and adults.

Class 2 allergens are heat labile and susceptible to digestive processes.⁴³ Consequently, symptoms occur when the food is ingested in the raw form, but not when cooked. For example, Bet v 1, a major allergen of birch pollen, shares homology with class 2 allergens in various fruits and vegetables (eg, apple, Mal d 1; carrot, Dau c 1). A similarity in the three-dimensional structures (rather than the overall sequence identity) between birch pollen epitopes and the epitopes of specific foods has been demonstrated.⁴⁵ IgE antibody recognition of structurally related epitopes among pollens and foods likely results in the fruit-vegetable-pollen cross-reactive allergy syndromes (also known as oral allergy syndrome).

REACTION MECHANISMS

IgE-Mediated Reactions

Food allergic reactions involving IgE antibodies occur when IgE binds to and cross-links the high-affinity IgE receptor (Fc ϵ RI) on mast cells and basophils. Following mast cell and basophil activation, preformed and newly synthesized mediators are released. The mediators include histamine, leukotrienes, numerous cytokines, chemokines, and proteases.⁴⁶

Perivascular mast cells are present in significant concentrations in areas that border the external environment, such as skin, and the respiratory and GI tracts. When activated, mediator release produces vasodilation, bronchoconstriction, and mucus production, which lead to the symptoms of an immediate hypersensitivity reaction. Six to 24 hours after the initial allergen encounter, a late-phase reaction may occur which is characterized by edema and an inflammatory cell influx.⁴⁶

IgE-mediated reactions usually occur within minutes to 1 hour following ingestion of the causal food. Multiple organ systems may be involved including the skin, respiratory tract, GI tract, and cardiovascular system.

Non-IgE-Mediated Reactions

Several food hypersensitivity disorders exist that are not solely IgE mediated. Cell-mediated hypersensitivity reactions, orchestrated by antigen-sensitized T cells, may be responsible for the manifestations of certain conditions. A few diseases are thought to result from cooperation between cell-mediated and IgE-mediated mechanisms, for example, atopic dermatitis, allergic eosinophilic esophagitis.

CLINICAL FOOD ALLERGIC DISORDERS

Food-Induced Anaphylaxis

Food-induced anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs rapidly after exposure to an allergy-causing food.⁴⁷ The majority of anaphylactic events are characterized by cutaneous symptoms, such as urticaria, angioedema, and flushing, although the absence

of skin involvement does not exclude the diagnosis. For example, cardiovascular collapse with resultant shock may occur without cutaneous symptoms due to decreased blood supply to the skin.⁴⁸ In fact, in a report of six food-induced, fatal and seven near-fatal anaphylactic reactions, 38% ($n = 13$) of reactions were not accompanied by cutaneous symptoms.⁴⁹

As with any IgE-mediated reaction, there may be a late-phase response associated with anaphylaxis. The incidence of such reactions is described to occur in up to 20% of food-induced events.⁴⁷ The only published series of anaphylactic episodes in a pediatric population reports the incidence of biphasic reactions to be 6%.⁵⁰ With biphasic reactions, a period of recovery after the initial reaction is followed by a recurrence of symptoms. Late-phase reactions are variable, may be severe, and severity cannot be predicted based on earlier symptoms.

Food-associated exercise-induced anaphylaxis usually occurs when exercise follows the ingestion of a specific food (such as wheat, shellfish, and celery) by approximately 2 to 4 hours. A less common form of food-associated exercise-induced anaphylaxis occurs with the ingestion of any food prior to exercise. The pathogenesis of food-dependent exercise-induced anaphylaxis is unclear.^{51,52}

Cutaneous Food Hypersensitivity Reactions (Table 2)

Acute urticaria and angioedema are the most common manifestations of food-induced allergic reactions.¹ The onset of symptoms may occur minutes after ingestion. Urticaria also frequently develops as a result of direct skin contact with food allergens. Contact reactions are typically localized to areas of direct exposure and are unlikely to provoke systemic reactions, unless inadvertent ingestion occurs.⁵³ Chronic urticaria and angioedema are defined as the presence of symptoms for more than 6 weeks and are infrequently due to food allergy.⁵⁴

Atopic dermatitis is a mixed IgE-mediated and cellular disorder. It is a chronic skin condition which often starts in childhood and is characterized by a relapsing and remitting course. Acute lesions are intensely pruritic and appear as erythematous macular and papulovesicular lesions. Scratching results in excoriation with crusting and exudation. The rash may progress to a subacute form with erythematous, scaling papules, and further advances with the chronic changes of skin thickening or lichenification.⁵⁵

