Food Allergies: Clinical Manifestations, Diagnosis, and Management

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Reactions to foods are extremely common and the etiology of these reactions determines their correct management. Adverse food reactions are not all allergic. The management of food adverse reactions ranges from complete avoidance of minute amounts of food to ingesting milk after lactase supplementation. It is, therefore, important to accurately classify reactions to foods. Adverse food reactions can be categorized into the 2 following groups: nonimmunologic and immunologic. Immunologic reactions to food are mediated by the immune system, while all other reactions fall into the nonimmunologic category. Nonimmunologic reactions are grouped into either toxic or nontoxic reactions.

A toxic reaction results from the pharmacologic actions of a substance within a food. These reactions can occur in anyone who is exposed to the food and do not depend on host factors. These substances may be enzymes or any agent that could cause reactions in the body. Examples of toxic reactions include nausea from bacterial food poisoning, heavy metal poisoning, and itching and flushing from histamine ingestion as seen in scombroid fish poisoning. The consumption of foods containing caffeine, such as coffee or tea, can cause jitteriness. Tyramine in aged cheeses can cause migraine headaches and alcohol ingestion is associated with a variety of well-known symptoms.[1]

All other nonimmunologic reactions to foods can be characterized as food intolerances. These are dependent on the host and the host-environment interaction. The nomenclature of the World Allergy Organization uses the term "hypersensitivity" to refer to a reproducible symptom or sign to a stimulus tolerated at the same dose by normal persons apart from an immunologic basis. Food intolerances are not mediated by the immune system (Table 1). Enzyme deficiencies such as lactase deficiency and galactosemia are examples of food intolerances. Pancreatic insufficiency, gallbladder or liver disease, hiatal hernia, and gustatory rhinitis are all conditions that can be associated with adverse events following food ingestion. Psychiatric illnesses, like anorexia nervosa with vomiting or the auriculotemporal syndrome, can also mimic food intolerance. Food intolerances, by definition, are nonallergic food hypersensitivities. The remainder of this review focuses on the immunologic responses to food.

Immunologic reactions to food are mediated by the immune system and these disorders are induced by 2 major mechanisms: IgE-mediated and/or non-IgE-mediated. It is most practical to classify immunologic reactions to food into the 3 following groups: IgE-mediated, non-IgE-mediated, and mixed disorders (Table 1).[2] Classically, IgE-mediated disorders occur when food-specific IgE antibodies on the surface of mast cells and basophils bind to circulating ingested food allergens, and activate the cells to release cytokines and other potent mediators, such as histamine. Typically, symptoms occur immediately after food ingestion, resulting in urticaria, angioedema, wheezing, cough, nausea, vomiting, and, in some cases, hypotension. This is the mechanism that mediates anaphylaxis after food ingestion. Most food-induced, IgE-mediated allergic reactions occur within minutes to a few hours after ingestion. IgE-mediated food allergy is excluded if symptoms occur >4 hours after ingestion. The non-IgE-mediated food allergies result from T cell activation, which produces cytokines like IL-4, IL-5, and IL-13 (called T_H2 cytokines), which further the allergic response. Eosinophilic inflammation can also result from this cascade of events. These reactions are generally slower in onset (greater than 4 hours after ingestion) and are primarily gastrointestinal in nature. Examples of non-IgE-mediated conditions include food protein enterocolitis syndrome,

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TABLE 1. Classification of adverse reactions to foods

Food allergy—(Immunologic)
IgE mediated
Urticaria, angioedema, morbilliform rashes, acute rhinoconjunctivitis, acute asthma exacerbation, anaphylaxis, food-associated exercise-induced anaphylaxis, oral allergy syndrome
Non IgE associated
Food protein–induced proctocolitis and/or enterocolitis, contact dermatitis, dermatitis herpetiformis, celiac disease
Mixed IgE-mediated/non-IgE-mediated
Atopic dermatitis, asthma, allergic eosinophilic esophagitis, and/or gastroenteritis
Intolerance (Nonimmunologic)
Nontoxic (enzyme deficiency)
Lactose intolerance, galactosemia
Toxic (pharmacologic)
Caffeine (jitteriness), tyramine in aged cheeses (migraine), alcohol, histamine (scromboid fish poisoning)
Heavy metal poisoning, bacterial food poisoning
Mimickers of food intolerance/allergy
Pancreatic insufficiency, gallbladder or liver disease, hiatal hernia and gustatory rhinitis, anorexia nervosa, auriculotemporal syndrome (facial flush with salivation)

Adapted with permission from Sicherer and Sampson.[1]

eosinophilic proctitis, dermatitis herpetiformis, celiac disease, and contact dermatitis.[2] In the mixed disorders, the IgE and non-IgE mechanisms can work together to exacerbate diseases like atopic dermatitis and eosinophilic gastrointestinal disease.[3]

Food Allergenic Proteins

The immunologic reactions in food allergy are directed toward the proteins or glycoproteins in the food, not the fat or carbohydrate components. These allergens are generally water-soluble glycoproteins, 10-70 kDa in size, heat-resistant, and acid stable.[4] The stability of the allergen contributes to the resistance of the allergen to denaturation and degradation with food processing. The stable food allergens are the most common offenders in food allergic reactions. It is important to realize that there are many different proteins in a single food, which makeup a combination termed the "food matrix." Each of the proteins in a food consists of many amino acids. Short combinations of amino acids are called epitopes. The epitopes in any particular protein can bind to IgE antibody or a T cell receptor. Epitope sites can be dependent on the folding of the protein, called confirmational epitopes, or they may be linear.[5]

Although many food proteins are theoretically capable of producing allergic responses, the clinically relevant number of food allergens is quite small. More than 85% of significant food allergic reactions occur to milk, egg, peanut, wheat, soybean, tree nuts, shellfish, and fish. Sesame seed is also an important emerging food allergen in the USA.[6] The first 3 foods listed above, milk, egg, and peanut, cause the most reactions with population prevalence rates of 2.5%, 1.3%, and 0.8%, respectively.[7]

The specific allergenic proteins have been identified for most of the "major" food allergens. Milk allergens are the alpha, beta, and kappa caseins or "curd" portion of milk, as well as beta-lactoglobulin in whey. The allergenic proteins of egg include ovomucoid, ovalbumin, ovotransferrin, and lysozyme. Peanut (Ara h 1-3), shrimp (tropomyosin), soy (Gly m BD 28K), and fish (parvalbumin) allergens have also been identified and characterized.

Pan-allergens are proteins in food, pollen, or plants that possess homologous IgE binding epitopes across species. The classes of allergens considered pan-allergens include tropomyosins, parvalbumins, bovine IgG, lipid transfer protein, profilin, and class 1 chitinases. A comparison of animal allergens and their human homologues revealed that food proteins with sequence identity greater than 62% were rarely allergenic.[8] Hence, in order for an epitope to be associated with an allergic reaction, the homology with human protein is typically less than 50%.

