Food allergy

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Adverse immune responses to foods affect approximately 5% of young children and 3% to 4% of adults in westernized countries and appear to have increased in prevalence. Food-induced allergic reactions are responsible for a variety of symptoms and disorders involving the skin and gastrointestinal and respiratory tracts and can be attributed to IgE-mediated and non–IgE-mediated (cellular) mechanisms. Genetic disposition and environmental factors might abrogate oral tolerance, leading to food allergy. Disease outcomes are influenced by the characteristics of the immune response and of the triggering allergen. Diagnosis is complicated by the observation that detection of food-specific IgE (sensitization) does not necessarily indicate clinical allergy. Therefore diagnosis requires a careful medical history, laboratory studies, and, in many cases, an oral food challenge to confirm a diagnosis. Novel diagnostic methods, including ones that focus on immune responses to specific food proteins or epitopes of specific proteins, are under study. Currently, management of food allergies consists of educating the patient to avoid ingesting the responsible allergen and to initiate therapy (eg, with injected epinephrine for anaphylaxis) in case of an unintended ingestion. Improved therapeutic strategies under study include oral and sublingual immunotherapy, Chinese herbal medicine, anti-IgE antibodies, and modified vaccines. (J Allergy Clin Immunol 2010;125:S116-25.)

Key words: *Food allergy, food hypersensitivity, oral tolerance, gastrointestinal food hypersensitivity, food allergens, anaphylaxis*

Abbreviations used
OFC: Oral food challenge
OIT: Oral immunotherapy
SPT: Skin prick test

The term *food allergy* is used to describe an adverse immune response to foods.[1] Considering allergy to milk, egg, peanut, and seafood in a meta-analysis of 51 studies, self-reported allergy ranged from 3% to 35%, whereas estimates from 6 studies using oral food challenges (OFCs) estimated rates of 1% to 10.8%.[2] In a meta-analysis including 36 population-based studies focusing on allergy to fruits and vegetables (excluding peanut),[3] only 6 included OFCs, and estimates of allergy varied widely from 0.1% to 4.3% for fruits and tree nuts to 0.1% to 1.4% for vegetables and less than 1% for wheat, soy, and sesame. Although an allergy could be triggered by virtually any food, "major allergens" responsible for most significant reactions include milk, egg, peanut, tree nuts, shellfish, fish, wheat, and soy. Allergy to additives and preservatives is generally uncommon.[4]

Food allergy rates vary by age, local diet, and many other factors. Studies in the United Kingdom and North America focusing on peanut indicate that prevalence rates in children have increased, essentially doubling, and exceed 1% in school-aged children.[5] A 2008 Centers for Disease Control and Prevention report indicated an 18% increase in childhood food allergy from 1997 to 2007, with an estimated 3.9% of children currently affected.[6] Extrapolation from US studies indicates approximately 125,000 emergency department visits[7] and 53,700 episodes of anaphylaxis[8] from foods each year. Fatalities are primarily reported from allergic reactions to peanuts and tree nuts, appear to be associated with delayed treatment with epinephrine, and occur more often in teenagers and young adults with asthma and a previously diagnosed food allergy.[9] The determination of accurate food allergy prevalence rates is hampered by the lack of studies applying reliable diagnostic methodologies, such as supervised OFCs, to large unselected populations. Table I presents estimated rates of food allergies in North America based primarily on data from studies conducted there when possible.[2,3,10]

Although prior studies indicated childhood food allergies typically resolved by age 3 years, recent studies, albeit possibly affected by selection bias because of referral patterns, indicated only 11% resolved egg and 19% resolved milk allergy by age 4 years; however, about 80% resolved these allergies by age 16 years.[11,12] Peanut allergy, which is typically considered a persistent allergy, can resolve for about 20% of young children by school age, although recurrence of peanut allergy has also been described primarily in those who tolerated an OFC but did not continue to consume the food.[5] Studies to address the reasons for increased prevalence and persistence of food allergies, focusing primarily on peanut, have included the hygiene hypothesis; changes in the components of the diet, including antioxidants, fats, and nutrients, such as vitamin D; the use of antacids, resulting in exposure to more intact protein; food processing, such as for peanut roasting and emulsification to produce peanut butter compared with fried or boiled peanut; and extensive delay of oral exposure, thus increasing topical (possibly sensitizing) rather than oral (possibly tolerizing) exposure to food allergens.[5,13] Evidence supporting this latter hypothesis is supported by one study showing peanut allergy rates in a school-aged cohort of Israeli Jewish children to be 0.17% compared with those in a cohort of Jewish children in the

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United Kingdom, where the rate was about 10-fold higher (1.85%, $P < .001$), in the context of data showing consumption of peanut at ages 8 to 14 months was 7.1 g in Israel compared with 0 g in the United Kingdom ($P < .0001$).[14] A case-control study additionally found that peanut allergy was associated with household peanut consumption rather than maternal or infant peanut consumption.[15] However, randomized controlled trials are needed to confirm the hypothesis that earlier ingestion of peanut is protective.

