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FOOD ALLERGIES: Prevalence, Molecular Characterization, and Treatment/Prevention Strategies

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■ **Abstract** A significant proportion of the population is either affected by or concerned about food allergy. Our knowledge about food allergens and how they stimulate the immune system has increased dramatically over the past decade. However, reasons for the increased prevalence of food allergy are not clear. The diagnosis of food allergy requires that the patient and caregivers examine all foods for the presence of potential allergens in order to prevent inadvertent ingestion and further reactions. Fortunately, many children develop tolerance to allergenic foods after a period of dietary elimination. Various immunotherapy approaches are under investigation to alleviate or prevent food-induced reactions in those who have persistent food allergies.

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INTRODUCTION

An early report of anaphylaxis to cow's milk in 1905 was quickly followed by reports of allergy to buckwheat, egg, almond, and oats (22a, 98, 112). The utility of scratch testing for diagnosing food allergy was also recognized in the early 1900s (98, 112). Almost 50 years later, blinded food challenges were designed to

objectively study the incidence of milk allergy, and May is credited with perfecting this technique for clinical and research purposes (60, 64). Double-blind placebo-controlled food challenges have subsequently allowed investigators to standardize definitions, determine the prevalence, and predict the natural history of food allergy. Unfortunately, the management of patients with food allergy has not advanced as rapidly as the diagnostic methods to recognize the disorder have. The only accepted therapy for food allergic patients is complete avoidance of the causal food. It is hoped that recent advances in the molecular characterization of food allergens and that a better understanding of the immune responses may lead to immunomodulatory methods for the treatment and/or prevention of food allergy.

DEFINITIONS

The term "food allergy" is often used inappropriately to represent a variety of disorders related only by their presumed relationship to food ingestion. A more suitable term for such reactions is an "adverse food reaction." Adverse food reaction is a broad term representing any abnormal clinical response associated with ingestion of a food or food additive (84). This term may be utilized by laypersons as well as clinicians because it does not require knowledge of the pathophysiologic mechanism responsible for the reaction.

Based on the proposed mechanism of the reaction, adverse food reactions may be further classified as food allergy or food intolerance (Table 1). Food allergy refers to an abnormal immunologic response to a food that occurs in a susceptible host (84, 88). These reactions are generally immediate and occur each time the food is ingested, even in small amounts. The best-characterized food allergy reactions are those mediated by immunoglobulin E (IgE) antibody, but cell-mediated mechanisms may also be involved (84).

Food intolerance refers to a variety of nonimmunologic reactions occurring after ingestion of a food (84). These abnormal physiologic responses may be due to inherent properties of the food or to physiologic characteristics of the host, may not be reproducible, and are often dose dependent (88). Food-related factors responsible for nonimmunologic reactions include histamine contamination of improperly stored scombroid fish or the presence of tyramine in aged cheeses, alcoholic beverages, and cured meats (88). Alternatively, food intolerance may be a result of a metabolic disorder in the host, such as lactase deficiency (88).

Previous schemes for classifying food allergy designated adverse food reactions as either toxic or nontoxic, with the latter including all immunologic as well as some nonimmunologic reactions to foods (84). The European Academy of Allergy and Clinical Immunology substitutes the term "food hypersensitivity" for adverse food reaction and "nonallergic food hypersensitivity" for food intolerance (46). A thorough understanding of and adherence to these standardized definitions may promote effective communication between patients and physicians, enhance compliance with elimination diets, and avoid unnecessary dietary manipulations.

TABLE 1 Classification of adverse reactions to foods

Adverse food reactions	
Food allergy	Food intolerance
1. IgE-mediated	1. Toxic
Urticaria	Bacterial food poisoning
Angioedema	Scombroid fish poisoning
Anaphylaxis	Heavy metal poisoning
Oral allergy syndrome	2. Pharmacologic
2. Mixed IgE and cell-mediated	Tyramine
Allergic eosinophilic esophagitis	Caffeine
Allergic eosinophilic gastroenteritis	Histamine
Atopic dermatitis	Alcohol
Asthma	3. Nontoxic
3. Cell mediated	Lactase deficiency
Food protein-induced enterocolitis	Galactosemia
Food protein-induced proctocolitis	Pancreatic insufficiency
Food protein-induced enteropathy	Gallbladder/liver disease
Heiner syndrome	Hiatal hernia
	Gustatory rhinitis
	Anorexia nervosa

Adapted from (88) and (98a).

PREVALENCE OF FOOD ALLERGY

As noted with other atopic diseases in Westernized cultures, the prevalence of food allergy appears to be on the rise. Peanut sensitization tripled, and reported peanut allergy in children doubled over only a five-year period in both the United States and United Kingdom (38, 105). Studies incorporating diagnostic food challenges currently estimate that the prevalence of peanut allergy in young children may be as high as 1.5% (38, 47). Methods of food preparation, increased use of antacids, and exposure to medicinal creams containing peanut oil have all been proposed as factors contributing to the recent rise in peanut allergy (10, 47, 55, 62, 117, 118).

Despite evidence indicating an increasing prevalence, the actual occurrence of food allergy remains considerably lower than perceived by the public. Two large population-based studies found that, although 40%–60% of parents believed their child's symptoms were related to food consumption, only 30%–40% reported symptoms supporting food allergy, and merely 4%–8% of children had symptoms reproduced by oral food challenges (11, 80). The marked disparity between perceived and physician-confirmed food allergy, even in more selected populations,

has not changed over the past few decades (10–12, 55). The prevalence of food allergy is highest in infants and toddlers. Cow's milk allergy is experienced by 2.5% of infants, and up to 8% of children under 3 years of age have allergy to a limited number of foods, mainly cow's milk, egg, soy, peanut, wheat, fish, shellfish, or tree nuts (10, 13, 24). The prevalence of food allergy decreases slightly with age, affecting almost 4% of the general population (14, 24).

FOOD ALLERGENS

When one considers the wide variety of foods consumed in the average diet, it is remarkable that allergic responses occur to so few foods. Milk, egg, peanut, soy, and wheat account for 90% of food-allergic reactions in children, whereas peanut, tree nuts, fish, and shellfish account for 85% of reactions in adults and adolescents (83). Foods associated with allergic reactions are generally a main component of one's diet and, therefore, differ according to age and societal eating patterns. For example, sesame seed is a common food allergen in Israel and allergy to bird's nest is frequent in Singapore, but peanut allergy is rare in these countries (29, 37).