Clinical Cross-Reactivity

Some food proteins are cross-reactive and can cause clinical reactivity in patients. Among patients allergic to 1 tree nut, 15%-40% will have allergy to at least 1 other tree nut. Thirty percent to 100 percent of patients allergic to fish are allergic to more than 1 species of fish. Twenty-five percent of patients with 1 grain allergy will react to at least 1 other grain. Patients may have positive tests for specific IgE to many foods but this only represents a sensitivity to the food. Not all patients have clinical reactivity with the presence of specific IgE to the food. For example, although almost 50% of peanut allergic patients test positive for legume-specific IgE, only 5% will react to the legume when it is ingested. The current recommendation is not to automatically restrict all members of a food family because of an allergic reaction to 1 member of the family. However, physicians should be aware of the possibility of development of cross-reactivity in sen-

sitized patients and the potential for cross contamination of allergenic proteins during food preparation.[9]

Prevalence and Risk Factors for Food Allergy

The prevalence of food allergy has been increasing over the past few years. The prevalence of peanut allergy has doubled over a 5-year time span in the USA[10] and the UK.[11] The reasons for the increase in prevalence are unclear but likely reflect the increase in general atopic disease. Thirty-five percent to 55 percent of anaphylaxis in children and adolescents is secondary to food allergy.[12,13]

Up to 30% of the general population believe someone in their family has an allergy to a food product.[14] Studies of parental reports of food allergy in children show that up to 12% of parents in Europe and 28% in the USA believe the child has an allergy to a food.[15,16] Oral food challenges are more definitive than self-report for diagnosis of food allergy and the double-blind placebo-controlled oral food challenge is the gold standard for diagnosis. Population studies with oral food challenges to confirm reports of allergy indicate 2%-3.7% of adults[17] and 6%-8% of children[15] have food allergy. Adverse reactions to dyes or preservatives are much less common, affecting less than 1%-2% of the population.[18,19] Double-blind challenges to dyes or preservatives reveal no significant difference between the additives and placebo, underscoring the rarity of reactions to these substances.[20]

The prevalence of food allergy depends on societal eating habits and cooking methods. For example, the occurrence of peanut allergy differs between countries with different peanut exposure. In China, the prevalence of peanut allergy is much lower than that in the USA because peanuts are commonly fried or boiled as opposed to dry roasted.[21] The boiling process decreases the allergenic properties of peanut proteins, mainly due to transfer of allergen into the water during cooking.[22] The prevalence of seafood allergy is higher in communities with increased seafood consumption. In Hong Kong preschool children, the parent-reported rate of shellfish allergy was higher than in the USA, affecting 1.28% of the total population and 15.8% of all children with adverse food reactions, compared to the estimated prevalence of 0.1% of children in the USA.[7] The average age of first intake of seafood in the Asian diet is 7 months, which may contribute to the significant rates of sensitivity to shellfish and fish.[23]

The risk of food allergy is higher in individuals with atopic dermatitis and certain pollen and latex sensitivities.[2] Up to one-third of patients with atopic dermatitis have skin exacerbations after the ingestion of specific allergenic foods.[15] In individuals with urticaria and/or angioedema of less than 6-weeks duration, the prevalence of food allergy is 15%-20%.[24] Four percent to 8% of individuals with asthma have food allergies.[25]

Risk factors for the development of food allergy include a younger age, as the prevalence in children, especially young children under 3 years old, is higher than that in adults. A family history of atopic disease increases the risk of food allergy for an individual 4-fold.[26] Familial atopic diseases, which place individuals at risk, include asthma, allergic rhinitis, atopic dermatitis, and food allergy. There are no particular genes known to be associated with food allergy and no genetic tests to identify persons at risk, but there is a higher concordance of peanut allergy for monozygotic twins than dizygotic twins (64% vs 7%). The sibling of a food allergic person has a 10-fold higher risk for the development of food allergy than the general population.[27] Because skin contact to food can elicit a T_h2 response in mice[28] and severe food allergy can result from skin contact to food allergens in infants,[29] transdermal exposure to food is also a potential risk factor for the development of food allergy. There are likely both environmental and genetic influences that contribute to this complex disease.

Natural History

The natural history of food allergy is not uniform and differs depending on the type of food, the allergenic proteins within the food, and the immunopathogenesis of the reaction. Development of food allergies occurs in the first year of life in 80% or more of children with food allergies.[30] The peak prevalence of confirmed food allergy is at ~1 year of age. Children who begin with 1 food allergy, especially if it is an IgE-mediated allergy, have an increased chance of developing additional food and inhalant allergies.[31]

Prognosis of food allergy disease in young children allergic to cow's milk, egg, soybean, or wheat is very good with resolution being the most common outcome. Most cases of cow's milk allergy resolve by the age of 3 years old, with resolution in 56% at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 years, and

97% at 15 years of age, as seen in a prospective birth cohort study.[32] Rates of resolution reported from a tertiary care center allergy/immunology clinic population were lower with 19% resolution by age 4 years, 42% by age 8 years, 64% by age 12 years, and 79% by 16 years.[33] Egg allergy, the second most common food allergy in young children, has a resolution rate of 16% at 12 months of follow-up, 28% at 24 months, 52% at 36 months, 57% at 48 months, and 66% at 60 months.[34] Patients in a referral population showed resolution of egg allergy in 4% by age 4 years, 12% by age 6 years, 37% by age 10 years, and 68% by age 16 years, likely because the patients had more significant allergic disease.[35] Hypersensitivity to soybean is outgrown rapidly with 50%-83% of cases resolving in within 2 years.[36,37] Two-thirds of children with atopic dermatitis and wheat allergy outgrow the hypersensitivity over 1-2 years.[36] More severely atopic children with wheat allergy have resolution rates of 29% by 4 years, 56% by 8 years, and 65% by 12 years.[38]

Non-IgE-mediated reactions to cow's milk disappear sooner than IgE-mediated reactivity with the vast majority of children growing out of the reactivity by 1 year of age. Resolution of cow's milk and soy infantile food protein enterocolitis syndrome occurred in 27.3% and 75.0% at 6 months of age, 41.7% and 90.9% at 8 months, and 63.6% and 91.7% at 10 months, respectively, in a prospective study. The median age at resolution of solid food (not including cow's milk or soy) protein enterocolitis syndrome was 24 months in a retrospective series[39] with only 75% of children having resolution by 3 years of age. Interestingly, rice, oats, sweet potato, and poultry were among the most common foods implicated in these T-cell-mediated reactions.[40,41]

The natural history of other food allergies is not as short-lived. Peanut, tree nut, fish, and shellfish allergies are more persistent than milk, soy, egg, and wheat allergy.[36] Although traditionally it has been assumed that peanut allergy is never outgrown, actually 21.5% of peanut allergic children will outgrow their allergy.[42,43] Resolution of peanut allergy has been shown in 16%-30% of adults. Recurrence can occur,[44,45] in individuals who eat small or large amounts of peanuts after tolerance is confirmed by an oral challenge, with 8% of patients who outgrow peanut allergy suffering a recurrence.[46] The vast majority of tree nut allergic people will not outgrow their allergy, with only 9 of 101 tree nut allergic individuals having resolution in a median time of 5.5 years.[46] The natural history of fish and shellfish allergy has not been adequately studied. A case-control study among children with food allergy showed that most children retained their allergy to fish over a 1-year follow-up[47] and a study of 11 adult patients with shrimp allergy did not show any decrease in the shrimp-specific IgE levels over a 2-year period.[48]

The proportion by which food-specific IgE levels decrease over time can predict development of tolerance. For a child with egg allergy below the age of 4 years, the probability of developing tolerance over the next 12 months was 52% for a decrease in the egg-specific IgE over 1 year of 50%, 65% for a decrease of egg-specific IgE of 75%, 78% for a decrease of egg-specific IgE of 90%, and 95% for a decrease of 99% in egg-specific IgE levels. For cow's milk allergy, the probability of developing tolerance over the next 12 months was 31% for a decrease of milk specific IgE over 1 year of 50%, 45% for a decrease of 70%, 66% for a decrease of 90%, and 94% for a decrease of 99% in the cow's milk-specific IgE levels. The probability of outgrowing the allergy in the next 5 years is less if the specific IgE values do not decrease significantly over a 1-year period.[49,50] Over 80% of children outgrow milk allergy within the first 3 years of life.[51] The majority (75%) of children with milk allergy tolerate extensively heated milk like that contained in baked goods and most subjects with egg allergy are tolerant of extensively heated egg in baked goods. Continued ingestion of baked egg products is well tolerated and associated with immunologic changes that parallel the changes observed with the development of clinical tolerance to regular egg. A serum-specific IgE for milk, egg, and peanut of <2 kUA/L has been correlated with a 50% chance of absence of reactivity to food ingestion, and development of clinical tolerance.[50]