TABLE I. Estimated food allergy rates in North America

Prevalence	Infant/child	Adult
Milk	2.5%	0.3%
Egg	1.5%	0.2%
Peanut	1%	0.6%
Tree nuts	0.5%	0.6%
Fish	0.1%	0.4%
Shellfish	0.1%	2%
Wheat, soy	0.4%	0.3%
Sesame	0.1%	0.1%
Overall	5%	3% to 4%

PATHOGENESIS

Oral tolerance induction and immune response to food proteins

The gastrointestinal tract encompasses the largest surface area in the human body and is comprised of a single-cell layer of columnar intestinal epithelial cells separating the internal sterile environment from the external world.[16] Its main function is to process ingested food into a form that can be absorbed and used for energy and growth, while at the same time preventing the penetration of harmful pathogens into the body. An intricate "gastrointestinal mucosal barrier" has evolved that consists of physiologic and immunologic components to accomplish this. The physiologic barrier includes a single layer of epithelial cells joined by tight junctions and covered with a thick mucus layer that traps particles, bacteria, and viruses. Trefoil factors are secreted by mucus-secreting cells of the stomach and intestine to help strengthen and promote restoration of the mucosal barrier. In addition, luminal and brush border enzymes, bile salts, and extremes of pH serve to destroy pathogens and render antigens less immunogenic. The immunologic component consists of innate (polymorphonuclear neutrophils, macrophages, natural killer cells, epithelial cells, and Toll-like receptors) and adaptive immune (intraepithelial and lamina propria lymphocytes, Peyer patches, secretory IgA, and cytokines) cells and factors, which also provide an active barrier to foreign antigens. However, the efficiency of this mucosal barrier in infants and young children is not optimal because of the developmental immaturity of various components of the gut barrier and immune system (eg, the activity of various enzymes is suboptimal in the newborn period and the secretory IgA system is not fully mature until 4 years of age).[16] Consequently, this immaturity might play a role in the increased prevalence of both gastrointestinal tract infections and food allergies seen in the first several years of life. Recently, studies in both murine models and human subjects have suggested that alteration of the physiologic barrier function (eg, decreased gastric acidity caused by potent antacids) can lead to increased IgE sensitization in both children and adults.[17] Additionally, altered intestinal permeability leading to increased exposure to intact proteins might promote sensitization and might enhance the severity of food-induced allergic reactions.[18]

Whereas the systemic immune system is typically confronted with relatively small quantities of foreign antigen and mounts a brisk inflammatory response, the mucosal immune system regularly encounters enormous quantities of antigen and must suppress immune reactivity to food and harmless foreign commensal organisms (ie, develop oral tolerance). Antigen-presenting cells, including intestinal epithelial cells and dendritic cells, and regulatory T cells play a central role in the development of oral tolerance.[16,19,20] Several types of regulatory T cells have been identified in conjunction with intestinal immunity: T_H3 cells, a population of $CD4^+$ cells that secrete TGF-β; T_R1 cells, a population of $CD4^+$ cells that secrete IL-10; $CD4^+$ and $CD25^+$ regulatory T cells; $CD8^+$ suppressor T cells; and γδ T cells.[16] In addition, intestinal epithelial cells can process luminal antigen and present it to T cells on an MHC class II complex but lack a "second signal," thus leading to anergy and suggesting their role in tolerance induction to food antigens as nonprofessional antigen-presenting cells. Despite the evolution of this elegant gastrointestinal barrier, about 2% of ingested food antigens are absorbed and transported throughout the body in "immunologically" intact forms, even through the normal mature gut.[21] In a series of experiments performed more than 75 years ago, Walzer and colleagues[22,23] passively sensitized volunteers with sera from patients with food allergy and demonstrated that immunologically intact antigens cross the mucosal barrier and disseminate rapidly throughout the body to activate local mast cells.

Several nonhost factors can influence the development of oral tolerance, such as physical properties of the antigen and the dose and frequency of exposure. Studies in murine models indicated differences in immune responses depending on the dose of antigen ingested: high-dose tolerance involves deletion of effector T cells, and low-dose tolerance is the result of activation of regulatory T cells with suppressor functions.[16]

Ongoing studies indicate that commensal gut flora also likely play a role in oral tolerance induction, as initially suggested by the observation that mice raised in a germ-free environment do not have normal tolerance.[24] In one study mice treated with antibiotics or lacking Toll-like receptor 4–recognizing bacterial LPSs and then exposed to a sensitizing regimen of peanut were more prone to peanut allergy than wild-type control animals.[25] Population-based observational studies relating the presence of atopic dermatitis to stool bacterial patterns and interventional studies administering probiotics suggest a potential for allergy prevention by creating a tolerogenic bacterial milieu, although clinical studies are conflicting.[26]

