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Allergic Disorders

Scott H. Sicherer

Definition of Food Allergy

Because individuals ingest food throughout the day, potentially any malady could be falsely associated with eating. In fact, surveys of adults have shown that 18 to 22% believe that they have a food allergy,[1-3] and 28% of parents suspect a food allergy in their infants and young children.[4] However, true food allergy affects 6 to 8% of children[4] and approximately 2% of adults.[3-5] The discrepancy between suspected and true allergy is due, in part, to the manner in which food allergy is defined. Technically, a food allergy is an adverse *immune response* toward protein in food.[6] This is in contrast to a larger number of non-immune mediated adverse reactions to food. These non-immune-mediated reactions include those caused by toxins in foods that would affect anyone ingesting the tainted food, and those caused by a particular condition of the affected individual (*food intolerance*). Examples of food intolerance/reactions to toxins are listed in Table 41.1.

Pathophysiology of Food Allergic Reactions

A vast number of potentially immunoreactive food proteins pass through the gut, but the normal response to these foreign proteins is tolerance. That is, the immune system recognizes these proteins (antigens), but does not process these proteins in a manner that results in adverse reactions. In fact, approximately 2% of ingested food enters the blood stream in an immunologically intact form,[7] but causes no symptoms in the normal individual. It remains unclear why some individuals develop food allergies, but a genetic predisposition toward allergic responses plays a role.[8] For those individuals predisposed to food allergies, food allergens can elicit specific responses in several ways.

The most common immunologic basis for food allergic responses involves the generation of proteins, IgE antibodies, that mediate immediate food hypersensitivity reactions.[9,10] When a protein enters the intestine, immune cells termed antigen presenting cells (APC) process the protein (usually a glycoprotein) and present a small portion of

TABLE 41.1

Examples of Food Intolerance/Toxic Reactions (Non-Immunologic, Adverse Reactions to Food)[21,140,141]

Disorder/Sensitivity	Pathophysiology/Symptoms
Lactase deficiency (lactose intolerance)	Bloating, diarrhea from inability to digest the lactose in cow's milk; may be dose-related
Tyramine sensitivity	Tyramine in hard cheeses, wine may trigger migraine headache
Scombroid fish poisoning	Oral pruritus, flushing, vomiting, hives from histamine released from spoiled dark meat fish (tuna, Mahi-Mahi)
Caffeine	Pharmacologic effects of jitteriness, heart palpitations
Myristicin	Hallucinogen in nutmeg
Gallbladder disease	Pain following ingestion of fatty foods

the protein to T-cells that specifically recognize the protein fragment (Figure 41.1). Cellular interactions between the APC and T-cell may direct the T-cell toward allergic responses (termed Th-2 responses). The sensitized T-cells replicate and then interact with B-cells in the context of further exposure to the food antigen, leading these B-cells to produce IgE antibodies that specifically bind a portion of the food protein (epitope). These IgE antibodies bind to specific receptors found on mast cells in body tissues and basophils in the bloodstream. The mast cells and basophils have preformed mediators (e.g., histamine) that, when released from the cell, cause tissue swelling (edema from capillary leakage of fluid) and pruritus. When the mast cell or basophil armed with the food-specific IgE antibody comes in contact with the particular allergenic protein, the IgE antibodies attach to the protein and crosslink, resulting in release of the mediators and the onset of the food-allergic reaction.