The structure of the allergic epitope for cow's milk and egg allergies have been identified as playing an important role in the development of tolerance. Patients with milk allergy persisting beyond the first 3 years of life were compared with those developing tolerance during this same time frame and children with "persistent allergy" possessed higher detectable levels of IgE antibodies to linear epitopes from cow's milk allergens, alpha(s1)- and beta-casein, than children who achieved tolerance. For egg allergy, patients with clinical tolerance by 11 years of age were compared with patients with clinical reactivity beyond 11 years of age and those with persistent egg allergy had IgE to more linear and conformational epitopes of

TABLE 2. Clinical features of anaphylaxis

Cutaneous	Urticaria, angioedema, pruritus, flushing, morbilliform rash
Respiratory	Upper airway—rhinorrhea, congestion, sneezing, stridor, hoarseness lower airway—cough, wheeze, dyspnea, chest tightness, cyanosis
Cardiovascular	Tachycardia, arrhythmia, syncope, hypotension, shock
Gastrointestinal	Pruritus or edema of the lips/tongue/palate, metallic taste in the mouth, nausea, vomiting, abdominal cramps, diarrhea
Neurologic	Anxiety, headache, seizure, syncope, loss of consciousness
Ocular	Pruritus, conjunctival injection, lacrimation

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ovomucoid and ovoalbumin than those with transient egg allergy.[52]

Clinical Syndromes of Food Allergy

Anaphylaxis

Food allergy is the leading cause of anaphylaxis treated in emergency departments and hospitals around the globe. It is the most severe form of an IgE-mediated allergic reaction to food. Food-induced anaphylaxis is an important cause of death in the USA, causing approximately 150 deaths per year.[3] It is estimated that 30,000 food-related anaphylactic reactions are treated in emergency departments each year with 2,000 patients hospitalized. Food-related anaphylaxis represents 13%-51% of all emergency department food allergic events in North America, Europe, Asia, and Australia.[53-56] Anaphylaxis is a rapid multisystem IgE-mediated allergic reaction that can be fatal. Onset is rapid, often within seconds to minutes of food ingestion.

Food-induced anaphylaxis encompasses many symptoms and most often affects multiple organ systems (Table 2). The clinical features can include cutaneous manifestations including urticaria, angioedema, pruritus, flushing, and morbilliform rash. These common symptoms occur in 80% of cases.[57] Respiratory symptoms include upper and lower airway symptoms, such as rhinorrhea, congestion, sneezing, stridor, hoarseness, cough, wheeze, dyspnea, chest tightness, and cyanosis. Gastrointestinal symptoms may include pruritus or edema of the lips/tongue/palate, metallic taste in the mouth, nausea, vomiting, abdominal cramps, and diarrhea. Pruritus, conjunctival injection, and lacrimation rarely occur in isolation but are most often seen in combination with other symptoms. Neurological symptoms may also occur.

TABLE 3. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis Is Highly Likely When Any One of the Following 3 Criteria Is Fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

And at least one of the following:

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end organ dysfunction [eg, hypotonia (collapse), syncope, incontinence]

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms [eg, hypotonia (collapse), syncope, incontinence]
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

[a]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than [70 mm Hg + (2 × age)] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
PEF, peak expiratory flow; *BP*, blood pressure.
Reproduced with permission from Sampson HA. Second symposium on the definition and management of anaphylaxis. JACI 2006;117:391-7.

Cardiovascular symptoms include tachycardia, arrhythmia, syncope, hypotension, and shock. The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis network defined criteria to facilitate rapid identification of individuals with anaphylaxis using an expert panel (Table 3).[58,59] In rare cases, hypotension has been reported as the primary symptom of anaphylaxis. Thirty-nine percent of food-allergic reactions have cardiovascular compromise.[60] Fluid extravasation and vasodilation can lead to a decrease in circulating blood volume of up to 35% within 10 minutes.[58] Therefore, epinephrine and aggressive fluid resuscitation as well as supine positioning and elevation of the legs are recommended. Some fatal food-induced anaphylactic events have been associated with upright posture.[59]

Most food-induced anaphylactic reactions occur within 1 hour of exposure, but the symptoms can occur within a few hours of exposure. These more delayed reactions can be associated with less severe symptoms.[61] Anaphylaxis can be classified as uniphasic or

biphasic. Biphasic reactions are defined as a recurrence of symptoms after the initial presentation resolves, usually within 8 hours of the initial reaction.[57] Biphasic anaphylaxis differs in children and adults. Biphasic reactions in children are more often triggered by foods, while drugs and insects are more common triggers in adults. Children have fewer cutaneous symptoms with anaphylaxis and more respiratory symptoms when compared with adults.[62] Predictors of biphasic reactions include receiving more than 1 dose of epinephrine and/or receiving a fluid bolus.[63] In a large series of pediatric anaphylactic patients, nearly half of patients with biphasic reactions were triggered by food with 27% involving tree nuts, 24% involving peanuts, and 16% involving seafood.[64]

Individuals at highest risk of near fatal or fatal food anaphylaxis are those with concomitant asthma and peanut, tree nut, and seafood allergies. Over half of fatal anaphylactic cases are associated with peanut or tree nut ingestion.[65] The time interval between ingestion of the food allergen and fatal collapse has been reported to be ~25-35 minutes.[66] In most cases, individuals have a known allergy to the food causing the fatal reaction. Teenagers are at particular risk and most reactions occur away from the home. Delayed administration of epinephrine is an extremely common feature of fatal food anaphylaxis.[67] There is no reliable laboratory test for the diagnosis of anaphylaxis. Tryptase, which is released by mast cells during anaphylaxis, is not consistently elevated in food anaphylaxis.[68]

Food-associated, exercise-induced anaphylaxis is a condition that is characterized by anaphylaxis after eating either a specific allergenic food or a nonspecific meal when exercise is performed close to the time of ingestion. Two types of individuals with food-associated exercise-induced anaphylaxis have been described. One subset of patients can develop anaphylaxis after exercising in temporal proximity to eating food in general and another group has symptoms only after exercising close to the time of eating a specific food. Anaphylaxis in this case only occurs when the food ingestion is combined with exercise. There are no symptoms with the ingestion alone or exercise alone. Several foods have been reported in this syndrome, including shellfish, celery, grapes, chicken, wheat, buckwheat, tomato, milk-containing items, and mushrooms. A case has even been described in which exercise preceded the food ingestion.[2] Jogging is the most common activity associated with food-associated exercise-induced anaphylaxis, but a variety of activities have provoked the reactions, including tennis, racquetball, basketball, skiing, dancing, aerobics, bicycling, and walking.[68]

There are several mechanisms proposed to account for the symptoms in food-associated exercise-induced anaphylaxis. A mast cell secretagogue may be released during exercise in affected individuals in a postprandial state, exercise may lower the mast cell releaseability threshold, and/or the mucosal enzyme activity or barrier function may promote intestinal absorption of the food. Immunoreactive gliadins appeared in the sera of individuals with a history of wheat-dependent exercise-induced anaphylaxis during a provocation test consisting of wheat ingestion followed by exercise. The appearance of the gliadin proteins was accompanied by allergic symptoms.[69] These individuals with food associated exercise induced anaphylaxis are encouraged to avoid food consumption 4 hours before or after exercising, which appears to prevent further episodes.[70]