Table 2 Cutaneous Food Hypersensitivity Disorders

<i>IgE mediated</i>
• Urticaria and angioedema, skin erythema, morbilliform rash
<i>Mixed IgE and cell mediated</i>
• Atopic dermatitis
<i>Cell mediated</i>
• Contact dermatitis, dermatitis herpetiformis

The cutaneous lesions of atopic dermatitis usually occur on the face, scalp, and extensor surfaces in young infants. The distribution tends to shift as children get older, affecting the flexural surfaces of the extremities.⁵⁵ Atopic dermatitis skin lesions are characterized by a Th2 cytokine profile (acute lesions IL-4, IL-5, IL-13; chronic lesions IL-5, IL-13). These cytokines result in an inflammatory state with upregulation of adhesion molecules on vascular endothelial cells, upregulation of the high-affinity IgE receptor on Langerhan cells and other antigen-presenting cells, recruitment of inflammatory cells to the skin, and local production of IgE.

Approximately, one-third of children and adolescents with moderate-severe atopic dermatitis have IgE-mediated food hypersensitivity.¹⁸ When patients with food allergy-related atopic dermatitis undergo food challenges, positive challenges are usually hallmarked by cutaneous symptoms such as pruritic, morbilliform, or macular eruptions with a tendency to occur in skin areas affected by atopic dermatitis. In addition to affecting the skin, the majority of positive food challenges trigger other organ system involvement (gastrointestinal or respiratory). Egg, milk, wheat, peanut, tree nuts, and soy are the most frequent foods to which patients are clinically reactive,⁵⁶ with egg affecting approximately two-thirds of patients with food allergy and atopic dermatitis.⁵⁷ If the history reveals food-related symptoms and tests for specific IgE to the food are positive, elimination is the best initial approach. However, caution is needed because although removal of a causal food may improve the skin disease, the patient develops an increased probability of an acute allergic reaction, even anaphylaxis, with reintroduction of the food.⁵⁸

Dermatitis herpetiformis is a polymorphous, pruritic rash characterized by erythematous, urticarial plaques, papules, and vesicles. It develops as a result of gluten sensitivity, usually in association with gluten-sensitive enteropathy (celiac disease). Patients with dermatitis herpetiformis have serum IgA autoantibodies to epidermal transglutaminase.⁵⁹

Contact dermatitis is a cell-mediated skin condition which may be provoked by food exposures. In a study investigating the causes of occupational skin diseases, food handlers were at risk for developing food-induced contact dermatitis.⁶⁰

Respiratory Food Hypersensitivity Reactions (Table 3)

Food-induced respiratory symptoms usually occur in conjunction with other organ system reactions.⁶¹ Respiratory symptoms consist of rhinoconjunctivitis, laryngeal edema, cough, and bronchospasm. Food-induced respiratory symptoms, specifically asthmatic reactions, are a risk factor for fatal and near-fatal anaphylactic events.⁶² Not only is asthma a risk factor for more severe food allergic reactions, but also having a

Table 3 Respiratory Food Hypersensitivity Disorders

<i>IgE mediated</i>
• Bronchospasm, cough, rhinitis, congestion, rhinorrhea, sneeze
<i>Mixed IgE and cell mediated</i>
• Asthma
<i>Cell mediated</i>
• Heiner's syndrome

food allergy has been shown to be associated with life-threatening asthma. In a case-control study, it was demonstrated that children requiring intubation at the time of asthma exacerbation were 5.9 times more likely to have a food allergy compared with matched children who had milder asthma exacerbations.⁶³

Rhinitis and nasal symptoms are commonly seen in patients who have reactions during food challenges. Just as it is uncommon to have isolated food-induced asthmatic symptoms, it is very unusual to have nasal symptoms as the only manifestation of an acute allergic reaction.⁶⁴

Allergic reactions can develop as a result of inhalation of airborne proteins. This modality of exposure is more significant when vapors or steams (from foods like fish or eggs) are being emitted during the cooking process.⁶⁵ Inhalation reactions secondary to peanuts, such as particulate matter from peanut dust when shells are opened, have also been reported.⁶⁶ In contrast, exposure of peanut allergic patients to the smell of peanut butter, a material that is unlikely to result in release of airborne allergens, has not been shown to result in systemic or respiratory symptoms.⁵³