The major food allergens are glycoproteins, 10–70 kd in size, that are abundant in the allergenic food. Food allergens are generally water-soluble and resistant to heat, acid, and proteolysis, which enables them to sensitize the host in the gastrointestinal tract (88). Similar types of animal and plant proteins account for most food allergens, with plant allergens being more abundant than animal ones (88). Plant allergens are classified into families and superfamilies according to their structural and functional properties (19, 88). Functional properties of plant allergens include enzymatic activity and defense against pathogens or adverse environmental conditions (19, 88).

IMMUNE-MEDIATED MECHANISMS

Immune responses to allergenic food proteins develop as a result of complex interactions between the food, a variety of effector cells, and their mediators. The majority of acute allergic reactions to foods are due to the engagement of allergen-specific IgE antibody with its high-affinity receptor (FcεRI) that is expressed on mast cells and basophils. The overt signs of food allergy, such as urticaria or angioedema, are often the direct result of circulating food antigen cross-linking IgE bound to its effector cell. This antigen-specific interaction stimulates a series of events that results in release of cellular mediators and cytokines. An unexpected finding was elevated plasma histamine levels in patients with atopic dermatitis and positive food challenges but normal serum tryptase levels in patients with food-induced anaphylaxis (93, 95). Other evidence supporting the central role of basophils, rather than mast cells, in IgE-mediated food allergy is that basophils from patients with food allergy and atopic dermatitis have increased spontaneous

release of histamine, which declines to control levels after the causal food is restricted from the diet (91).

The manifestation of allergic reactions to foods not only depends upon a humoral response but also is largely dependent upon preceding cellular mechanisms that are just being elucidated. The critical step for the development of IgE-mediated immune responses is the differentiation of CD4+ T lymphocytes into one of two distinct phenotypes, Th1 or Th2, which differ in their cytokine profiles. Th1 cells produce high levels of IFN-gamma and IL-2, which promote cell-mediated immune responses to intracellular pathogens by activation of cytotoxic T cells or macrophages (56, 81). Th2 responses enhance humoral immune responses to extracellular organisms and also provide support for eosinophils and mast cells (56, 81). Atopic patients favor a Th2 phenotype, characterized by secretion of interleukin (IL)-4, IL-5, and IL-13 and IgE antibody production in response to foreign proteins (42, 56). The skewed Th2 response observed in atopics may manifest early in life as a result of genetic susceptibility and intrauterine exposures (122).

Lymphocytes isolated from patients with atopic dermatitis and food allergy proliferate when stimulated in vitro with food antigens to which they are sensitive (52, 97). Unfortunately, increased lymphocyte proliferation is too nonspecific of a sign of cellular activation to prove a link between the food and a clinical reaction. Furthermore, lymphocyte proliferation to food antigens does not necessarily indicate an abnormality because it may also be observed in cells from subjects without food allergy (41, 97). Therefore, lymphocyte proliferation assays with specific food antigens are not helpful in the diagnosis of food allergy (41), but they have enabled investigators to characterize the food-specific T cells involved in food allergy.

Patients with food allergy display a characteristic Th2 phenotype compared with nonatopic controls after in vitro stimulation of peripheral blood mononuclear cells (PBMCs) with mitogens or food antigen (2, 24). However, T cell clones (TCCs) derived from polyclonal T cell responses in food antigen-induced proliferation assays provide the most detailed analyses of the immune responses at the individual-cell level. In agreement with previous studies of PBMCs, food-specific TCCs from allergic donors show highly polarized Th2 responses (7, 30, 97, 116).

Peanut antigen stimulates Th2 cells in peanut allergic donors but Th1 cells in children who have either outgrown their peanut allergy or who are tolerant to peanut, similar to that seen after stimulation with nonallergenic food antigens (116). Patients with atopic dermatitis and egg allergy demonstrate analogous profiles when the atopic dermatitis is inactive and egg is tolerated (68). Similarly, Th2-skewed responses were observed in TCCs from patients with atopic dermatitis and cow's milk allergy when compared with patients with atopic dermatitis who were tolerant to milk (97). The observation that the same foods stimulate T helper cells with distinct cellular phenotypes predicted by host factors and clinical reactivity suggests that food tolerance in nonatopic patients or resolution of food allergy in atopic ones is accompanied by the development of a Th1 response.

Clinical implications of defining cellular phenotypes or observing a transition from one phenotype to another are uncertain. However, analyses of the antibody responses to food proteins may have clinical implications. Several individual major and minor allergens often comprise allergenic foods. Casein is one of the major allergens for cow's milk allergy and ovomucoid for egg allergy (25, 28). Numerous epitopes on each allergen have been identified based on their ability to stimulate T-cell proliferation and to bind IgE or IgG. The structure of these epitopes is generally either linear or conformational. In general, food allergen epitopes are linear, whereas airborne allergens are conformational. Epitopes often have overlapping regions that bind both IgE and IgG, but they may also have unique amino acid sequences that are only recognized by one or the other antibody (28). Immunodominant epitopes are defined as those recognized by >50% of allergic patients (9).

Sera from food allergic patients show significant variability with respect to epitope binding by antibody. Patterns of epitope binding and clinical correlates have been demonstrated with a few food allergens. IgE binding to linear, rather than conformational, epitopes may predict persistence of egg and cow's milk allergy (25, 28, 119). With regards to peanut, differential epitope binding of IgE distinguishes those patients with symptomatic peanut allergy from those who either outgrew peanut allergy or who were merely sensitized but clinically tolerant to peanut (9). The size of the skin-prick test or level of food-specific IgE does not correlate with the severity of clinical reactions, but patterns of epitope binding may correlate with the severity of clinical reactions to peanut (101, 104). IgE binding to many epitopes correlated with a history of multisystem reactions to peanut, whereas IgE binding to only a few epitopes correlated with reactions limited to the skin (101). Greater specific IgE diversity has also been observed in patients with persistent allergy to milk, egg, and peanut compared with those with transient allergy (9, 26, 28, 45).