Cutaneous Symptoms

In persons who do not experience anaphylaxis, cutaneous symptoms are among the most common manifestations of IgE-mediated food allergies. These cutaneous manifestations are typically acute (less than 6 weeks in duration) and consist of urticaria and/or angioedema. Urticaria upon contact of the food with the skin is also a common symptom and must be differentiated from irritant and allergic contact dermatitis. Foods that can cause urticaria on contact with the skin include shellfish, raw meats, fish, raw vegetables, fruits, rice, egg, mustard, beer, and milk.[2] Urticaria and angioedema lesions are defined as chronic if manifestations are persistent or recur over a period of more than 6 weeks, but food allergy is rarely an etiology of chronic urticaria and/or angioedema.[71] Contact dermatitis can occur from handling foods and is typically seen as a manifestation of occupational allergy. The most commonly implicated foods are raw seafood, and less commonly, meats, vegetables, fruits, and spices. The affected skin area is eczematous, with erythema and vesiculation.[72]

At least one-third of individuals with atopic dermatitis have food hypersensitivity reactions. Therefore, if persons with eczema are unresponsive to routine therapy or continue to need daily treatment after several months, evaluation for food allergy is warranted. The most frequently incriminated foods are egg, milk, and peanut.[73-75] Food allergy as a trigger of

atopic dermatitis in adults is extremely rare.[76] Eggs, cow's milk, soybean, and wheat account for about 90% of allergenic foods in children with atopic dermatitis.[76,77] Three clinical responses to foods in individuals with atopic dermatitis can occur. In the first pattern, immediate type reactions occur within a few minutes of ingestion with classic cutaneous manifestations and can be accompanied by gastrointestinal, respiratory, or cardiovascular symptoms. The second clinical pattern results in pruritus occurring soon after ingestion, which leads to scratching and subsequent exacerbation of atopic dermatitis. The third clinical pattern is termed a "late reactions" and can occur after 6-48 hours. This manifests as an increased rash along with pruritus with repetitive exposure to specific food.[78]

Respiratory Symptoms

Upper and lower respiratory tract symptoms may manifest as rhinoconjunctivitis, laryngeal edema, and asthma. These symptoms are typically associated with gastrointestinal and cutaneous symptoms. Isolated chronic rhinitis, however, is extremely rarely associated with food allergies. Inhalational exposure to food proteins in occupational settings and nonoccupational settings like restaurants, home, school, and airliners may affect individuals who are allergic to specific foods. The most commonly reported foods that cause symptoms upon inhalation are wheat flour, crustaceans, soybean, peanut, egg, and milk. Asthma is one of the most commonly reported reactions to food by inhalation.[79]

Baker's asthma is an example of a food-related occupational disease that affects workers regularly exposed to flour. It affects up to 9% of bakers, particularly in Europe. Any worker exposed to bakery allergens, such as confectioners, flour millers, and food processors, can develop the disease. Interestingly, people affected by Baker's asthma can ingest wheat products without symptoms.[79] Although this entity is most common in adults, children and adolescents can also be affected with repeated inhalational exposure to flour. It has been reported in a 2 year old after frequent visits to his grandfather's bakery and a in a 6 year old living in a confectionary store.[80,81]

Oral Allergy Syndrome

Oral allergy syndrome or pollen-food syndrome is characterized by the rapid onset of oral pruritus after the ingestion of raw fruits or vegetables. Other symptoms can be associated with this syndrome such as burning and edema of the lips, tongue, palate, and throat. The symptoms typically start within minutes of eating the offending food.[82,83] Persons with the oral allergy syndrome already have an IgE-mediated sensitization to pollens. The most common pollen sensitizations causing oral allergy syndrome are birch, ragweed, grass, and mugwort. The raw fruits and vegetables sharing common proteins with these pollens, called lipid transfer proteins or profilins, cause symptoms of the oral allergy syndrome.[84,85] The responsible cross-reacting proteins are heat labile and can therefore be changed upon food processing. Individuals with this syndrome can typically tolerate baked, cooked, or canned fruits and vegetables.[86] Ragweed-sensitive patients may have symptoms when they eat banana or melon; birch-sensitive patients have symptoms with raw carrot, celery, cherry, pear, walnut, potato, apple, hazelnut, and other foods. Grass allergy is associated with symptoms caused by melon, tomato, and orange[2] and mugwort allergy is associated with mango, apple, peach, celery, and chestnut[84,87] (Table 4).

TABLE 4. Pollen-food cross-reactivity in oral allergy syndrome

Pollen	Cross-reacting fruits and vegetables
Birch	Carrot, celery, cherry, pear, walnut, potato, apple, hazelnut
Ragweed	Banana, cucumber, melons
Grass	Melon, tomato, orange
Mugwort	Melon, apple, peach, celery, chestnut

In most instances the symptoms of oral allergy syndrome do not progress to anaphylaxis. The syndrome should be distinguished from mild oral reactions, which may occur from allergy to more stable proteins, which have a higher likelihood of causing systemic reactions, such as peanut. The symptoms may be more prominent during the pollen season; causal proteins are concentrated in the peel in some fruits and clinical reactions to all potentially cross-reactive foods are unlikely. The evidence of IgE to the food is commonly seen for several potentially cross-reacting foods, indicating sensitization and only possible clinical reactivity.[88-90]

Latex Fruit Syndrome

Thirty percent to 50% of individuals with latex allergy are sensitive to some fruits secondary to cross-reacting IgE to common proteins in the fruit and latex. The allergenic protein in latex responsible for allergic reactions is *Hevea brasiliensis*. The fruits

associated with the syndrome include banana, avocado, chestnut, kiwi, papaya, tomato, cherimoya, passion fruit, mango, and wheat.[91] Heating these fruits and vegetables abrogates the symptoms.[92] Latex-sensitive patients should be made aware of the possibility of fruit and vegetable reactivity, and fruit-allergic patients should be aware of the potential for the development of latex allergy because the syndrome can develop in those initially sensitive to either fruit or latex.[93]

Gastrointestinal Syndromes

Food allergy can also manifest as gastrointestinal anaphylaxis or an immediate gastrointestinal allergy, which is IgE mediated. The symptoms are an acute onset of emesis, diarrhea, and abdominal pain after eating the allergenic food. The symptoms may occur within minutes to several hours after the ingestion and can be a part of an anaphylactic reaction or may be the only symptom associated with the allergy.[65]

Food protein-induced enterocolitis syndrome is a non-IgE-mediated syndrome with manifestations including emesis, abdominal pain, and diarrhea within hours of ingestion. Cow's milk and soy protein-based formulas are the most common foods implicated in this syndrome in infants, although it can occur in response to almost any solid food. Older infants and children can develop enterocolitis because of egg, wheat, rice, oat, peanut, nuts, chicken, turkey, and fish.[94] Rarely, it may result from food proteins passed in maternal breast milk. Hypotension occurs in about 15% of cases and stools may contain occult blood, neutrophils, eosinophils, and Charcot-Leyden crystals. Because the syndrome is not IgE mediated, tests to detect food-specific IgE like skin prick testing or in vitro specific IgE testing are negative.[94] Patch testing for delayed non-IgE-mediated reactions in this syndrome may be helpful in selected cases.[95]

More commonly, gastrointestinal disorders seen in food allergies are of a mixed IgE and non-IgE pathogenesis and include eosinophilic esophagitis and/or gastroenteritis. These disorders result in some distinguishing features when compared with the strictly IgE-mediated and non-IgE-mediated gastrointestinal allergic reactions. Eosinophilic esophagitis is the most common syndrome associated with food allergy and can be associated with gastroesophageal reflux disease (GERD)-like symptoms such as dysphagia, food impaction, and weight loss in adolescents, and failure to thrive, irritability, and sleep disturbances in children[96] (Table 5).