Food-induced pulmonary hemosiderosis (Heiner's syndrome) is a non-IgE-mediated hypersensitivity reaction primarily to milk, which results in the development of recurrent pneumonia, hemosiderosis, GI blood loss, iron-deficiency anemia, and failure to thrive. Removal of milk from the diet results in symptom resolution.⁶¹

GI Food Hypersensitivity Disorders (Table 4)

Food-induced reactions affecting the GI tract may be IgE mediated, cell mediated, or due to an interplay of IgE and cell mediated reactivity. Gastrointestinal anaphylaxis is an IgE-mediated reaction that includes symptoms of acute nausea, abdominal pain, colic, vomiting, and/or diarrhea. More indolent symptoms may occur in infants with atopic dermatitis and food allergy who are chronically ingesting the allergen. In these patients, intermittent vomiting and failure to thrive may be part of the symptom constellation.²⁸

Pollen-food allergy syndrome (also known as oral allergy syndrome) is also an IgE-mediated reaction that occurs in pollen-allergic individuals due to homologous proteins shared between foods and specific airborne pollens.⁶⁷ Patients with birch allergy may develop symptoms with raw apple, carrot, potato, celery, pear, kiwi, stone

Table 4 Gastrointestinal Food Hypersensitivity Disorders*IgE mediated*

- Nausea, abdominal pain, colic, vomiting, diarrhea
- Pollen food allergy syndrome—usually only oropharyngeal symptoms

Mixed IgE and cell mediated

- Allergic eosinophilic esophagitis, eosinophilic gastroenteritis

Cell mediated

- Food protein-induced enterocolitis, proctocolitis, celiac disease

fruits, hazelnut, almond, and peanut; patients with ragweed allergy may be sensitive to various melons and banana; patients with grass allergy might become symptomatic with tomato, melons, and kiwi; and patients with mugwort allergy may develop symptoms with celery, carrots, and spices.⁶⁸ Symptoms of pollen-food allergy syndrome are usually confined to the oropharyngeal cavity, and the foods are usually tolerated in the cooked form because the allergens do not retain their structure with high temperatures.

Eosinophilic esophagitis and gastroenteritis are disorders mediated by IgE-dependent and/or cell-mediated mechanisms. Eosinophils infiltrate the walls of the esophagus, stomach, and small intestine. Peripheral eosinophilia is found in approximately half of the patients.⁶⁹ When evaluating these patients, other known causes of eosinophilia must be excluded, such as drug reactions, parasitic infections, and malignancy.⁷⁰ Patients with GI eosinophilic disorders have a high incidence of concomitant atopy, with many having sensitizations to foods and environmental allergens.⁷¹

In a disease-free state, eosinophils are usually not present in the esophagus. Eosinophilic esophagitis may occur at any age from infancy through adolescence and into adulthood. Symptoms include abdominal pain, spitting-up or vomiting, food refusal, and gastroesophageal reflux symptoms in younger patients, and dysphagia and food impaction in adolescents and adults, with a poor response to antireflux medications in both age groups. This symptom complex in association with esophageal biopsies revealing greater than 24 eosinophils per high-powered field is diagnostic. Eosinophils may be located in the proximal and distal esophagus. Esophageal tissue may have thickened mucosa, papillary elongation, and basal zone hyperplasia. On gross appearance, the esophagus may have furrowing (vertical, linear creases), mucosal rings, strictures, ulcerations, and whitish papules.^{69,70,72}

Allergic eosinophilic gastroenteritis may occur at any age. Most notably, patients frequently present with weight loss and failure to thrive. Additional symptoms include abdominal pain, emesis, nausea, and diarrhea.^{69,71} Especially in young infants, presentation may consist of gastric outlet obstruction or symptoms resembling pyloric stenosis.⁷⁰ Diagnosis is made through biopsies, which reveal significant eosinophilic

infiltration of the gastric and/or duodenal mucosa, with no other identifiable medical cause (ie, infection, inflammatory bowel disease, drug reaction).⁷³ A subgroup of patients develop anemia and hypoalbuminemia, likely secondary to fecal loss of blood and protein resulting in protein-losing enteropathy.²⁹

Allergic proctocolitis is a non-IgE-mediated, eosinophilic disorder that typically presents in the first few weeks to months of life. Infants appear in good health; however, they have blood and mucus in the stool, which increases in frequency unless the causal allergen is removed from the diet.⁷⁴ Growth delay and poor weight gain are not usual presenting features. Case series reveal that patients with proctocolitis may have peripheral eosinophilia, elevated serum IgE, and a family history of atopic disease.^{75–77}