In addition to demonstrating varied humoral responses to foods, patients also exhibit differences in cellular characteristics that may determine the clinical manifestations of their immune response to the food. Cutaneous lymphocyte antigen (CLA) is a homing receptor expressed on memory T cells that infiltrate the skin. Stimulation of PBMCs with casein from patients with milk-induced urticaria or milk-induced atopic dermatitis selectively activates CLA-bearing CD4+ lymphocytes compared with nonatopic controls or patients with milk-induced gastrointestinal symptoms (1, 8). Therefore, differential expression of this homing receptor on antigen-specific T cells may determine the skin as the target organ for abnormal immune responses to food. In contrast, $\alpha 4\beta 7$, a T-cell surface molecule expressed on memory T cells in the gut-associated lymphoid tissue, is upregulated in PBMCs isolated from children with cow's milk allergy after stimulation with beta-lactoglobulin, but its expression does not correlate with clinical reactions involving the gastrointestinal tract (32). Antigen-presenting cells may also play an important role in the development and manifestation of food allergy based on their ability to induce either a Th1 or Th2 response and to influence target organ involvement

by migrating to various sites (18, 27, 53). Last, regulatory cell populations may play a role in the development of IgE and cell-mediated food allergy by failing to induce or maintain oral tolerance (7, 27, 49, 73).

The Th1/Th2 paradigm provides a working model for the development of allergic responses to foreign proteins whereby Th2 lymphocytes stimulate IgE production, recruit eosinophils, induce an inflammatory response, and provide positive feedback to effector cells. In this regard, IgE mediates classic food allergic reactions: those that are immediate, reproducible, and readily diagnosed by detection of food-specific IgE. However, it is clear that other immunologic reactions to food occur in the absence of demonstrable food-specific IgE antibody in the skin or serum. These reactions are labeled cell-mediated or non-IgE-mediated responses to food. They are less well characterized, typically a result of chronic inflammation in the gastrointestinal tract.

CLINICAL PRESENTATION

The spectrum of clinical symptoms associated with food allergies mainly includes the gastrointestinal, integumentary, and respiratory systems. Regardless of the targeted organ system, the clinical characteristics of the abnormal immune responses usually distinguish those mediated by IgE antibody from those that are not (Table 1). IgE-mediated food allergy occurs rapidly, often within minutes but not longer than two hours, after ingestion of the causal food (13, 14, 22, 89, 94). IgE-mediated symptoms are also reproducible: They occur after each ingestion of the food, even of trivial amounts, and each food tends to affect the same target organ(s) in an individual (96). By characterizing food allergies according to their relationship to IgE antibody, the investigator is able to purposefully choose appropriate diagnostic tests to evaluate an individual's symptoms.

The most common symptoms associated with IgE-mediated food allergy involve the skin and gastrointestinal tract: urticaria, angioedema, pruritis, nausea and vomiting, abdominal pain or cramping, and diarrhea (13, 14, 22, 88, 89, 94). Respiratory and ocular symptoms of IgE-mediated food allergy often accompany skin and gastrointestinal symptoms but rarely occur in isolation (13, 14, 16, 22, 94). These symptoms may include ocular injection, sneezing, rhinorrhea, nasal congestion, coughing, hoarseness, stridor, and wheezing. Anaphylaxis is the most severe IgE-mediated response to food. This term implies multisystem organ involvement and varies in severity from mild to fatal (20, 87).

Pollen–food allergy syndrome (oral allergy syndrome) is an unusual manifestation of IgE-mediated food allergy where the primary sensitization occurs in the respiratory tract to inhaled pollens that cross-react with food allergens (72). Sensitized patients then develop immediate, localized oropharyngeal symptoms (itching, burning, swelling, erythema) when they ingest fresh fruits and vegetables with proteins homologous to the pollen (84, 90). The symptoms rarely extend beyond the lips and oropharynx and do not occur when the food is cooked, although

TABLE 2 Pollen-food allergy syndrome: cross-reactive pollens and foods

Birch pollen	Apple
	Apricot
	Carrot
	Celery
	Cherry
	Hazelnut
	Peach
	Pear
	Plum
Ragweed pollen	Banana
	Cucumber
	Kiwi
	Melon
Mugwort pollen	Carrot
	Celery

exceptions have been reported to celery, soybean, carrot, and hazelnut (3–5, 39, 63, 66, 84, 90). The list of foods associated with pollen–food allergy syndrome is continually expanding, and there is considerable in vivo and in vitro cross-reactivity between related fruits (Table 2).

The main pollens associated with pollen-food allergy syndrome are birch, ragweed, and mugwort. When foods with cross-reacting proteins are ingested, clinical symptoms may be more prominent after the relevant pollen season (84, 90). The allergens are thought to be heat and acid labile, which is different from most food allergens (88). The sensitivity to heat also makes diagnosis with commercial food extracts less reliable because the causative allergens may not be present after processing. The diagnosis of pollen-food allergy syndrome can be made by first pricking the proprietary skin test device into the fresh food and then into the skin (71). This procedure should be performed on a nonallergic control and appropriate positive and negative controls should be placed on the patient. Assays using recombinant allergens may be more sensitive than those using purified food extracts, but they are not yet commercially available (63, 72). Patients with severe symptoms or those who remain sensitive to cooked forms of the fruits or vegetables may be sensitized to pathogenesis-related proteins, such as the lipid transfer protein, which are not cross-reactive with pollens (72). Severe reactions to the lipid transfer protein in peach, hazelnut, cherry, apple, and maize have been reported in southern European patients without birch pollen allergy (72). Although these patients react to foods typically associated with pollen–food allergy syndrome, several unusual features (absence of pollinosis, reactions that extend beyond the oropharynx, and heat-stable allergens) are more consistent with conventional food allergy than with the pollen–food allergy syndrome.