IgE-mediated hypersensitivity responses are attributed to the generation of T_H2 cells that produce IL-4, IL-5, and IL-13. Murine models demonstrate a role of T_H2 skewing at the time of gut antigen presentation by dendritic cells.[27,28] To explore the relative role of a T_H2- or T_H1-biased immune response in food allergy, Turcanu et al[29] expanded human peanut-specific T cells *in vitro* from the peripheral blood of patients with peanut allergy using peanut antigen and then stimulated the cells with phorbol 12-myristate 13-acetate and ionomycin to maximize cytokine secretion. Expanded T cells from 9 subjects with peanut allergy were found to be T_H2 biased. However, Thottingal et al[30] measured peanut allergen–driven cytokine responses in short-term primary cultures of PBMCs from adults with peanut allergy and peanut-tolerant adults with or without peanut-specific IgE.

Subjects with positive skin test responses had more frequent or intense IL-5 and IL-13 responses than those without, irrespective of whether they had clinically symptomatic peanut allergy. Surprisingly, the 3 groups were not distinguishable based on IFN-γ responses, which were absent, suggesting that a protective T_H1 bias does not explain the distinction in clinical outcomes, whereas a spectrum of T_H2 responses might.

In susceptible hosts oral tolerance might not develop after antigen ingestion, or it might be bypassed altogether by presentation of proteins through alternate routes, such as the respiratory tract or skin. Oral allergy syndrome/pollen-food–related syndrome is an example in which oral tolerance is bypassed because sensitization occurs through the respiratory route.[31] Respiratory sensitization to Bet v 1 in birch pollen might lead to oral pruritus in allergic patients when eating raw apples because of cross-reactivity to a homologous apple protein, Mal d 1. Application of food proteins to the skin of mice has been shown to result in systemic allergic symptoms after oral exposure.[32,33] As described above, there are epidemiologic studies from Israel and the United Kingdom that support the notion that environmental, rather than or perhaps in the absence of, oral exposure to peanut might promote sensitization and allergy.[13,15] The loss of skin barrier provides a portal for sensitization to food allergens in the environment and is increasingly being considered a potential route by which food allergens can evade oral tolerance.[13]

The immunopathophysiology of non–IgE-mediated gastrointestinal food allergy disorders are also being evaluated. In infants with food protein–induced enterocolitis syndrome, detection of TNF-α from PBMCs cultured *in vitro* with food proteins responsible for the reaction has been shown.[34] Chung et al[35] found increased staining for TNF-α and decreased staining for the regulatory cytokine receptor TGF-β1 in duodenal biopsy specimens of affected infants. More work is clearly needed to elucidate the immunologic basis of this disorder, but these studies suggest that a deficit in TGF-β1 response and excessive TNF-α response might be important pathogenic factors.

Healthy subjects without food allergy frequently have low concentrations of food-specific IgG, IgM, and IgA antibodies in their serum. Food protein–specific IgG antibodies tend to increase in the first months after the introduction of a food and then generally decrease, even though the food protein continues to be ingested.[36] Subjects with various inflammatory bowel disorders (eg, celiac disease, inflammatory bowel disease, and food allergy) frequently have high levels of food-specific IgG and IgM antibodies, but there is no evidence that these antibodies are pathogenic.[37]

The role of food proteins

Allergic reactions to egg, milk, peanut, tree nuts, fish, shellfish, wheat, and soy account for most significant food allergies in the United States, although any food can trigger an allergic response.[38] However, relatively few protein families account for the vast majority of allergic reactions.[39] In a study by Jenkins et al[40] comparing animal food allergens and their human homologs (considering protein families, sequence analysis, and evolutionary relationships), they noted that sequence identities to human homologs of greater than 62% typically excluded the protein from being allergenic in human subjects. Major food allergens share a number of common features; they are water-soluble glycoproteins, 10 to 70 kd in size, and relatively stable to heat, acid, and proteases.

However, it is clear that additional aspects, such as food preparation, can affect allergenicity. One theory proposed to explain a higher rate of peanut allergy in westernized countries, where peanut is consumed roasted, compared with lower prevalence rates in China, where peanut is primarily boiled or fried, regards the differential effect of these preparation methods.[5] The high temperature of roasting (180 °C) peanuts leads to a Maillard reaction that appears to increase stability and allergenicity.[41,42] Another theory posits that emulsification (peanut butter) increases allergenicity through an adjuvant effect.[5] Additional characteristics of the manner in which foods are ingested might be relevant. For example, recent studies suggest that 70% to 80% of young children allergic to milk or eggs can tolerate baked (heat-denatured) forms of the protein but not the unbaked form.[43,44] It is suggested that these children make IgE antibodies primarily to conformational epitopes on the food proteins and represent the children who will naturally outgrow their food allergies.