Proctocolitis commonly occurs in breast-fed infants (as many as 60% of cases),^{76,78,79} with milk and soy formulas being the causative foods in the majority of the remaining cases.^{75,77,80} For infants who develop proctocolitis while breastfeeding, it is believed that cow's milk proteins consumed by the mother are the triggering agents in breast milk, and it has been demonstrated that β -lactoglobulin (one of the major allergens in milk) is detectable in the majority of breast milk samples following maternal cow's milk consumption.⁸¹ Elimination of cow's milk from the mother's diet will usually bring about gradual resolution of symptoms^{76,78,79}; however, if cessation of bleeding does not occur with maternal dietary manipulation, a casein hydrolysate formula or in rare instances, an amino acid-based formula⁸² eliminates gross symptoms, typically within 48 to 72 hours. For formula-fed infants drinking cow's milk formula, a large percentage who have milk-induced proctocolitis will also become symptomatic to other foods if introduced in the first 6 months of life, for example, soy ingestion.^{75,83} A casein hydrolysate or amino acid formula is the recommended treatment.

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy, which usually occurs in formula-fed infants, although it has been reported to a variety of foods (especially cereal grains) in older infants, and is characterized by irritability, excessive, vigorous vomiting, and diarrhea. Diarrhea may have occult blood and stool smears may reveal leukocytes and eosinophils. The stool may also be positive for reducing substances. Depending on the severity of symptoms, patients may develop dehydration with accompanying hypotension and lethargy. Metabolic derangements such as acidosis and hyponatremia can occur as does leukocytosis and a "left shift."^{84–86} In severe cases, children may even present with methemoglobinemia.⁸⁷

Symptoms may follow a more indolent course for children who are fed the causal food from birth or shortly thereafter. Failure to thrive and hypoalbuminemia in conjunction with chronic emesis and diarrhea may be presenting features. When the causal food is removed and later reintroduced, extreme vomiting within 2 to 3 hours

and late-onset diarrhea occur.^{88,89} Milk and soy are most frequently the causative foods in FPIES; however, solid foods (such as oat, barley, rice, chicken, and turkey) may be responsible.^{88,89} Approximately 50% of patients reactive to milk also develop reactivity to soy,^{85,88} necessitating treatment with a casein hydrolysate formula or, in rare instances, an amino acid-based formula.⁹⁰ FPIES due to a grain, for example, oat, increases the risk of reactivity to other grains, milk, soy, meats, and legumes, necessitating cautious food introduction, especially in the first 6 to 8 months of life.

Celiac disease is a chronic inflammatory disorder of the small intestine (see Chapter 50, Celiac Disease for more details). An interplay between genetic risk factors and dietary triggers are thought to result in the manifestations of this disease, which include intestinal villus atrophy, malabsorption, and chronic inflammation of the small intestinal mucosa. The major associated haplotypes are HLA-DQ2 and HLA-DQ8, with approximately 95% of patients having HLA-DQ2. Celiac disease is strongly associated with dermatitis herpetiformis, and patients with celiac disease are at increased risk for other autoimmune conditions, such as type 1A diabetes mellitus and autoimmune thyroiditis.⁹¹

As a result of the immunologic imbalance, patients with celiac disease react to peptide sequences of gluten proteins. Responsible gluten proteins are present in wheat, rye, and barley. Unlike IgE-mediated allergy to wheat, barley, or rye, the T-cell cytokine profile from patients with celiac disease has a Th1 bias. Removal of gluten from the diet leads to symptom resolution. Patients with untreated disease are at increased risk for T-cell non-Hodgkin's lymphoma.⁹¹

The diagnostic gold standard for celiac disease is the intestinal biopsy, which demonstrates a loss of villi, lymphocytic and plasma cell infiltration of the lamina propria and intraepithelial compartments, and crypt lengthening. Enzyme-linked immunosorbent assays for IgA anti-recombinant human tissue transglutaminase can be utilized as a screening tool. Antigliadin antibodies alone should not be used for screening due to high rates of false-positive results.⁹¹ Importantly, testing for celiac disease, either by biopsy or through serologic studies, must be performed while the patient has a diet that includes gluten; otherwise, false-negative results may occur.