Mixed IgE- and cell-mediated food allergy includes the allergic eosinophilic gastrointestinal disorders, atopic dermatitis, and asthma. These are chronic disorders characterized by eosinophilic infiltration of the skin, esophagus, stomach, intestine, and/or lung. Many patients have peripheral blood eosinophilia and demonstrate food-specific IgE (51, 90, 114). Patients with eosinophilic gastrointestinal disorders often have relapsing symptoms that may not respond by only restricting foods to those in which IgE is detected, suggesting an alternative pathophysiologic mechanism (114). Symptoms of eosinophilic esophagitis or gastroenteritis often mimic those of gastroesophageal reflux but do not respond to conventional treatment (50, 114). Specific symptoms that favor eosinophilic esophagitis or gastroenteritis over a pure IgE-mediated food allergy include profound disinterest in eating, food impaction, gastric outlet obstruction, emesis of material resembling uncooked egg whites, abdominal pain, early satiety, gastric bleeding, and failure to thrive (50, 51, 70, 90, 114).

A subset of patients with eosinophilic esophagitis are responsive to limited dietary manipulations, whereas others require treatment with steroids or an L-amino acid–based formula (33, 50, 51, 59, 70, 90, 113, 114). It is difficult to predict which patients will need more aggressive treatment based on history and allergy testing alone. In those situations, in addition to first-line diagnostic testing, patch testing, diet diaries, prolonged trial elimination diets to allow for resolution of tissue eosinophilia, and repeated food challenges coupled with tissue biopsies may be necessary to establish a pathophysiologic role for food.

More than one third of patients with moderate to severe atopic dermatitis have IgE-mediated food allergy, and limited food elimination diets improve the skin condition (21, 22, 82, 83, 89, 94). The late-phase IgE response, characterized by infiltration of eosinophils, neutrophils, monocytes, and lymphocytes, contributes to exacerbations of atopic dermatitis (21, 22, 83). Therefore, these patients may not provide a history to suggest food allergy or develop immediate food-induced symptoms, especially if the food is routinely ingested. After a period of dietary elimination, reintroduction of the food results in immediate cutaneous and/or gastrointestinal symptoms. Because of its frequent association with food allergy, clinicians caring for patients with refractory atopic dermatitis ought to consider referral for allergy testing to a limited panel of foods (21).

Asthma is a chronic inflammatory disorder of the airways due to a complex interplay of genetics, the environment, and the immune system. It is characterized as a mixed IgE- and cell-mediated immune response due to its involvement of mast cells, eosinophils, and T lymphocytes as well as specific IgE antibody production to inhaled and ingested allergens. Asthma is clearly a risk factor for fatal food-induced anaphylaxis (15, 95). Recently, the corollary has been studied and sensitization to food allergens appears to be a risk factor for severe asthma (79, 121).

Cell-mediated food allergy represents a heterogeneous group of disorders caused by ingestion of common food proteins that do not initiate mast cell or basophil degranulation. Immunologic mechanisms for these disorders are supported by the presence of lymphocytes, eosinophils, and/or mast cells in relevant tissues.

Food protein-induced enterocolitis affects young infants and is characterized by irritability, lethargy, and/or dehydration from protracted vomiting and diarrhea (90, 103). As expected in this age group, cow's milk and soy protein are the most frequently implicated proteins. Infants with this disorder appear chronically ill if continued ingestion of the protein leads to anemia and failure to thrive (90). Because food challenges can cause rapid onset of symptoms and hypovolemic shock, the diagnosis is often made with a suggestive history if the symptoms remit after elimination of cow's milk or soy protein. In contrast to IgE-mediated cow's milk allergy where only 14% are also allergic to soy protein, at least half of infants with food protein-induced enterocolitis are sensitive to both proteins (103, 127). Fortunately, the symptoms resolve within about one week after introducing a hydrolyzed casein- or amino-acid-based formula, and the sensitivity resolves between 18 and 36 months of life (90).

Food protein-induced proctocolitis also occurs in the first few months of life but does not result in systemic illness. Infants appear healthy and present with normally formed, blood-streaked stools (90). Infants with this disorder are sensitive to cow's milk or soy protein, and most are exclusively breastfed. The hematochezia usually resolves within 72 hours of eliminating the allergen, including that in the maternal diet for breast-fed infants, and the foods are generally tolerated by one year of age (90). A similar syndrome associated with shellfish has been described in adults (88).

Food protein-induced enteropathy is mainly distinguished from the other non-IgE-mediated disorders by a malabsorptive process leading to diarrhea or steatorrhea, failure to thrive, hypoproteinemia, and edema (90). With the most frequent cause of this disorder, hypersensitivity to cow's milk, milk-specific IgA and IgG are elevated, but IgE is not (90). This disorder may affect toddlers as well as infants, and symptom resolution requires a longer amount of time after elimination of the causal protein, up to three weeks. Food challenges for dietary protein enteropathy may take several days to produce symptoms but do not cause the severe symptoms associated with protein-induced enterocolitis. The sensitivity resolves in two to three years.

Celiac disease is a specific, but more extensive, type of the dietary protein enteropathy described above (90). Patients with celiac disease are sensitive to cereal grains containing gluten, including wheat, barley, and rye. The sensitivity is lifelong and is strongly associated with HLA-DQ2 (and DQ8) haplotypes (31, 54, 90). Patients with celiac disease present with a variety of gastrointestinal symptoms, mainly diarrhea, but they may also be asymptomatic (31). Disorders associated with an increased prevalence of celiac disease include selective IgA deficiency, Down syndrome, diabetes mellitus, thyroid disease, and dermatitis herpetiformis (90). Detecting antigliadin, antiendomysial, and antitissue transglutaminase of the IgA isotype and antigliadin of the IgG isotype may support the diagnosis, but the diagnosis is best made with a small bowel biopsy demonstrating total villous atrophy. A biopsy is essential for diagnosing celiac disease in patients with selective IgA deficiency or other disorders of immunoglobulin synthesis. Two small bowel biopsies, first to support the diagnosis and second to demonstrate mucosal

recovery after instituting a gluten-free diet, are generally recommended to confirm the diagnosis of celiac disease (31). A second biopsy is also useful to detect noncompliance with the gluten-free diet, which is associated with increased risk of malignancy (90). The inclusion of oats in gluten-free diets remains controversial, mainly due to the potential contamination of oats with gluten-containing grains (44, 54).