Two recent studies suggest that the carbohydrate moiety of certain glycoproteins might play a significant role in the allergenicity of food proteins. Shreffler et al[45] showed that glycosylated Ara h 1, a major peanut allergen, but not the deglycosylated form, acted as a T_H2 adjuvant by activating dendritic cells to drive the maturation of T_H2 cells. Additionally, Ara h 1 acts as a ligand for DC-SIGN (dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin, an ITAM I [immunoreceptor tyrosine-based activation motif–containing type II member of the C-type lectin family]), which also has been shown to interact with schistosome glycoproteins and induce T_H2 responses.[46] Commins et al[47] identified 24 adults who reported urticaria, angioedema, or anaphylaxis 3 to 6 hours after ingesting beef, lamb, or pork. These patients were all found to have positive skin test results and serum IgE antibodies to galactose-α-1,3-galactose, the carbohydrate moiety of these glycoproteins. This is the first demonstration of IgE antibodies directed at a carbohydrate epitope leading to clinical symptoms.

CLINICAL DISORDERS

In addressing possible food-induced allergic disease, the clinician must consider a variety of adverse reactions to foods that are not food allergies, especially because more than 20% of adults and children alter their diets for perceived adverse reactions/allergies.[2] Adverse reactions that are not classified as food allergies include host-specific metabolic disorders (eg, lactose intolerance, galactosemia, and alcohol intolerance), a response to a pharmacologically active component (eg, caffeine, tyramine in aged cheeses triggering migraine, and histaminic chemicals in spoiled dark-meat fish resulting in scombroid poisoning masquerading as an allergic response), or toxins (eg, food poisoning). Additionally, psychologic (food aversion and anorexia nervosa) or neurologic (eg, auriculotemporal syndrome manifested by a facial flush from tart foods or gustatory rhinitis manifested by rhinorrhea from hot or spicy foods) responses can mimic food allergies.

It is conceptually and diagnostically helpful to categorize food-induced allergic disorders based on immunopathology among those that are and are not mediated by IgE antibodies. Disorders with an acute onset of symptoms after ingestion are typically mediated by IgE antibody. Food-specific IgE antibodies arm tissue mast cells and blood basophils, a state termed *sensitization*.

On re-exposure, the causal food proteins bind to the IgE antibodies specific for them and trigger the release of mediators, such as histamine, that cause the symptoms. Another group of food hypersensitivity disorders are subacute or chronic and are mediated primarily by T cells. A third group of chronic disorders attributed to food allergy are variably associated with detectable IgE antibody (IgE-associated/cell-mediated disorders). Table II lists the features of a spectrum of the most common food-induced allergic disorders categorized by pathophysiology.[4,48] The table does not include disorders such as recalcitrant childhood gastroesophageal reflux, constipation, and irritable bowel syndrome, which are sometimes attributed to food allergy.[49] Detection of IgG antibodies to foods is not considered diagnostic of food allergy.[1,4,37] However, Heiner syndrome, a rare infantile disorder characterized by pulmonary hemosiderosis triggered by milk protein, is associated with increased milk-specific IgG antibodies. Celiac disease and the related skin disorder dermatitis herpetiformis can be considered food allergies because an immune response to gluten in grains, such as wheat, rye, and barley, is responsible, but these disorders are not discussed further here. Dietary (food) protein–induced enteropathy is another malabsorption syndrome, but unlike celiac disease, it is usually caused by cow's milk, is transient, is not associated with malignancy or dermatitis, and, for unclear reasons, has been rarely described in the past decade. Although symptoms of mucous and bloody stools in breast-fed infants have typically been attributed to dietary proctitis/proctocolitis caused by immune responses to maternal ingestants, such as cow's milk, studies have recently emphasized that alternative causes, such as infection or other inflammatory disorders, should be considered.[50,51] Thus empiric maternal dietary interventions should be undertaken with consideration that alternative explanations might exist, and retrials of the avoided allergen can be considered shortly after resolution of symptoms if other signs of allergy are absent. Lastly, contact dermatitis has also been attributed to foods, particularly with occupational exposure.

DIAGNOSIS

The evaluation requires a thorough history and physical examination to consider a broad differential diagnosis, to ascertain possible trigger foods, and to determine a likely general pathophysiologic basis, specifically whether the food-induced allergic disorder is likely IgE mediated, which guides testing. The history should determine the possible causal food or foods, quantity ingested, time course of reaction, ancillary factors (exercise, aspirin, and alcohol), and reaction consistency.[4] The history also focuses on details that might contribute to estimating the prior probability of an allergic reaction to a specific food. For example, reasoning dictates that a food ingested infrequently is more likely responsible for an acute reaction than one previously tolerated; that contamination of a meal by a previously diagnosed allergen should be considered ahead of a less likely explanation, such as development of a new allergy to a previously tolerated food; and that major allergens are inherently more likely to be triggers than other foods. To arrive at a diagnosis, the clinician should consider the epidemiologic aspects of the disease (eg, common triggers and common associations) and the details of the specific history and then consider appropriate testing that can be evaluated in the context of these prior probability estimates.[4]