DIAGNOSIS

The diagnosis of food allergies (Table 5) requires a comprehensive history, specifically focusing on adverse reactions to particular foods, the time frame of such reactions, whether other contributing factors were present (ie, exercise), the extent of organ system involvement, and required treatment. Attention to accompanying atopic conditions in the patient and family history of allergy are important. Diet diaries may be helpful in recognizing patterns of reactivity, in identifying commonly consumed allergens, and in identifying foods that may have "hidden allergens" which have provoked the reaction.

Table 5 Methods of Diagnosing Food Allergy

History ± diet diary
Oral food challenge
IgE-mediated and mixed disease
• Prick skin testing
• Serum-specific IgE testing
Cell-mediated and mixed disease
• One patch testing

The history may be more helpful in situations when food ingestions are causally linked to a reaction, such as the development of urticaria and cough immediately after cashew consumption. For chronic disorders, such as atopic dermatitis, asthma, and GI disorders, the history has a poor predictive value. This point is highlighted by a study in which double-blind placebo-controlled food challenges (DBPCFCs) were conducted in 38 children with severe persistent asthma, where the asthma symptoms were attributed to food allergy. Only 20% of the food challenges (70 challenges conducted) resulted in symptoms. Furthermore, the challenges elicited symptoms predominantly affecting the GI tract despite the chronic respiratory complaints.⁹²

Diagnostic Modalities for IgE-Mediated Disorders

Prick skin testing is a rapid screening method for IgE-mediated food hypersensitivity. A small amount of food allergen extract is placed on the skin and then subjected to a prick or puncture, which breaks the skin integrity. A negative control (saline) and a positive control (histamine) are also placed on the skin. Wheals which are 3 mm larger than the negative control are considered positive.

Unfortunately, the positive predictive value of a positive prick skin test is less than 50% when compared to results of DBPCFCs.⁹³ Therefore, the medical history becomes important because tests must be interpreted in light of the clinical situation. Positive skin tests may be helpful especially when a clear-cut history of food reactivity is present. Additionally, when hypersensitivity is suspected to milk, egg, or peanut, “diagnostic prick skin test (SPT) mean wheal diameters” have been defined (cow’s milk ≥ 8 mm, egg ≥ 7 , peanut ≥ 8 ; for children ≤ 2 years of age, cow’s milk ≥ 6 mm, egg ≥ 5 mm, peanut ≥ 4 mm).⁹⁴ However, test results are highly dependent on reagents used (which are not standardized), application technique, and interpretation by the physician. Negative skin tests essentially exclude IgE-mediated allergy.

Intradermal skin testing has no place in the diagnosis of food allergy. In addition to having poor specificity and positive predictive value, fatalities have been reported with the use of this diagnostic modality.⁹⁵

Detection of food-specific IgE antibodies (ie, UniCAP System FEIA, Phadia, Inc.; Uppsala, Sweden) has been shown to be predictive in symptomatic IgE-mediated food allergy.^{96,97} The Phadia UniCAP system contrasts with qualitative

RAST assays because standardized allergens are used, the dose-response curve is calibrated against the World Health Organization IgE standard and the matrix binds more antigen, which provides a steep dose-response curve.⁹⁶ Diagnostic “decision points” have been generated for common food allergens, namely, milk, egg, peanut, and fish (see Figure 2). The decision points indicate reaction

likelihood (a greater than 95% probability of reaction), but do not predict reaction severity.⁹⁶ As serum-specific IgE levels decrease to undetectable, the likelihood of reaction decreases. However, reactions may still occur for a subset of patients when serum-specific IgE levels are undetectable. One study notes that 32 of 120 patients (especially young infants), who reacted to milk,