Symptoms of mixed IgE- and cell-mediated food allergy often overlap (vomiting, diarrhea, failure to thrive, and pain) but the disorders are very different in regard to the pathophysiology, response to diet, and natural history. Table 3 provides brief clinical characteristics to help differentiate the gastrointestinal disorders associated with mixed or cell-mediated immunologic responses to food.

The last cell-mediated food allergy disorder involves the respiratory system. Heiner's syndrome is a rare, potentially fatal, form of pulmonary hemosiderosis induced by cow's milk (88). Otitis media, migraine headaches, and behavioral complaints have not been convincingly linked to food allergy (10, 55).

DIAGNOSIS

The diagnosis of food allergy can often be made or eliminated with a focused history and physical examination. Critical elements of the history include (*a*) food suspected of provoking adverse reaction, (*b*) quantity of food required to provoke symptoms, (*c*) length of time from ingestion of food to onset of symptoms, (*d*) detailed description of symptoms, (*e*) reproducibility of symptoms with other ingestions of same food, (*f*) additional factors required to elicit symptoms such as exercise or eating fresh versus cooked food, and (*g*) length of time since last reaction or ingestion of suspected food (67).

Because these reactions typically occur unexpectedly outside of a medical setting and may provoke a great deal of anxiety, the history is often inaccurate and easily subject to observer bias. Accordingly, the majority of suspected food allergic reactions are not substantiated by a DBPCFC (11, 13, 14, 80). The most favorable history for establishing a link between a food and reported symptoms is that of a recent episode of anaphylaxis occurring immediately after the ingestion of an isolated food such as fish or peanut.

If the medical history does not clearly reveal an association between a suspected food and the patient's symptoms or if it fails to identify a specific food, a diet diary may be useful. The ability of diet diaries to prospectively evaluate a patient's response to food ingestion without relying on the patient's or parent's recollection of the event is especially valuable for chronic diseases with fluctuating symptoms such as atopic dermatitis or highly variable behavioral reactions. Patients and/or their parents are asked to record all foods ingested and any symptoms that they experience over a designated period. The evaluating physician then reviews the diary for evidence that a particular food and clinical symptoms are related. For example, ingestion of a particular food consistently followed by the symptom

TABLE 3 Brief clinical characteristics of mixed IgE and cell-mediated gastrointestinal food allergy

	Age at onset	Symptoms	Response to diet	Natural history	Unique characteristics
Allergic eosinophilic esophagitis	Biphasic: infancy or adolescence	Disinterest in eating Food impaction Mucoid emesis Dysphagia	Variable May need hydrolyzed or L-amino acid formula	Relapsing	Responsive to local, nonabsorbed (inhaled) steroids
Allergic eosinophilic gastroenteritis	Any age	Projectile vomiting Gastric outlet obstruction Early satiety Abdominal pain Ascites	More likely in younger patients	Often prolonged	Steroid responsive
Food protein-induced enterocolitis	Infancy	Irritability Dehydration Lethargy Anemia	3–10 days Hydrolyzed casein formula	Resolves by 3 years	May have life-threatening reaction to food challenge
Food protein-induced proctocolitis	<6 months	Blood-streaked stools Irritability	3 days Hydrolyzed casein formula Possibly restricted maternal diet	Resolves by 1 year	Healthy appearance Often breastfed newborns
Food protein-induced enteropathy	Infancy to 2 years	Malabsorption Edema Anemia	3 days–3 weeks Specific antigen elimination	Resolves 2–3 years	Steatorrhea Hypoproteinemia
Celiac disease	>6 months	Malabsorption Edema Iron-deficiency anemia Oral ulcers	3 days–3 weeks Gluten-free diet	Lifelong	Genetic predisposition Associated disorders

being evaluated suggests a food allergy and the diagnostic workup may proceed. Rather than disclosing unrecognized food allergy, diet diaries often rule out allergy by revealing ingestions of the suspected food that are clearly not associated with clinical symptoms. In these cases, no further evaluation is required.

Given that most evaluations for suspected food allergy take place after the event in question, the physical examination is likely to be unrevealing. Regardless, the physical examination should not be overlooked because it may reveal clues that the patient is at increased risk for food allergy, as is the case with atopic dermatitis (21, 22, 82, 94). Additional features noted in the history or on the physical examination may also affect therapeutic decisions. For example, all asthmatics with food allergy, regardless of the severity, require self-injectable epinephrine for emergency use (15, 87, 95).

The gold standard for diagnosing food allergy is the DBPCFC. Although this procedure can be performed in an office setting, it is time consuming and not practical for the initial evaluation of suspected food-induced symptoms. Fortunately, the history and physical examination may help in the selection of other appropriate tests for the initial evaluation of reported symptoms, thereby limiting the need for food challenges.

Reproducible symptoms such as hives, repetitive vomiting, or angioedema occurring within two hours of ingestion of a food suggest an IgE-mediated mechanism. Techniques that detect food-specific IgE include in vivo allergy skin-prick tests and in vitro assays. Allergy skin testing is easily and safely performed, even in small infants, by applying purified food extract (1:10 or 1:20 w/v) by the prick or puncture technique (14, 67).

Allergy skin-prick tests with food extracts are very sensitive, but they lack specificity. In patients with atopic dermatitis, the sensitivity of skin-prick tests is generally $\geq$90%, but the specificity only approximates 50% (92). In other words, a positive skin test merely indicates that the patient has been sensitized to a particular food. This high rate of asymptomatic sensitization to foods mandates that allergy skin-prick testing be reserved for those foods historically associated with adverse reactions. Otherwise, overdiagnosis of food allergy and unnecessary food-elimination diets may result from utilizing a large panel of allergy skin tests in nonatopics, patients who eat the foods without experiencing adverse reactions, or patients who have never eaten the food.

The value of allergy skin-prick tests can be further addressed by their correlation with DBPCFCs. In this regard, the positive predictive accuracy of allergy skin-prick tests to foods is rarely higher than 50%, whereas the negative predictive accuracy is greater than 95% (13, 89, 92).