For IgE-mediated disorders, skin prick tests (SPTs) provide a rapid means to detect sensitization.[4] Negative SPT responses essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy, >90%). However, a positive test response does not necessarily prove that the food is causal (specificity, <100%). Consideration of the clinical history and disease pathophysiology is required to maximize the utility of test results. For example, a positive SPT response can be considered confirmatory when combined with a recent clear history of a food-induced allergic reaction to the tested food. Additionally, increasing SPT wheal size is correlated with an increasing likelihood of clinical allergy.[4,52] Studies have attempted to define wheal sizes above which allergy is virtually confirmed based on the test result alone[53,54]; however, these studies have been limited to a few foods in infants using specific techniques in only a few populations.[4] In one study of 140 children evaluated for peanut allergy, 64 had positive SPT responses, and 18 reacted during oral peanut challenge.[55] Of 17 children with an SPT wheal of greater than 10 mm, only 8 reacted during the challenge. Thus additional studies are needed to continue to define the diagnostic accuracy of skin test wheal sizes for different foods, ages, disease, and populations; wheal size has not been correlated to severity of outcomes. When evaluating allergy to many fruits and vegetables, commercially prepared extracts are often inadequate because of the lability of the responsible allergen, and therefore the fresh food might be used for testing.

Serum immunoassays to determine food-specific IgE antibodies (the term RAST is now antiquated) provide another modality to evaluate IgE-mediated food allergy.[56] Increasingly higher concentrations of food-specific IgE levels correlate with an increasing likelihood of a clinical reaction but do not generally correlate very well with reaction severity.[57-62] Different predictive values are being generated from emerging studies, which might represent nuances of diet, age, disease, and challenge protocols.[60,61,63] Particular values associated with a high likelihood of clinical allergy (eg, >95%) are often referred to as diagnostic values. Undetectable serum food-specific IgE might be associated with clinical reactions for 10% to 25%.[57,64] Consequently, if there is a suspicion of possible allergic reactivity, a negative SPT response, negative physician-supervised food challenge result, or both are necessary to confirm the absence of clinical allergy. Nomograms are available where prior probabilities can be used along with likelihood ratios (determined from studies evaluating the diagnostic utility of tests) to predict a diagnosis; however, there are few studies providing likelihood ratios, and results vary.[4] A decrease in specific IgE concentration is associated with an increasing chance of allergy resolution.[65] A complete primer of food allergy diagnosis is beyond the scope of this review, but Table III provides additional insights and information that are key to accurate diagnostics.[57-62,66-68]

Although not commercially available, determination of specific IgE-binding epitopes on an allergen might provide increased diagnostic utility.[69] The specific profiles of epitopes bound might reflect distinctions in binding to areas of an allergen that are dependent on protein folding (conformational epitopes) and are a feature of mild/transient allergy versus areas that represent linear binding regions that are stable, reflecting a severe persistent allergy. Additionally, IgE responses to specific proteins in foods might account for particular outcomes.[70] For example, identification of IgE binding to labile birch pollen–related proteins is associated with mild reactions, whereas binding to stable lipid transfer proteins in the same foods is associated with more severe reactions. This observation forms the basis for an approach termed component-resolved diagnostics.

TABLE II. Food-induced allergic disorders (also see text)

Immunopathology	Disorder	Key features	Additional immunopathology	Typical age	Most common causal foods	Natural course
IgE antibody dependent (acute onset)						
	Urticaria/ angioedema	Triggered by ingestion or direct skin contact (contact urticaria); food commonly causes acute (20%) but rarely chronic (2%) urticaria		Children > adults	Primarily major allergens	Depending on food
	Oral allergy syndrome (pollen–food related)	Pruritus, mild edema confined to oral cavity Uncommonly progresses beyond mouth (~7%) or anaphylaxis (1% to 2%) Might increase after pollen season	Sensitization to pollen proteins by the respiratory route results in IgE that binds certain homologous, typically labile food proteins (in certain fruits/ vegetables (eg, apple Mal d 1 and birch bet v 1)	Onset after pollen allergy established (adult > young child)	Raw fruit/vegetables Cooked forms tolerated Examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)	Might be long-lived and vary with seasons
	Rhinitis, asthma	Symptoms might accompany a food-induced allergic reaction but rarely an isolated or chronic symptom Symptoms might also be triggered by inhalation of aerosolized food protein		Infant/child > adult, except for occupational disease (eg, baker's asthma)	General: major allergens Occupational: wheat, egg, and seafood, for example	Depending on food
	Anaphylaxis	Rapidly progressive, multiple organ system reaction can include cardiovascular collapse	Massive release of mediators, such as histamine, although mast cell tryptase levels not always increased Key role of platelet-activating factor	Any	Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg	Depending on food
	Food-associated, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion followed temporally by exercise	Exercise is presumed to alter gut absorption, allergen digestion, or both	Onset more commonly later childhood/adult	Wheat, shellfish, and celery are most described	Presumed persistent
IgE antibody associated/cell-mediated (delayed onset/chronic)						
	Atopic dermatitis	Associated with food in ~35% of children with moderate-to-severe rash	Might relate to homing of food-responsive T cells to the skin	Infant > child > adult	Major allergens, particularly egg and milk	Typically resolves