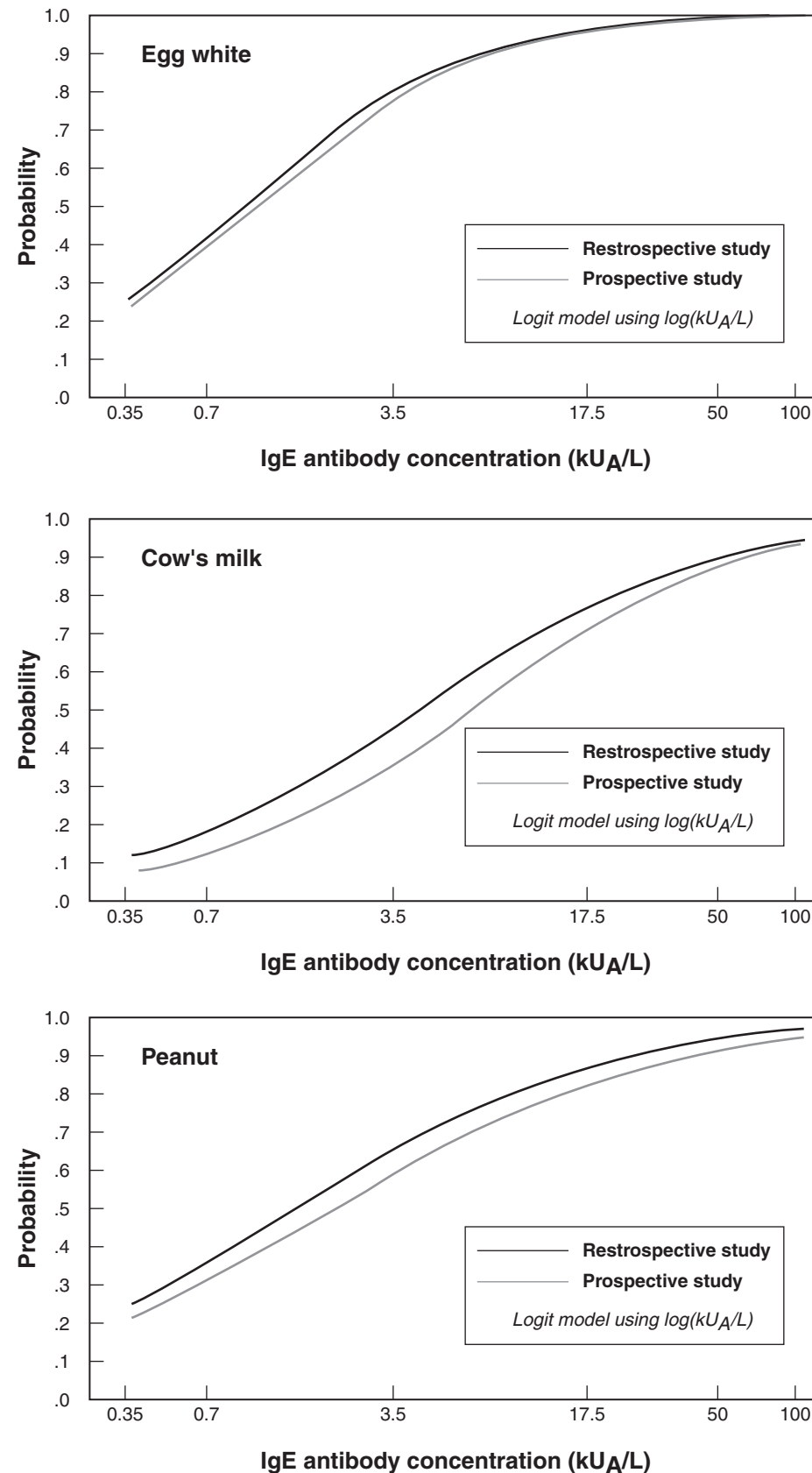


Figure 2 Diagnostic decision points for specific foods.

egg, or peanut challenges, had negative serum-specific IgE levels to the food.⁹⁸

With newer technologies, it has been possible to map sequential allergenic epitopes of many major food allergens. So far it has been shown that detection of IgE antibodies against specific epitopes can be used as a marker for persistent allergy,⁹⁹ and some patients who produce IgE antibodies to sequential epitopes have more persistent allergy compared with patients who produce antibodies to conformational epitopes (epitopes dependent upon tertiary, native structure).^{100,101} Recent enthusiasm has been generated by the microarray immunoassay, which allows for the determination of IgE binding to thousands of overlapping peptide sequences. This technique is an attractive epitope recognition assay because it has the potential for screening a large number of patients with minimal quantities of sera to a wide variety of antigens. To date, data produced with this methodology have shown that peanut-allergic patients with severe reaction histories recognize a greater number of epitopes than patients with less severe reaction histories.¹⁰² In the future, microarray may become a useful clinic-based diagnostic modality for determination of transient versus persistent allergy.