In summary, the diagnostic characteristics of allergy skin-prick tests indicate that negative tests essentially rule out IgE-mediated food allergy, whereas positive tests often require further investigation to confirm a cause-and-effect relationship between food ingestion and clinical symptoms (13, 89). The exception to this approach is the case of anaphylaxis after ingestion of an isolated, common allergenic food, where a positive skin test sufficiently confirms the diagnosis. Intradermal

TABLE 4 Diagnostic food allergen-specific IgE levels (CAP FEIA System®)

Food	kU_A/L	Positive predictive value
Egg	7	98%
Infants ≤2 years	2	95%
Milk	15	95%
Infants ≤2 years	5	95%
Peanut	14	100%
Fish	20	100%
Tree nuts	~15	~95%

Adapted from (88).

testing with food extracts is not recommended due to the increased risk of systemic reactions and poor predictive accuracy (85).

Food-specific IgE may also be detected by in vitro methods including radioallergosorbent tests or enzyme-linked immunosorbent assays. In general, they are no better able to predict reactions on DBPCFC than are skin-prick tests (89). A modified in vitro assay, CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden), increases the allergen-binding capacity of previous techniques and quantitates the results as kilounits of allergen-specific IgE per liter (kU_A/L) (92). This quantitative method is more sensitive than were previous qualitative or semiquantitative ones. More importantly, diagnostic levels have been established for a few foods (egg, milk, peanut, fish) that correlate well with positive outcomes on oral food challenges (17, 36, 86, 92) (Table 4). With a compatible history, a result greater than the diagnostic level supports the diagnosis of food allergy for egg, milk, peanut, and fish.

For other foods, CAP system FEIA is able to quantify food-specific IgE, but diagnostic levels have not been established. It is important to note that, although the likelihood of clinical reactivity increases with increasing levels of food-specific IgE, the actual level has no correlation with the severity of the reaction. This point is important for patients and parents to understand so that those with higher food-specific IgE levels are not overwhelmed by the fear of anaphylaxis and those with lower levels are not tempted to stray from a strict food-elimination diet.

Results lower than diagnostic levels do not indicate a lack of clinical reactivity; patients with those levels require an oral food challenge to determine clinical reactivity. In brief, the food-specific IgE level should not affect any clinical decisions other than whether food allergy is present (with 95% certainty). In recent years, appropriate use of CAP system FEIA tests has reduced the need for oral food challenges that carry the additional risk of a severe allergic reaction (75).

The oral food challenge is the only test with the capacity to definitively diagnose food allergy and is not limited to those reactions mediated by IgE antibody (16, 103). Food challenges are performed by feeding the patient sequential, graded amounts of the food in question and carefully observing for adverse effects. To

ensure that the procedure yields meaningful information, the food in question must eliminated from the diet for at least two weeks prior to the challenge and the patient should be asymptomatic at the time of the challenge. Tolerance of a typical serving size of the food or 8–10 grams of lyophilized food protein provides strong evidence against allergy. The initial serving size is typically less than that required to elicit symptoms (25–500 mg) and doses are increased at intervals longer than that reported between ingestion and onset of symptoms (15–60 minutes). Depending upon the circumstances, oral food challenges may be open, single blind, or double blind.

For an open challenge, the food as it is normally prepared is fed to the patient. Typical serving sizes for open challenges are 8 oz milk, 1 egg, 1 slice of bread, and 2 tablespoons of peanut butter. The simplicity of open challenges makes them ideal as screening tools for foods unlikely to cause symptoms. The obvious disadvantage is that they are subject to observer bias and may need to be verified by a DBPCFC.

Single-blind challenges use a vehicle to mask the food being challenged so that the patient, but not the investigator, is unaware of the ingredients being fed. Vehicles used for blinding include applesauce, grape juice, oatmeal, or any food that the patient tolerates. Capsules may also be used to blind foods for older children. Single-blind challenges are generally employed to remove subject bias but may also be necessary to disguise an undesirable odor or taste of the food.

DBPCFCs are best utilized for equivocal open challenges or as a research tool because they require more time and staff support. For this type of challenge, both the food and placebo are masked in a vehicle and fed to the patient in a random order. Neither the investigator nor the patient is aware of the contents being fed. DBPCFCs are essential for evaluating the role of food allergy in chronic disorders such as atopic dermatitis and for subjective or behavioral symptoms because they completely eliminate observer bias. False negatives rarely occur with DBPCFCs and are usually due to administering an insufficient dose to elicit a reaction. For this reason, a negative DBPCFC must be followed by an open feeding of the food.

If the symptoms under evaluation are not consistent with an IgE-mediated reaction, oral food challenges may be the only valid diagnostic approach. Other situations in which oral food challenges are helpful include (*a*) when many foods are implicated and symptoms resolve only after removal of all of those foods, (*b*) if removal of a food from the diet had no effect on symptoms but the food is still suspected of causing symptoms, and (*c*) to determine when a child is no longer clinically sensitive to a food (16, 102). Utilizing oral food challenges in these settings more often results in liberalizing the patient's diet rather than restricting it. Although allergy skin-prick tests and food-specific IgE levels may indicate sensitization to different foods in the same botanical family or animal species (e.g., soybean and peanut or cow's milk and beef), patients rarely have positive food challenges to related foods (21, 22, 94).

When the patients are carefully selected and the challenge is performed according to standard protocols, oral food challenges are safe procedures. Although positive reactions to oral food challenges are not infrequent, most reactions are

not severe (16, 75, 102). The majority of positive reactions are cutaneous or gastrointestinal and require no treatment or antihistamine only (75). These risks are undoubtedly outweighed by the improved quality of life that likely follows a negative challenge.

If allergy skin tests, CAP-FEIA levels, and/or food challenges fail to identify food allergy, elimination diets may be utilized. Suspected foods are eliminated from the diet, and the patient is observed for a change in symptoms. If many foods are under suspicion, an elemental diet may be necessary to ensure complete elimination of offending foods. Resolution of symptoms after elimination of the food and recurrence of symptoms after its reintroduction suggest a pathophysiologic role for the food. If there is no resolution of symptoms, food allergy is not likely. Often these diets are attempted without medical supervision and then prompt referral to a subspecialist, either for further evaluation of nonresponders or for confirmation of positive results. Similar to that of food diaries, these diets are often of little diagnostic value except for in the evaluation of non-IgE mediated processes (90).