(*Continued*)

TABLE II. (*Continued*)

Immunopathology	Disorder	Key features	Additional immunopathology	Typical age	Most common causal foods	Natural course
	Eosinophilic gastroenteropathies	Symptoms vary on site(s)/degree of eosinophilic inflammation Esophageal: dysphagia and pain Generalized: ascites, weight loss, edema, and obstruction	Mediators that home and activate eosinophils play a role, such as eotaxin and IL-5	Any	Multiple	Likely persistent
Cell-mediated (delayed onset/ chronic)						
	Dietary protein enterocolitis	Primarily affects infants Chronic exposure: emesis, diarrhea, poor growth, and lethargy Re-exposure after restriction: emesis, diarrhea, and hypotension (15%) 2 hours after ingestion	Increased TNF-α response, decreased response to TGF-β	Infancy	Cow's milk, soy, rice and oat	Usually resolves
	Dietary protein proctitis	Mucus-laden, bloody stools in infants	Eosinophilic inflammation	Infancy	Milk (through breast-feeding)	Usually resolves

Increasingly, studies are evaluating the utility of the atopy patch test for disorders in which symptoms are delayed after food ingestion, such as atopic dermatitis,[71] eosinophilic esophagitis,[72] and food protein–induced enterocolitis syndrome.[73] The test is performed by placing foods under Finn chambers in a manner akin to testing for contact allergens. Although the atopy patch test shows promise, there are currently no standardized reagents, methods of application, or interpretations, and the additional diagnostic information in some studies appears marginal.[71,72] Additional future diagnostic modalities might include the basophil activation test.[74] Various tests and procedures (eg, endoscopy/biopsy and breath hydrogen tests) might be required to evaluate possible gastrointestinal allergy.[75] Unproved or disproved tests, such as the pulse test, applied kinesiology (muscle strength tests), cytotoxic tests, electrodermal tests, and IgG testing, should not be used.[76]

The OFC is comprised of a gradual feeding of a possible allergen under medical supervision to determine tolerance or clinical reactivity. Severe reactions could be elicited, and therefore the procedure is undertaken by properly trained personnel with medications and equipment to treat anaphylaxis on hand. Feeding is generally stopped when objective or persistent subjective symptoms are elicited.[62] For chronic disorders in which an ingested food is currently a part of the diet, diagnosis typically includes a period of elimination of the possible trigger food or foods to determine whether symptoms resolve before an OFC. Caution is advised because acute severe reactions are sometimes noted after reintroduction of a potential allergen (eg, positive test result for IgE or suspicion of allergy) after prolonged dietary elimination.[77] Open or single-blind OFCs are often used to screen for reactions. The double-blind, placebo-controlled OFC is the gold standard for the diagnosis of food allergies because bias is minimized.[78] If the blinded challenge result is negative, it must be confirmed by means of an open supervised feeding of a typical serving of the food in its natural form to rule out a false-negative challenge result (approximately 1% to 3%). A number of reviews have outlined the procedures involved for OFCs,[78,79] and a comprehensive clinically oriented guide has been recently published.[80]

MANAGEMENT

The primary therapy for food allergy is to avoid the causal food or foods. Education about avoidance includes careful attention to label reading, care in obtaining foods from restaurants/food establishments, and avoidance of cross-contact of foods with an allergen during meal preparation, such as avoiding shared cutting boards, slicers, and mixers. Food-labeling laws in the United States require simple English terms, such as "milk" instead of "casein," to indicate the presence of specific regulated food allergens, including only milk, egg, wheat, soy, peanut, tree nuts, fish, and crustacean shellfish. Patients and caregivers should be encouraged to obtain medical identification jewelry, taught to recognize symptoms, and instructed on using self-injectable epinephrine and activating emergency services. Comprehensive educational materials are available through organizations such as the Food Allergy & Anaphylaxis Network (Fairfax, Va; 1-800-929-4040 or http://www.foodallergy.org).