Whereas prick skin tests and serum-specific IgE tests are instrumental in the diagnosis of IgE-mediated food allergy, for cell-mediated and mixed disorders, their diagnostic utility has little or no value. Patch testing is a modality being considered for diagnosing delayed-contact hypersensitivity reactions, where T lymphocytes are the major effector cell. For testing, the food allergen is placed on a small area of the skin under an occlusive dressing. The patch is removed after 48 hours, and the area is examined at 48 hours and again at 72 hours. Positive tests demonstrate erythema, edema, papules, vesicles, and/or bullae, and are graded 0 to 3 based on severity of reactivity. Although patch testing is a common diagnostic practice for cutaneous contact allergy due to chemicals, its use is not standardized for the diagnosis of food-related conditions. For children with atopic dermatitis, studies have shown that patch testing to food allergens in combination with prick skin testing slightly increases positive predictive value for the diagnosis of food hypersensitivity.^{103,104} Investigators have also studied the use of patch testing in conjunction with prick skin testing for determining the causal foods that trigger allergic eosinophilic esophagitis.^{105,106} Although this testing modality may have utility in some situations, lack of patch testing standardization and spurious results (due to skin irritation from the underlying disease and the testing media) makes widespread implementation complex.

The DBPCFC remains the gold standard for diagnosing food hypersensitivities.⁹³ For the DBPCFC, neither the patient nor the physician knows whether the challenge material is the allergen or the placebo. This approach reduces both patient and observer bias. Single-blind challenges and open challenges are other options best

utilized for foods that are unlikely to produce a reaction. For single-blind challenges, the physician knows the content of the challenge material and the patient is blinded, and for open challenges, all participants know the challenge content. The decision to pursue a food challenge should be based on the clinical history in conjunction with prick skin test and serum-specific IgE results. Food challenges are not benign procedures. Positive challenges may produce mild, moderate, or severe symptoms, and often require treatment^{107,108}; therefore, a properly equipped environment is essential.

Prior to food challenges, patients should be instructed to avoid medications that may interfere with interpretation of results, such as antihistamines and β -adrenergic bronchodilators. For IgE-mediated food allergies, the aim is for the patient to eat approximately 8 g of dry food mixed within a vehicle.¹⁰⁷ A negative-blinded challenge must be followed by an open challenge to assure that the patient can ingest the food safely in natural, meal-sized portions. For non-IgE-mediated FPIES, 0.3 to 0.6 g of protein per kilogram of body weight is given in one or two doses.⁸⁴ A reaction typically occurs 1 to 3 hours later, but when symptoms occur, they may be severe with excessive vomiting and possibly result in hypotension; therefore, intravenous access is necessary prior to the start of the challenge. For other conditions such as the eosinophilic GI disorders, several feedings of the food over a few days may be necessary to induce symptoms.¹

MANAGEMENT OF FOOD ALLERGY

Dietary avoidance of the causal food allergen is the key element for management of food hypersensitivity at this time. To practice strict avoidance, patients and their caregivers must be supplied with appropriate education materials to prevent ingestion of foods that may have had inadvertent cross contact with allergens or foods that have hidden allergens. One study illustrated that for 156 reactions to peanut and tree nuts, 50% of accidental ingestions in food establishments were due to "hidden ingredients," such as an ingredient in a sauce or dressing.¹⁰⁹ Although just one study, it illustrates the difficulties that food-allergic patients face with daily experiences, such as purchasing prepared foods or eating in restaurants. The Food Allergen Labeling and Consumer Protection Act (FALCPA), effective as of January of 2006, now requires food manufacturers to clearly label their products that contain any of the eight major food allergens (milk, egg, peanut, tree nuts, wheat, soy, shell fish, and fish). This will benefit patients allergic to those foods; however, the labeling does not necessarily include labeling for all other food allergens. An excellent educational resource for patients and families affected by food allergies is the Food Allergy and Anaphylaxis Network (www.foodallergy.org).

Patients and caregivers must be prepared to respond in case of an accidental ingestion. Written

Table 6 Treatment Approach to Food Allergy

Food avoidance
Anaphylaxis action plan
• Epinephrine, antihistamines, six corticosteroids
FPIES action plan
• Intravenous fluids six corticosteroids
Possible future therapies
• Monoclonal anti-IgE
• Recombinant protein immunotherapy
• Sublingual immunotherapy
• Traditional Chinese herbal medicine

anaphylaxis action plans should explicitly state the symptoms of anaphylaxis and when epinephrine should be administered (Table 6). Antihistamines are useful in treating mild symptoms, particularly cutaneous and oral symptoms, but will not reverse systemic reactions. Epinephrine is the treatment of choice for acute anaphylaxis (1:1000 dilution, 0.2 to 0.5 mL; 0.01 mg/kg in children with a maximum of 0.3 mg). Fatalities from anaphylactic events often appear to result from the late administration of epinephrine and subsequent irreversible cardiopulmonary complications.⁴⁸