Other tests employed in the evaluation of adverse food reactions include endoscopy and biopsy for non-IgE-mediated food allergy and the breath hydrogen test for lactase deficiency. Allergy patch testing has been proposed by some to have utility in determining foods associated with allergic eosinophilic esophagitis, but the technique and testing materials have not been standardized (113). Presently, basophil histamine release assays are best utilized as a research tool (91). Applied kinesiology, food-specific IgG or IgG_4 antibody levels, food immune complex assays, cell-mediated cytotoxicity assays, and lymphocyte stimulation tests should be regarded as unproven or unconventional methods for the diagnosis of adverse food reactions (41, 65, 115).

TREATMENT

There is no effective method to cure food allergy. Therefore, the management of children with food allergy focuses on the prevention of food-induced symptoms by elimination of the causal food(s) from the diet. Parents and caregivers are advised to scrutinize all food labels for the presence of those allergens that should be avoided. Compliance with an elimination diet is time-consuming, inconvenient, and requires a great deal of education and commitment on the part of the patient and all caregivers. In this regard, the Food Allergy and Anaphylaxis Network (http://www.foodallergy.org), a nonprofit patient advocacy group, is an invaluable resource for parents as well as physicians. Registered dieticians can often provide additional educational assistance on an ongoing basis.

Avoidance of ubiquitous food proteins such as egg or milk is particularly difficult. Even the most vigilant patients accidentally ingest a food to which they are sensitive (12). These accidents occur most frequently away from the home such as in daycare, school, or restaurants, where a person unfamiliar with food allergy may

be responsible for determining the safety of the food (15, 95). Cross-contamination of food may also lead to inadvertent ingestion of restricted foods. The food may be contaminated during the manufacturing process if the same equipment used to process foods with and without a food allergen is not cleaned adequately between batches. Cross-contamination is likely to occur in other settings, such as in bulk food bins and at salad bars, or during the preparation of different foods with shared cooking utensils. Fortunately, there is little risk from topical or inhaled environmental exposures to food allergens (74, 110).

Incorrect or ambiguous food labels may result in accidental ingestion of the offending allergen. The United States Food and Drug Administration requires food manufacturers to declare all functional ingredients on food labels. However, some of the terms used do not clearly indicate the presence of a food allergen. For instance, "natural flavorings" may contain several individual ingredients including whey, or "vegetable proteins" may include soybean. The Food Allergen Labeling and Consumer Protection Act (FALCPA) took effect January 1, 2006; it addresses some of the limitations of current food-labeling practices. FALCPA requires food manufacturers to state explicitly the presence of the eight major food allergens: milk, egg, wheat, soybean, peanut, tree nuts, fish, and shellfish. Under this legislation, the language must be understandable to the average consumer, and colorings, flavorings, or any other additives are not exempt.

Because inadvertent food ingestions cannot always be avoided, patients and their caregivers must be equipped to manage acute food-induced reactions. Individualized treatment plans should be prepared in advance and medications readily available. Epinephrine (0.01 ml/kg aqueous epinephrine 1:1000, maximum dose 0.3–0.5 ml) is the drug of choice for the treatment of food-induced anaphylaxis (87). Delayed administration of this medication correlates with poor outcomes (15, 95, 125). Prompt elevations in plasma epinephrine levels are desirable and achieved more readily after intramuscular injection compared with the subcutaneous route (108, 109).

The EpiPen™ (Dey; Napa, California) contains a fixed dose of epinephrine in a self-injectable device allowing for rapid, intramuscular administration of the medication. Use of an auto-injector is preferable to withdrawing a designated dose of the medication from an ampule prior to injection because the latter method leads to imprecise dosing and delayed administration (107). The EpiPen Jr™, which contains 0.15 mg epinephrine, is prescribed for children 15–30 kg; the EpiPen™, which contains 0.3 mg epinephrine, is prescribed for children >30 kg. Another device, Twinject™ (Verus Pharmaceuticals, Inc.; San Diego, California), will soon be available for self-administration of epinephrine. It will contain one of the same two fixed doses as the EpiPen™ but will have the option to administer a second dose of epinephrine from the same device. The first dose is administered with an auto-injector; the second is injected manually with a prefilled injector.

Epinephrine is clearly indicated for patients experiencing respiratory, cardiovascular, or neurologic compromise, but more specific guidelines for its use have

not been established (87). The importance of gastrointestinal symptoms is particularly controversial because they may signify a more serious reaction or quickly resolve without any medical intervention (20). In uncertain situations, the decision to treat with epinephrine not only depends upon the symptoms that the patient is acutely experiencing but also upon factors known to correlate with outcomes of food-induced anaphylaxis. A history of a previous life-threatening reaction, allergy to peanut, tree nuts, or seafood, concomitant diagnosis of asthma, or a reaction occurring outside of the home all correlate with poor outcomes; patients with these risk factors should be treated aggressively. These factors may also be considered when determining which of the two fixed doses of epinephrine to prescribe for children (87, 106). Children between 20 and 30 kg with risk factors for severe food-induced anaphylaxis may be prescribed a dose of 0.3 mg, which will provide more epinephrine than the recommended 0.01 mg/kg, rather than a subtherapeutic dose (87). The importance of asthma as a risk for fatal food-induced anaphylaxis is particularly important and is not limited to those with poorly controlled respiratory symptoms.

Future directions in food allergy research are focusing on decreasing clinical reactivity after food allergy is established. Rush immunotherapy specifically for the treatment of peanut allergy demonstrated efficacy in some patients, but significant adverse reaction rates made it unsuitable for clinical use (69). More recently, a phase I trial with humanized, monoclonal anti-IgE antibody (TNX-901) proved beneficial for some patients with peanut allergy by increasing the threshold dose of peanut required to elicit symptoms (57). Although ongoing treatment would be required to prevent a reaction that may or may not occur again, one advantage of this approach would be its applicability as a single therapy for a patient with multiple food allergies.