TABLE 5. Symptoms suggestive of eosinophilic esophagitis

Children	Adult
Feeding aversion/intolerance	Dysphagia
Vomiting/regurgitation	Food impaction
"GERD refractory to medical management"	"GERD refractory to medical management"
"GERD refractory to surgical management"	
Food impaction/foreign body impaction	
Epigastric abdominal pain	
Dysphagia	
Failure to thrive	

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The prevalence and incidence of eosinophilic esophagitis has increased over the past 15-30 years.[97-99] Eosinophilic esophagitis is a clinicopathologic disease defined by esophageal symptoms associated with a severe isolated esophageal eosinophilia and absence of pathologic GERD as evidenced by normal pH monitoring of the distal esophagus or lack of response to high-dose proton pump inhibitor (PPI) treatment.[100] The condition is more common in males and 33%-70% of patients with eosinophilic esophagitis have atopic diseases including food allergies. Patients with eosinophilic esophagitis do not seem to grow out of their food sensitivities as rapidly as individuals with IgE-mediated food allergy.[99] Anaphylaxis can occur in 10%-25% of eosinophilic esophagitis patients, so physicians should ask about severe food reactions in these patients.[101]

The diagnostic criteria for the diagnosis of eosinophilic esophagitis consists of isolated esophageal eosinophilia typically involving greater than 15-20 eosinophils in the most densely affected ×40 high powered field[100] (Table 6). The involvement of the esophagus is variable so multiple sections are required from the distal and midesophageal regions to obtain the most accurate diagnosis.[102] Endoscopic findings include pallor, linear furrows, concentric rings, white exudates, and strictures. A subset of patients with associated food allergies respond to an elemental diet with improvement or resolution of eosinophilic infiltration of the esophagus.[103] Screening for food allergy in mixed IgE and non-IgE-mediated gastrointestinal syndromes includes prick or in vitro testing for specific IgE to detect IgE-mediated food allergies and/or patch testing to detect delayed reactions in non-IgE-mediated food hypersensitivity.

Unproven Symptoms

There are several disorders worth mentioning that have been linked to food allergy in the lay press and a

TABLE 6. Diagnostic guidelines of EE

Clinical symptoms of esophageal dysfunction
≥15 Eosinophils in 1 high-power field
Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/d) or
Normal pH monitoring of the distal esophagus

Reproduced from Furuta G, et al.[100]

large amount of misinformation has been disseminated regarding their link to food allergy. Migraine headaches, behavioral and/or developmental disorders like attention deficit disorder, autism, arthritis, seizures, inflammatory bowel disease, multiple sclerosis, and chronic fatigue syndrome have not been scientifically proven to be related to or associated with food allergy, defined as an immunologically mediated reaction to food.[2] No scientific peer-reviewed studies have definitively implicated food allergy as an etiology for these disorders. It is important for health care providers of children or adolescents with these disorders to give the correct information to patients and families regarding the lack of evidence of a link to food allergy.

Diagnosis of Food Allergy

History

The diagnosis of food allergy should begin with an accurate history with attention to pertinent details. Some general guidelines apply for the evaluation of food allergy (Table 7). It is important to note that, despite the most skilled medical history taking, the parent's history is notoriously inaccurate in identifying food allergies. The medical history for chronic disorders triggered by food allergies (atopic dermatitis, asthma, and allergic eosinophilic gastroenteritis) has a poor predictive value for the identification of food allergic patients. Acute reactions after the isolated ingestion of a single food, like peanuts, have a much higher predictive value.[104,105] This is demonstrated by the fact that 28% of parents in the US[15] believe their child has an allergy to a food but only 6%-8% of these suspected allergies are confirmed with positive oral challenges.[7] Also, reacting to 3 or more foods is very rare. The historical details which may help delineate the causative food include the quantity ingested, time course of reaction, activities or other medications surrounding the ingestion (ie, exercise, aspirin, alcohol), reaction consistency, treatment, and the nature and time course of the response to the treatment.

TABLE 7. General guidelines to consider when evaluating potential food-induced allergic reactions

1. Patient history is notoriously inaccurate.
2. Food allergy is most common in young children, especially with atopic dermatitis.
3. Relatively few foods are responsible for the vast majority of allergic reactions.
4. Except in allergic eosinophilic esophagitis or gastroenteritis, it is rare for patients to react to more than 3 foods.
5. When a child with food allergy has "new" or "multiple" food allergies, it is most likely that he or she is ingesting "hidden" sources of common food allergens.
6. Except in gastrointestinal allergies, most food-induced allergic symptoms develop within minutes to a few hours of ingesting the food allergen.
7. True food allergies generally involve "classical" signs and symptoms affecting the skin, gastrointestinal, and/or respiratory systems.
8. Subjective or behavioral symptoms as a sole manifestation of food allergy are very rare.
9. "Adverse reactions" to dyes and additives are rare.

Reproduced with permission from Sampson HA.[105]

True IgE-mediated food allergies involve the previously described signs and symptoms affecting the skin, gastrointestinal tract, and respiratory systems. A child can react to trace amounts of the food allergen very quickly (within minutes to ~4 hours). The reactions are reproducible on each exposure with IgE-mediated allergies, and each exposure may result in anaphylaxis. With IgE-mediated food allergies, a prior reaction does not predict the severity of a future reaction. Anaphylaxis may occur even if the previous reaction resulted in urticaria alone. The treatment with diphenhydramine (for reactions localized to the skin) or epinephrine for anaphylaxis results, in most cases, in a rapid reversal of symptom progression.

If a child eats a food, is suspected to have an IgE-mediated reaction afterward, and subsequently tolerates the food, this food should be removed from the list of potential offending foods. Also, it is reasonable that a food that is ingested infrequently is more likely to be responsible for reactions than a food that is regularly ingested. The ingredients on the label of a processed ingested food may be important in identifying the suspect allergen. The manner of preparation of the suspected food may be important as children may tolerate the food cooked but not raw. It is rare, but occasionally added spices may be the culprit for a reaction.[104] Only a very small number of additives have been implicated in food adverse reactions.[106]

All physicians must be aware of the possibility of ingestion of 1 of the major food allergens (cow's milk, egg, soy, wheat, peanut, tree nuts, shellfish, or fish)

through cross-contamination or through "hidden ingredients." An example of cross-contamination may occur when sufficient milk contamination, provokes an allergic reaction, ie, when a "boxed" fruit drink is packaged on a "nondedicated" line used to package milk drinks. Another example would be a shellfish-contaminated hamburger cooked on a grill that was previously used to cook shellfish without cleaning the grill between preparations. "Hidden ingredients" may also be peanut or nut products added to flavor or to thicken sauces (ie, spaghetti sauce, gravies, and barbecue sauces) or in baked goods.[105]

Trace amounts of food in non-IgE-mediated hypersensitivity usually do not cause clinically relevant reactions. Non-IgE-mediated or mixed IgE and non-IgE-mediated food allergic reactions are characteristically more delayed and result in symptoms 4 hours up to 5-7 days after food ingestion. The history is not as clear because, in many instances, the clinical symptoms are not associated with the food by the parents or patients. For individuals with atopic dermatitis and allergic eosinophilic esophagitis, diet diaries may be helpful in identifying a trigger food. Effective treatment for these disorders includes T cell suppressive agents, including steroids. Diphenhydramine and epinephrine do not typically abate the symptoms quickly. The response to steroid therapies may take days to weeks. Sometimes, symptoms resolve after months of avoidance of the food.