Various medications can provide relief for certain aspects of food-induced disorders. Antihistamines might partially relieve symptoms of oral allergy syndrome and IgE-mediated skin symptoms. Anti-inflammatory therapies might be beneficial for allergic eosinophilic esophagitis or gastroenteritis.[81] It is

TABLE III. Pearls and pitfalls regarding the diagnosis of food allergy

<table>
<tr><th>Pearl/observation</th><th>Additional details</th><th>Clinical application</th></tr>
<tr><td>A positive skin test or serum food-specific IgE test result indicates sensitization but not necessarily clinical allergy</td><td>Screening with indiscriminate panels of tests is poorly informative</td><td>The history and epidemiologic considerations should guide test selection
Tolerated foods generally need not be tested
Differential diagnosis should include alternative allergen triggers (environmental aeroallergens) and nonallergic diseases (eg, intolerance)</td></tr>
<tr><td>Dose, manner of preparation, and ancillary (eliciting) factors might alter reaction outcomes</td><td>Alcohol, NSAIDs, and exercise are among eliciting factors that might facilitate a reaction
Heating can alter allergenicity (eg, bakery products with egg/milk might be tolerated when whole forms are not, and cooked fruits might be tolerated when raw fruits are not)
A low dose might be tolerated, whereas larger amounts might not</td><td>The history should focus on amounts triggering a reaction and ancillary factors
The history should explore the types of foods tolerated or not tolerated</td></tr>
<tr><td>IgE binding to homologous proteins among food groups and between foods and pollens might have variable clinical relevance</td><td>Rates of clinical cross reactivity:
<table><tr><th>Allergy to:</th><th>Related food</th><th>Approximate clinical reaction rate</th></tr><tr><td>Peanut</td><td>Most beans</td><td>5%</td></tr><tr><td>A tree nut</td><td>Other tree nut</td><td>35%
Higher for: walnut-pecan, almond-hazel, cashew-pistachio</td></tr><tr><td>A fish</td><td>Other fish</td><td>50%</td></tr><tr><td>Shellfish</td><td>Another shellfish</td><td>75%</td></tr><tr><td>Grain</td><td>Another grain</td><td>20%</td></tr><tr><td>Cow's milk</td><td>Goat/sheep milk
Mare's milk
Beef</td><td>>90%
5%
10%</td></tr></table></td><td>Care should be used in not overtesting
For some categories and foods, avoidance of the entire group might be prudent, especially to avoid cross-contact in preparation, but individualization might be possible</td></tr>
<tr><td>Tests for serum food-specific IgE might not provide comparable results among manufacturers</td><td>In the United States there are 3 major test manufacturers</td><td>Care must be taken in evaluating test results over time when different manufacturers are used</td></tr>
<tr><td>Serum/skin tests might be negative despite clinical reactivity</td><td>Might be due to reagent lacking relevant protein
Might be because reaction is not IgE mediated</td><td>Do not discount a convincing history because of a negative test result
Consider testing with fresh food (prick-prick test)
Be cognizant of non–IgE-mediated allergic reactions</td></tr>
<tr><td>Increasingly high serum food-specific IgE levels or increasingly larger skin test wheal sizes indicate greater chances of clinical allergy</td><td>Correlation of tests with outcomes vary by centers, age, and disease (equivalent results are generally more predictive of allergy in a younger patient)
Results are not strongly reflective of severity</td><td>Tests should not be viewed solely as positive/negative
Results can be followed over time to monitor allergy persistence/resolution
Specific correlative values might not be applicable over all patient groups</td></tr>
<tr><td>At specific high levels of IgE or large skin tests, clinical reactivity is highly likely; however, studies are limited, and variations in diagnostic cutoff values are reported</td><td><table><tr><th>Food</th><th>Mean age 5 y, 50% react</th><th>Mean age 5 y, ~95% react</th><th>Age <2 y, ~95% react</th></tr><tr><td>Egg (kUa/L)</td><td>2</td><td>7</td><td>2</td></tr><tr><td>Milk (kUa/L)</td><td>2</td><td>15</td><td>5</td></tr><tr><td>Peanut (kUa/L)</td><td>2/5</td><td>14</td><td></td></tr></table></td><td>Oral food challenges might be deferred, particularly if there is a clinical history</td></tr>
</table>

NSAIDs, Nonsteroidal anti-inflammatory drugs.

TABLE IV. Selected immunotherapeutic strategies

Therapy	Immune rationale	Benefits	Observations to date
Standard subcutaneous immunotherapy (native allergens)	Antigen presentation in nonmucosal site results in T_H1 skewing	Proved for venom and respiratory allergy, possible benefit (pollen) for oral allergy syndrome	Primarily avoided for risk of anaphylaxis (eg, peanut)
Sublingual/OIT	Antigen presentation to mucosal site provides desensitization and might induce tolerance	Natural foods, reduced risk of systemic anaphylaxis compared with injections	Mounting evidence for desensitization and relative safety; unclear effect on tolerance
Modified protein vaccine	Reduced IgE activation by mutation of IgE-binding epitopes	A safer form of immunotherapy compared with injection of native protein	Murine models show promise, human studies are planned
Peptide vaccine (overlapping peptides)	Peptides are less likely to cross-link IgE, avoiding mast cell activation	No requirement for IgE epitope mapping/mutation	Limited
Conjugation of immune stimulatory sequences to allergen and additional adjuvant methods	Enhance T_H2 response by activating innate immune receptors (using specific sequences or whole bacteria)	Increased efficacy, possibly improved safety	Preclinical studies
Plasmid DNA-encoded vaccines	Endogenous production of allergen might result in tolerance	Possible 1-dose treatment	Murine models reveal strain-specific response
Anti-IgE antibodies	Targeted toward Fc portion of antibody, can inactivate IgE with reduced risk for activating mast cells	Not food specific Some response in eosinophilic gastroenteropathy (pilot study)	Preliminary study showed improved threshold overall but did not show uniform protection
Chinese herbal medicine	Mechanism unknown	Not food specific	Murine models show efficacy Human safety studies are underway
Cytokine/anti-cytokine (eg, anti–IL-5)	To interrupt inflammatory signals	Might allow directed interruption of inflammatory processes without need for food restriction	Preliminary study shows benefit for eosinophilic esophagitis.