Other novel types of vaccines for immunotherapy under investigation for the treatment of food-induced anaphylaxis include (*a*) plasmid-DNA immunotherapy, (*b*) peptide fragments: "overlapping" peptides, (*c*) cytokine-modulated immunotherapy, (*d*) immunostimulatory sequence-modulated immunotherapy, (*e*) bacterial-encapsulated allergen immunotherapy, (*f*) "engineered" recombinant protein immunotherapy, (*g*) homologous protein immunotherapy, and (*h*) oral or sublingual immunotherapy (23, 58, 78, 123).

NATURAL HISTORY AND PREVENTION

Historically, allergies to foods such as milk, egg, wheat, and soybean are expected to be outgrown after a period of dietary exclusion, whereas allergies to peanut, tree nuts, fish, and shellfish are not (94, 96, 124). Although these generalizations are useful for the initial management of most patients with food allergy, exceptions are not uncommon in children. A thoughtful approach to individual children includes serial assessments of their clinical reactivity, either to inadvertent ingestions of the causal food or with supervised food challenges.

The natural history of allergy to foods responsible for the majority of adverse reactions has been studied in detail. Allergy to milk and egg is often outgrown by three to five years of age, but estimates of those who do not achieve tolerance may be low (86, 99, 100, 124). An oral food challenge to milk or egg may be considered around three years of age if more than one year has elapsed since the last clinical reaction. Persistence of a positive skin-prick test does not indicate persistent food allergy; reliance on this diagnostic method alone may unnecessarily prolong the period of dietary exclusion (94, 96).

In addition to age and time from last reaction, declining food-specific IgE levels may help determine when to perform oral food challenges. In children with atopic dermatitis, the greater the decline in egg- and milk-specific IgE levels over a one-year period, the higher is the likelihood of passing a food challenge (100). This relationship is stronger in those patients less than four years of age and weaker if the same overall change in IgE levels is observed, but over a longer period of time (100). Food challenges may also be considered when no clinical reactions have occurred for at least one year and egg- and milk-specific IgE levels decline below 2 kU_A/L; greater than 50% of these patients have negative challenges (76). It is important to note that a declining or low food-specific IgE level does not distinguish transient from persistent food allergy but merely suggests when an oral food challenge is likely to be negative.

Foods less commonly associated with allergy lack established diagnostic IgE levels and prognostic data. To confirm ongoing allergy to these foods, oral food challenges may be scheduled every one to two years if no clinically significant reactions have occurred. Other indications for performing periodic oral food challenges include (*a*) allergy to multiple foods compromising nutritional requirements, (*b*) allergy to an essential food or to one difficult to exclude from the diet, (*c*) poor quality of life, and (*d*) behavioral or eating disorders as a result of the exclusion diet. The presence of atopic dermatitis or other food allergies, severity of initial reaction, age at presentation, and initial size of skin-prick response or level of food-specific IgE are not sufficient prognostic indicators by themselves but may be considered when designing individual food challenges. For instance, an infant with atopic dermatitis who previously experienced wheezing and vomiting after wheat ingestion might be challenged with a smaller initial dose than would a child whose wheat allergy manifested as isolated urticaria.

The natural history of peanut allergy in young patients is still evolving. It is now apparent that about 20% of these children may develop tolerance to peanut (34, 43, 111). Favorable, but not conclusive, factors for outgrowing peanut allergy include the absence of atopic dermatitis or other food allergies, mild symptoms limited to the skin, and a small initial skin-prick response (<6 mm) or low (<10 kU_A/L) peanut-specific IgE level (34, 43, 111). The current approach to children with newly diagnosed peanut allergy is to measure peanut-specific IgE levels annually and to perform an oral food challenge in patients four years of age or older if the peanut-specific IgE level decreases to <2 kU_A/L (34, 111). Children who outgrow

their sensitivity to peanut are then advised to consume peanut routinely and to have epinephrine available until peanut has been tolerated for one year because up to 8% may develop a recurrence of their allergy (35). Children over five years of age whose peanut-specific IgE level remains >15 kU_A/L or who fail an oral challenge at a lower level are less likely to develop tolerance.

Given the rising prevalence of food allergy, interest in preventing its onset is increasing among parents and practitioners. Primary intervention studies are difficult to design because patients cannot be adequately randomized and compliance with diets cannot be confirmed. Efforts to prevent the development of food allergy focus on high-risk infants, defined by the American Academy of Pediatrics as having one parent or sibling with atopy. Based on interpretations of existing studies for the primary prevention of food allergy in high-risk infants, the American Academy of Pediatrics has encouraged exclusive breastfeeding for four to six months and supplementing with or weaning to an extensively hydrolyzed casein formula. Feeding a partially hydrolyzed formula instead of an extensively hydrolyzed one may not be as protective but certainly calls for further study (120).

Literature reports used to support these recommendations are exceedingly difficult to interpret owing to differences in selection criteria, cointerventions, primary outcomes, and methods to confirm allergy. The most consistent benefit from prolonged breast-feeding and hypoallergenic diets in infancy is a decrease in infantile atopic dermatitis and cow's milk allergy (61, 126). Maternal dietary interventions during the third trimester and lactation have not convincingly shown decreased cow's milk allergy in infancy or decreased food allergy, atopic dermatitis, or asthma at older ages (40, 126). Furthermore, dietary manipulations after four to six months of age, such as delaying introduction of egg, cow's milk, peanut, and/or fish, are not likely to prevent or delay the development of atopy. The use of probiotics to induce a Th1 cytokine profile is an exciting approach to preventing food allergy, but it also requires further study (48, 77).

SUMMARY

Although the prevalence of food allergy seems to be increasing, the number of foods associated with food allergy is still restricted to a relatively short list. Egg, milk, and peanuts account for more than 80% of clinically significant reactions to foods. A wide spectrum of symptoms is often attributed to food allergy. The accurate diagnosis of IgE-mediated food allergy is essential because dietary elimination of implicated foods is currently the only accepted treatment. A detailed clinical history and judicious use of tests that measure food-specific IgE have significant utility in selecting causal foods to eliminate from the diet. Oral food challenges are useful to confirm the diagnosis of food allergy and prevent overly restrictive diets. It is hoped that one or more of the food-specific immunotherapy strategies under study will be effective in desensitizing those patients who do not develop tolerance to foods after a period of dietary elimination.

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