Physical Examination

The physical examination is used to evaluate cutaneous, gastrointestinal, and respiratory systems. For suspected food allergic patients, the skin should be examined carefully, with special attention to intensely pruritic, erythematous papulovesicles associated with excoriation, serous exudate, xerosis, lichinification, papules, and keratosis pilaris. Distribution and skin reaction pattern of the rash are important, with the pattern in infants and young children generally involving the face, neck, and extensor skin surfaces. In contrast, in older children with longstanding skin disease, lichenification and localization of the rash to the flexural folds of the extremities usually are found.[107] The presence of atopic dermatitis increases the likelihood that the patient has food allergies because up to 34% of patients with atopic dermatitis have a food allergy.[74] Physical findings, like allergic shiners, conjunctival injection, clear rhinorrhea, nasal congestion with a pale, edematous nasal mucosa, a transverse nasal crease, and wheezing suggest the presence of other atopic disease and increase the likelihood of coexistent IgE-mediated sensitivity to foods.

Occasionally, a physical finding will lead the diagnosis away from food allergy, such as for dermatitis herpetiformis, a classic skin manifestation of celiac disease. Evidence of weight loss or failure to thrive is more common in non-IgE-mediated allergy or gastrointestinal enteropathies than in IgE-mediated food allergy. After dietary intervention and adequate calorie intake, if weight loss or failure to thrive is persistent, further evaluation is needed to exclude other diseases.[104]

The next step is the determination of the general approach for testing and management. The reaction can likely be categorized into either a food intolerance or an allergy. If an immunologically mediated process is suspected, the reaction can be categorized as IgE-mediated, non-IgE-mediated, or a mixture of both. Based on the history and physical examination, the probable clinical syndrome can be delineated by categorizing the reactions as (1) immediate acute reactions (<4 hours) (likely IgE-mediated), or (2) delayed (6-48 hours or chronic) (likely non-IgE-mediated). The presence of the classic signs and symptoms of IgE-mediated reactions (ie, urticaria, angioedema, anaphylaxis) would suggest an IgE-mediated food allergy. The presence of gastrointestinal symptoms (nausea, vomiting, abdominal pain, or diarrhea without other symptoms) or atopic dermatitis on physical examination would suggest involvement of a non-IgE-mediated food allergy. The determination of the presence of IgE to the suspected foods is helpful in any immunologically mediated condition. If the food-specific IgE testing is negative, IgE-mediated, or mixed disease pathophysiology is excluded.

Diagnostic Testing Methods

The 2 methods of measuring specific IgE to food are the immediate hypersensitivity skin prick test and the in vitro serum-specific IgE test, which is also called an ImmunoCAP FEIA test. RAST testing is a method not currently used, but the term is sometimes still used to describe serum-specific IgE testing in general. These tests are highly sensitive (>90%) but only modestly specific (50%). Therefore, panels or broad screening should not be performed without supporting history because of the high rate of false positives. These tests

should only be performed when the clinical suspicion is very high for allergy to a food. Both of these modalities detect the presence of IgE to specific foods, but this is not synonymous with clinical reactivity.[2] When a child or adolescent has the presence of food-specific IgE, this is called "sensitization." The amount of specific IgE that correlates with clinical reactivity differs depending on the specific kind of food.[108]

Prick skin tests using commercial extracts are typically used in the evaluation of food allergy, but fresh extracts must be used for fruits and vegetables because the proteins in these foods are easily degradable and labile.[109] The prick/puncture skin test is performed by placing a drop of the allergen extract on the skin. One of several available devices is used to puncture the skin through the drop, and results are read in 15-20 minutes. The wheal and flare around the puncture is measured to determine positivity. There is a strong correlation between the wheal size and the likelihood of a clinical reaction and positive tests are considered those with a mean wheal diameter of greater than 3 mm above the saline control prick test.[110] Immediate hypersensitivity skin testing by an allergist is also a method of discerning the probability of the development of tolerance in individuals. A wheal diameter of ≥7-8 mm of the commercial extract predicts an allergic outcome to food challenge to peanut.[111,112] Food-specific skin prick test wheal diameters that are "100% diagnostic" for allergy in children to cow milk, egg, and peanut have been determined.[113]

The risk of systemic reactions to skin prick test using food allergens has been estimated at 0.005%-0.008%. The risk seems to be highest in adults and neonates.[114] Intradermal testing (insertion of 0.1 mL food extract subcutaneously) for food allergies is not recommended secondary to the high degree of false positivity and poor predictive accuracy.[115]

Positive predictive values have been determined for prick skin testing for milk, egg, and peanut for patients seen in a tertiary care allergy/immunology clinic. All the patients studied were being followed for food allergies. Based on 555 open food challenges in 467 children (median age, 3.0 years), food-specific skin prick test (SPT) wheal diameters that were "100% diagnostic" were defined for allergy to cow's milk (≥8 mm), egg (≥7 mm), and peanut (≥8 mm). In children <2 years of age, the corresponding wheal diameters were ≥6 mm, ≥5 mm, and ≥4 mm, respectively.[113] In a similar population, a retrospective study of egg allergic patients confirmed that increased wheal diameter correlates with decreased likelihood of passing oral challenge. The negative predictive accuracy of negative skin tests for major food allergens is greater than 95% in children greater than 1 year of age. Therefore, a negative skin test virtually excludes food allergy in this population. The negative predictive value in children less than 1 year of age is lower at around 80%-85% because the number of mast cells in the skin may be too low to detect a response. The positive predictive accuracy of skin prick tests is lower, at approximately 50%.[44,105,109,116,117] Therefore, if a skin prick test is positive in an individual with a vague history of reaction, a food challenge is needed to confirm the allergy.[115]

There are limitations to the skin prick/puncture methodology of detecting specific IgE to foods. As mentioned above, the threshold for cutaneous response in children less than 2 years old is lower than in older children. A clear surface for testing is required, and this is not always possible in a child with severe eczema. In order for the skin test to be performed accurately, the individual's histamine responses must be intact, so antihistamine therapy must be discontinued before the visit. Highly allergic patients cannot tolerate the increased symptoms while off the antihistamines in preparation for the testing. Test results may vary depending on the prick device, pressure,[118] and location of the test placement: as the back is approximately 20% more reactive than the arm.[119] There is also some variability in the protein content of commercial extracts for easily degradable proteins, as seen in raw fruits, nuts, and vegetables.[109,120]

In vitro serum food-specific IgE testing can be performed if the limitations of skin prick/puncture immediate hypersensitivity skin testing prevent its use. In the most frequently used assay, a serum or plasma sample is incubated with a solid immobilized preparation containing 1 allergen. This allergen containing solid phase material captures antibodies in the serum, which bind specifically to the allergen. The bound specific IgE is then detected and quantified with a labeled IgE-specific antibody detection system, such as an enzyme conjugated monoclonal anti-IgE antibody (Fig 1). The detection system detects either the amount of radioactivity or the fluorescence produced, which correlates to the amount of specific IgE. In all commercial assay systems based on immobilized allergens, a standard curve is established and used to convert the results to international units per milliliter of serum or plasma.[121] Many commercial assays are

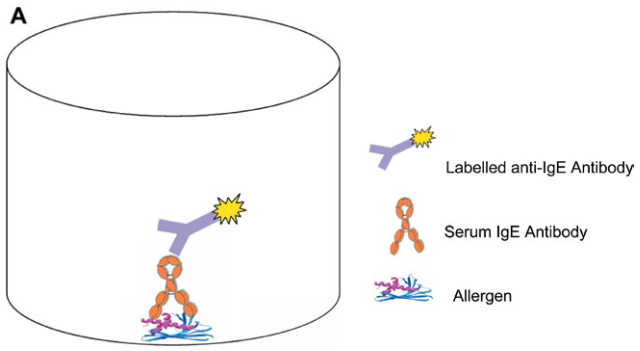

FIG 1. Food specific IgE detection assay. This assay is used to quantify the amount of allergen specific IgE antibodies in human serum samples. (Reproduced with permission from Asero et al.[121]). (Color version of figure is available online.)