important to recognize that the key treatment for food-induced anaphylaxis is prompt administration of epinephrine.

PREVENTION

There are limited data on primary prevention of food allergy through dietary means, although numerous studies possessing various limitations have addressed outcomes of atopic disease, such as atopic dermatitis and asthma. Based on review of the available literature, professional organizations[82,83] have generally concluded that there is insufficient evidence regarding reduced atopic disease to recommend maternal avoidance of allergens during pregnancy or lactation, although there is some evidence that allergen avoidance during lactation might be related to reduced atopic dermatitis. For infants with a family history of atopy placing them at increased risk, data primarily support the practice of exclusive breast-feeding for at least 4 months compared with feeding intact cow's milk formula to decrease the cumulative incidence of atopic dermatitis and cow's milk allergy in the first 2 years. Similarly, avoidance of solid foods for the first 4 to 6 months is associated with reduced risk of atopic dermatitis. Additionally, for infants not being exclusively breast-fed, whole protein formula (cow's milk or soy) compared with the use of studied extensively or partially hydrolyzed formulas in the first few months appears to be associated with increased risks for atopic dermatitis. After 4 to 6 months, there are insufficient studies/data that specific allergen avoidance alters atopy outcomes.

FUTURE THERAPIES

Future therapeutic options for food allergy include strategies that target specific foods and ones that block allergic responses and are not food specific.[48,84,85] Table IV summarizes some of the current strategies. Of note, immunotherapeutic approaches now under study attempt to avoid serious adverse effects that would otherwise be triggered by injection of native allergens, as noted in a study of injection immunotherapy for peanut allergy,[86] by changing the route of administration or by modifying (engineering) the treatment proteins. The approach undergoing the most current research is oral immunotherapy (OIT), in which doses of the food protein are given in gradually increasing amounts toward a maintenance dose. Jones et al[87] enrolled 39 children with peanut allergy in an open study of OIT; the study did not use initial OFCs, but after therapy for 4 to 22 months, initially aiming for 300 mg as a maintenance dose, 27 of 39 children completing the maintenance phase tolerated the targeted 3.9-g open peanut food challenge (18 of them without symptoms). Immune parameters followed during the study revealed a decrease in skin test and basophil activation, a decrease in peanut-specific IgE levels, and an increase in IgG levels.[4] In a first double-blind trial of milk OIT by Skripak et al,[88] 20 children (12 completed active treatment and 7 received placebo) underwent a regimen of an initial escalation day (aiming for 50 mg), 8 weekly updosings to a final dose of 500 mg, and maintenance for 3 to 4 months. The median dose eliciting a reaction at baseline was 40 mg, which increased to 5,140 mg (range, 2,540-8,140 mg) in the treated group but was unchanged in the placebo group. OIT is presumed to restore or induce a tolerant state. However, a distinction must be made between desensitization, in which the allergen is ingested without symptoms during treatment but requires daily ingestion, and tolerance, in which the food might be ingested without allergy symptoms despite periods of abstinence. Studies to date indicate that OIT induces desensitization, but it remains unclear whether tolerance is achieved.[89] Staden et al[90] randomized children to egg or

milk OIT (n = 25) or observation during dietary elimination (n = 20); after OFCs at about 21 months on therapy, the treatment group discontinued daily therapy for 2 months and were rechallenged. Although 64% of the treatment group had a good or at least partial response to OIT while on treatment, food challenges performed 2 months off treatment revealed only 36% continued to have true tolerance, a percentage that exactly matched tolerance achieved in untreated control subjects. More studies are required to assess safety,[91] efficacy, and mechanisms.

SUMMARY

Food allergies are common, result in both acute and chronic disease, might be increasing in prevalence, affect quality of life, and can be severe and potentially fatal. Diagnosis currently relies on a careful history and an appreciation of epidemiologic aspects of the disorder, the role and limitation of simple diagnostic tests, and, if needed, the use of an OFC to confirm allergy or tolerance. Treatment currently relies on avoidance of triggers and appropriate prompt response to allergic reactions, such as using epinephrine for anaphylaxis. Insights on pathophysiology are leading to the development of improved methods for prevention, diagnosis, and management, including clinical studies that are currently underway that might reduce risks for allergic subjects or possibly cure these allergies.

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