The treatment of eosinophilic disorders requires allergen avoidance. Frequently, multiple foods must be eliminated from the diet. Corticosteroids result in clinical and histopathologic improvement^{72,110}; however, the side effects which accompany prolonged corticosteroid therapy are unacceptable, and the disease typically returns with discontinuation of the medication. Many patients with eosinophilic GI disorders have evidence of sensitization to foods (by prick skin tests and/or serum-specific IgE assays); however, immediate reactions to foods are infrequently reported. Dietary elimination based on prick skin test and serum-specific IgE results alone is frequently insufficient to promote disease resolution of eosinophilic disorders. Multiple foods may be causative in the same patient, with the most common ones including milk, soy, egg, and wheat.¹¹¹ A common approach is to place the patient on an elemental (L-amino acid) formula and slowly add foods back into the diet when symptoms have resolved. Several weeks on an elemental formula is usually required for diminution of symptoms and for regression of the GI eosinophilic infiltrate.¹¹² Open challenges with the causative foods, following elimination, have been shown to frequently provoke symptoms indistinguishable to those experienced before the elimination diet.¹¹¹ Recently a six-food elimination diet has been proposed for the initial evaluation of food-induced symptoms; resolution of symptoms reportedly occurs in about two-thirds of patients.¹¹³

For proctocolitis, progression to a normal diet, including the eliminated allergen, is usually possible by 1 to 2 years of age.^{69,78} If the prick skin tests and serum-specific IgE levels are negative, gradual introduction typically takes place at home. For FPIES, action plans must be in place in the event of accidental

ingestions. First-line treatment is fluid resuscitation rather than epinephrine and antihistamines (although these medications should be administered if there is concomitant IgE-mediated disease). Corticosteroids should be considered, especially when past history reveals serious reactions. Corticosteroids likely suppress a presumed T-cell immune response. When food reintroduction is considered, challenges in a properly equipped environment are necessary, and challenges are not recommended until the patient has had at least 18 months with no reactions to the causal food. The high risk of developing FPIES to multiple foods, for example, milk and soy, multiple cereal grains, often necessitates multiple food challenges. Up to 50% of patients reactive to milk may react to soy; up to 65% of patients reactive to grains may react to milk or soy; up to 50% of patients reactive to one grain may react to another grain.¹¹⁴ More than half of the patients with FPIES due to milk become tolerant by age 3 years. Resolution of FPIES varies by age and is influenced by the primary causative food and the presence of concomitant IgE-mediated disease.¹¹⁴

Much recent attention has focused on means of altering the immune system to either eliminate food allergy or increase tolerance to allergenic food. Allergen immunotherapy with peanut extract administered subcutaneously has been attempted to increase oral tolerance to peanut. Although increased tolerance was achieved in four of six patients studied, the adverse reactions from such treatment were not tolerable.¹¹⁵ Sublingual immunotherapy with standardized hazelnut extract was compared to placebo in a group of hazelnut allergic individuals, and subjects receiving the active treatment developed increased tolerance to hazelnut while remaining on therapy.¹¹⁶ The implementation of recombinant proteins with an altered IgE-binding epitope may be a form of immunotherapy that holds future promise. The altered IgE-binding epitopes prevent binding of the patient's IgE to the engineered protein within the vaccine. In a murine model of peanut anaphylaxis, recombinant proteins coadministered with heat-killed *Listeria monocytogenes* or *Escherichia coli* markedly decreased symptoms when mice were challenged to peanut.^{117,118}

Allergen nonspecific forms of treatment include anti-IgE therapy and Traditional Chinese medicine. Humanized IgG1 monoclonal antibody against IgE (TNX-901) was tested in peanut-allergic subjects and was shown to enable subjects to tolerate increased quantities of peanut following therapy. Although, not a cure for food allergy, the medication offered protection in the event of inadvertent ingestion.¹¹⁹ Recent enthusiasm has been generated by the potential value of Traditional Chinese medicine, which has been used in Asia for centuries, as an effective form of treatment for allergic disease. Experiments administering a Chinese herbal medicine formula have been able to block anaphylaxis in a murine model of peanut allergy.¹²⁰

SUMMARY

Food allergy is a general term that includes a wide range of conditions. The pathogenesis involves IgE-mediated and/or cell-mediated processes with varying manifestations depending on the mechanisms of disease. Diagnosis requires a skillful history, physical examination, and targeted diagnostic testing. Treatment requires avoidance of the causal allergen(s). Hopefully, in the future, diagnostic modalities will be more fine tuned and additional treatment options will be available.

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