TABLE 8. Predictive value of food allergen specific IgE levels.

Allergen	95% Predictive level (kIUA/L)	PPV
Egg	7	98
Infants ≤2 y	2	95
Milk	15	95
Infants ≤2 y	5	95
Peanuts	14	100
Fish	20	100
Tree nuts	~15	~95
Soybean	30	73
Wheat	26	74

Reproduced with permission from Sampson.[7]
Abbreviation: PPV, positive predictive value.

available, including the Phadia ImmunoCAP, Agilent Turbo-MP, and Siemens Immulite 2000. For each different food assayed, there may or may not be correlation between the assays. Clinicians must be careful not to make the mistake of comparing absolute values from differing assays. The correlation or lack of correlation between the assays must be considered.[122] The ImmunoCAP FEIA is the method that has been most extensively investigated in the context of food allergy.

There is significant correlation between increased concentration of specific IgE and the probability of a reaction on controlled challenge for several foods, including cow's milk, egg, peanut, tree nuts, soybean, wheat, and fish.[49,123-127] Positive predictive values for a 95% probability of reacting to a food in a population of children presenting to an allergy/immunology clinic for the evaluation of food allergy have been determined (Table 8). Although some exceptions occur, these values have proven to be very helpful in the management of food allergy in clinical practice and may be used to eliminate the need for food challenges in patients with values above the cut-off levels.[106] Even though the probability of allergic reactivity increases with increasing magnitude of sensitization, there is no absolute cut-off level above which symptoms always occur. Cross-reactivity can occur between different allergen sources, like pollen and fruit, for example. Therefore, in a general population without clinical suspicion of reactivity, a positive test likely indicates sensitization, not clinical reactivity. The specific IgE antibody levels should be performed only in the context of the patient history, physical examination, and other laboratory studies. Positive tests should only be considered to correlate with clinical reactivity when the 95% positive predictive value has been obtained for the foods (Table 8) or when there is a clear history of reaction with the specific food ingestion. Hence, the skin prick tests and in vitro serum-specific IgE assays should be performed only for clinical suspicion.

If the history and physical examination suggest a non-IgE-mediated immunologic reaction to a food, a clinician may consider other tests to confirm their suspicions. Other tests that are appropriate include endoscopy and biopsy of the gastrointestinal tract to diagnose eosinophilic gastrointestinal disease or celiac disease. Patients with severe allergic eosinophilic gastroenteritis may have anemia, blood in the stool, and decreased serum protein, albumin, and IgG levels. In patients with suspected celiac disease, IgA antitissue transglutaminase antibodies have a sensitivity ranging from 92% to 100% and a specificity of 91%-100% for celiac disease.[7,128] Breath hydrogen testing may be useful to diagnose lactose intolerance as an etiology of diarrhea with milk ingestion. To exclude cystic fibrosis as a cause of GERD symptoms, frequent stooling, abdominal pain, and failure to thrive, a sweat test may be appropriate. If the sweat test is indeterminate, fecal elastase-1 or genetic testing may be pursued.

Many families request "allergy blood testing" and it is important to mention that there are other tests that have not been validated to correspond to clinically relevant allergic disease. The tests that are unproven or have been disproved include IgG or IgG4 antibodies directed to food, hair analysis, food immune complexes, cytotoxic tests, provocation neutralization by intracutaneous testing, electrodermal testing, and applied kinesiology (muscle strength testing). Large commercial laboratories offer the food-specific IgG and IgG4 tests, which have been shown to correspond to regular ingestion of the food whether the individual

has allergic manifestations or not. If the food is avoided, the levels of antibody or immune complexes decrease.[129,130] There is currently no evidence suggesting these tests are helpful in the evaluation or management of food allergy.[131] All the above unproven tests are typically applied in situations when behavioral or developmental symptoms are suspected to be the result of food allergies. The positive tests are then used to severely restrict the diets of patients unnecessarily.[115] It is important for practitioners to be able to dispel the myths regarding these unproven tests.

Food Challenges

After a detailed history is taken, the patient is examined, and testing is obtained for specific IgE or evidence of non-IgE-mediated immunologic reactions to food, food challenges are helpful to determine if food allergy is causing clinical symptoms. Three types of challenges may be performed: open, single-blind placebo-controlled, or double-blind, placebo-controlled. The open challenge is an unblinded feeding with a food in its natural form if the concern for patient bias is low and objective symptoms like urticaria and wheezing are expected to occur with a reaction. Both the patient and the physician are aware of the challenge content and, therefore, interpretation of the challenge is subject to bias. This approach is useful to eliminate potential food culprits when the history or laboratory testing indicates the food is unlikely to be causative. It is usually performed in the office setting with an observation period of about 1-2 hours. For challenge in young children, this is, in most instances, acceptable. If this type of challenge is positive with only subjective symptoms, a blinded challenge is indicated. Blinding and masking by mixing the challenge food with a masking vehicle or placing food in opaque capsules reduces bias. Examples of challenge foods and masking vehicles include nonfat dry milk powder in applesauce, egg white powder in pudding, or whole wheat flour in mashed potatoes.[132,133]

In the single-blind placebo-controlled challenge, the patient is unaware of the challenge content but the physician is aware. It is fairly reliable if the observer's attitude is consistent throughout the challenge. Inconsistency can potentially "telegraph" to the patient or parent by the observer's unspoken action about which food is the challenge food. The placebo portion is another food that is similar in taste, consistency, texture, appearance, smell, and mouth feel to the challenge food and is known to be tolerated by the patient.[133-135] After a negative blinded challenge, the food must be consumed in its natural form followed by observation for an additional 1-2 hours because there is a 3% possibility of detecting a reaction to an open feeding in children after a negative blinded challenge.[136] The double-blind, placebo-controlled food challenge remains the gold standard for diagnosis of food allergy for both clinical and research purposes. Neither the patient, the parents, nor the physician is aware of the challenge food content. It is the most rigorous challenge design given that test foods and placebos are prepared and coded by a third party not involved in evaluating the patient, minimizing both patient and observer bias. The sequence of the administration of the test food and placebo food is concealed until the challenge is completed. Then, the results are discussed. This kind of challenge is indicated for the evaluation of subjective symptoms and is best administered by a specialist in food allergy. Primary care physicians should be aware that numerous precautions are taken before, during, and after these challenges to ensure the safety of the patient.[115] All challenges are best performed with children having discontinued any medications that could mask symptoms of an allergic reaction to the food such as antihistamines and beta-adrenergic bronchodilators.[7]

For patients with a history of delayed responses to foods, such as in chronic diseases like atopic dermatitis and gastrointestinal syndromes, elimination diets are very useful. Elimination of the food for up to 8-12 weeks with improvement in symptoms followed by recurrence of symptoms with reintroduction can delineate causative foods. There are 3 types of elimination diets that are useful in these situations. In the first, the suspected food is eliminated from the diet. In the other types, the patient is instructed to eat either a limited "eat-only" diet or an elemental diet.[103,137,138] If elimination diets are prescribed or children are allergic to a large number of foods, a nutritionist should be involved in patient care to assist with dietary management and monitor growth at a minimum of every 3 months.

Management of Food Allergies

Once the diagnosis of food allergies is established, the strict avoidance of the specific food allergen is the only proven therapy. Patients and caregivers must be

educated about food allergen avoidance through label reading, avoiding high-risk situations like buffets and the early management of allergic reactions.[7] Educational materials are available through excellent patient advocacy groups like the Food Allergy and Anaphylaxis Network (http://www.foodallergy.org) and assistance with coping methods are offered through this organization and others. Because most patients with fatal food-induced anaphylaxis did not receive epinephrine at the time of their reaction,[67] this is an extremely important aspect of the management of food allergic patients. All patients with food-related anaphylaxis should be prescribed epinephrine and patients with a history of suspected or proven IgE-mediated systemic reactions (including generalized urticaria) to food should be prescribed self-injectable epinephrine and instructed on its use. Patients at highest risk of fatal anaphylactic reactions include those with concomitant asthma and peanut, tree nut, fish, and shellfish allergies.[2] Video instruction on the use of the epinephrine and/or use of a "trainer" to practice administration is important at the time the autoinjector is prescribed. The manufacturers of these medications produce these educational materials. It is important for patients to be comfortable using epinephrine in the event of an emergency because questionnaires of families of children with food allergy have revealed that only 32% can correctly demonstrate the use of the injectable epinephrine device.[139] The practical demonstration of the use of an epinephrine auto-injector and prior consultation with an allergy specialist are associated with at least a 4- to 5-fold greater chance that parents will be able to use the device.[140] Patients must also know that after epinephrine is administered, emergency medical personnel should be contacted for transport to the nearest hospital for observation. This is to ensure additional therapy is available if needed for continued symptoms or if a biphasic reaction occurs. Food allergy action plans can be administered to help caregivers understand which symptoms warrant epinephrine use. Identifying bracelets/medallions are commercially available to alert others in the event of an emergency of the individual's food allergy diagnosis. These can be found online through food allergy advocacy group web sites.

Antihistamines are helpful to alleviate pruritus in the oral allergy syndrome[141] and can give relief to IgE-mediated skin symptoms. These agents, however, do not block systemic reactions. Epinephrine is still the most effective therapy for systemic reactions. Topical corticosteroids or, in severe cases, systemic corticosteroids are helpful in chronic syndromes like atopic dermatitis and eosinophilic esophagitis.[142,143]

The American Academy of Pediatrics has recently published guidelines regarding the prevention of atopic disease in infants and children. The recommendations from the Committee on Nutrition state that infants at high risk of developing atopic disease [ie, infants with at least 1 first-degree relative (parent or sibling) with documented allergic disease] should continue exclusive breastfeeding for at least 4 months and introduction of solid foods should begin at 4-6 months of age. The committee concluded that there were insufficient data to support a protective effect of any dietary intervention beyond the above recommendations on the development of atopic disease.[144] This reverses prior recommendations that cow's milk be introduced after 1 year of age, egg after 2 years, and peanuts, tree nuts, and fish after 3 years of age.[145,146] There is currently no clear recommendation regarding the introduction of solid foods in children with preexisting atopic disease. A summary of the current guidelines regarding the diagnosis and management of food allergy is seen in Figure 2.[2] An allergist can be very helpful to primary physicians in the care of these patients for education and performance of skin testing to help predict the development of tolerance.

Future Immunomodulatory Approaches

Several new therapies are under investigation for the treatment of food allergic disorders because the current avoidance therapy is not optimal. The avoidance of specific foods can be nutritionally and socially limiting. Sublingual and oral immunotherapy with standard food allergens like milk, egg, peanut, fish, and hazelnut are in clinical trials. The gradual exposure to food proteins orally is thought to avoid acute allergic reactions by the induction of oral tolerance mechanisms through the production of inhibitory cytokines and regulatory T cells. Oral immunotherapy protocols have been variably successful and failures appear more common in patients with higher specific IgE. These procedures are still experimental as systemic allergic reactions occur even while subjects are on stable doses.[147]

Nonspecific therapies that dampen the allergic response to food allergens have also been explored.

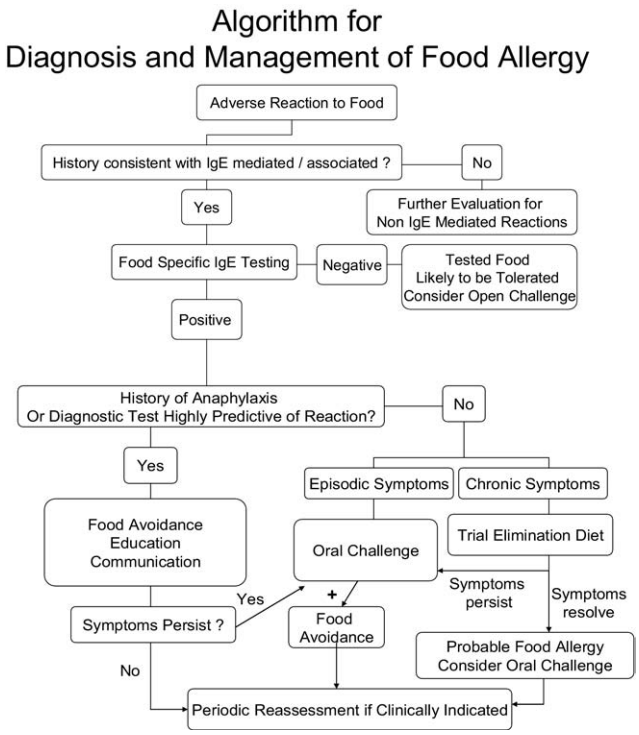

FIG 2. Algorithm for diagnosis and management of food allergy. (Adapted with permission from American College of Allergy and Immunology.[2])

Anti-IgE monoclonal antibodies have been used to neutralize IgE to reduce or eliminate food-induced anaphylaxis. This therapy would be useful for a variety of food allergens but a preliminary study, although showing an improved threshold for reactivity to peanut, did not demonstrate uniform protection.[148] No clinical trials are underway using anti-IgE monoclonal antibodies. The Chinese herbal remedy Food Allergy Herbal Formula, a mixture of 9 herbs that completely blocked anaphylaxis in a mouse model of peanut allergy,[149] is currently in safety trials in humans.[150] Cytokine antagonists like anti-IL-5 have shown promise in disorders like eosinophilic esophagitis,[151] but trials are lacking in children. Strategies to create vaccines composed of small peptides or proteins with mutated B cell epitopes have been effective in animal models but human studies have not been performed.[150,152] Other strategies being explored include attaching immune stimulatory sequences to allergens, which provide steric hindrance to reduce IgE binding and enhance inhibitory responses. This has been shown to be effective in animal models and in humans for environmental allergens. It has not yet been explored with food allergens.[153]

Conclusions

The prevalence of food allergies is increasing, but the public perception of the problem is greater than the true prevalence. Correct diagnosis of food allergy depends on evidence of both clinical reactivity and food-specific IgE by in vivo skin prick/puncture testing or in vitro serum assays. Oral food challenges are an important aspect of the evaluation of food allergy and assessment of the development of tolerance. Research is ongoing in therapeutic interventions, especially the use of oral immunotherapy and herbal remedies. Effective management of food allergy is dependent on complete avoidance of the food allergen, patient education, and emergency treatment of anaphylaxis with epinephrine. An allergist can be of great help in the diagnosis of food allergy by identifying the causative food, developing a specific elimination diet, educating about food allergen avoidance, and developing an action plan for families in the event of an accidental exposure.

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