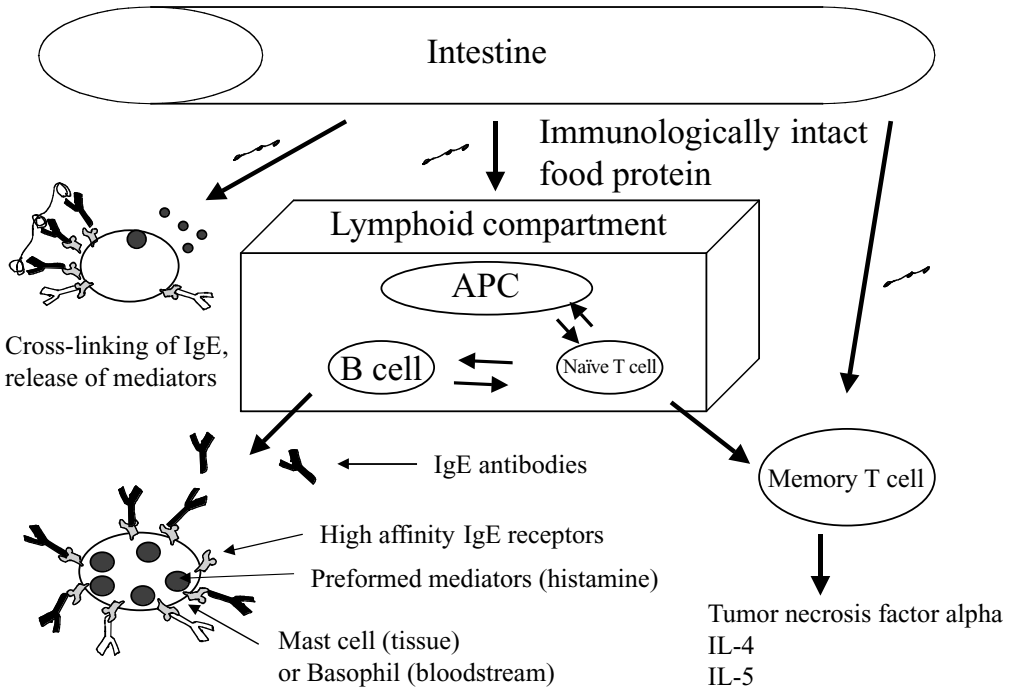

FIGURE 41.1
APC-antigen presenting cells, IL-interleukin. See text for details.

TABLE 41.2

Foods Responsible for the Majority (85 to 90%) of Significant Allergic Reactions[3,5,12,13]

Infants/Young Children	Older Children/Adults
Egg	Peanut
Cow's milk	Tree nuts
Soy bean	Shellfish
Peanut	Fish
Wheat	
Fish	
Tree nuts (walnut, Brazil, hazel, almond, cashew, etc.)	
Shellfish	

A second way in which the immune system may react adversely toward a food protein does not involve the generation of IgE antibody (non-IgE-mediated). In this case the T-cell may, through direct interaction with specific receptors on the cells, elaborate mediators (cytokines) with direct effects. An example is the release of tumor necrosis factor alpha that causes gut edema in certain forms of cow's milk allergy.[11] Further research is under way to better delineate the mechanisms of non-IgE-mediated food allergy.

Food Allergens

Many studies have indicated that a rather short list of foods accounts for the majority (85 to 90%) of food-allergic reactions: chicken egg, cow's milk, wheat, soybean, peanut, tree nuts, fish, and shellfish.[3,12-15] However, virtually any food protein could elicit an allergic response. Many of the allergenic food proteins have been characterized and are generally heat-stable, water-soluble glycoproteins from 10 to 70 kd in size.[16,17] For many of these proteins, the particular allergenic epitopes that bind IgE or T-cell receptors have been mapped.

Epidemiology

Population-based studies utilizing oral food challenges to confirm reactivity have determined that food allergy affects 6 to 8% of young children[4] and almost 2% of adults.[3] The foods causing significant allergic reactions in different age groups are listed in Table 41.2. Most children outgrow their sensitivity to milk, egg, soy, and wheat, but allergy to peanut, tree nuts (e.g., walnut, cashew, Brazil nut, etc.), fish, and shellfish account for the majority of significant food allergies in adults, and are foods for which tolerance rarely develops.[12,18] Peanut and tree nut allergy alone affects 1.3% of the general population of the U.S.[19] Allergic reactions to food dyes and additives are comparatively rare, affecting up to 0.23% of the population.[20] Food allergy is a cause of a number of particular illnesses, as shown in Table 41.3.

TABLE 41.3

Epidemiologic Role of Food Allergy in Various Disorders

Disorder	Prevalence of Food Allergy as a Cause of the Disorder
Anaphylaxis[95,96,142]	34-52%
Asthmatic children[91]	6%
Asthmatic adults[92]	<1%
Atopic dermatitis (moderate-severe) in children[30]	37%
Atopic dermatitis in adults[34]	Rare
Acute urticaria[143]	20%
Chronic urticaria[144]	1.4%
Infantile refractory reflux[145]	42%
Childhood refractory constipation[73]	68%

Food Allergic Disorders

Food allergic disorders affect the skin and the gastrointestinal and respiratory tracts.[21] The pathophysiologic basis of the disorders may be IgE-mediated, non-IgE-mediated, or combined. In general, disorders with acute onset occurring within minutes to an hour after food ingestion are mediated by IgE antibody, while those that are more chronic and occur hours after ingestion are not IgE-mediated. Particular food allergic disorders are discussed below.

Disorders Affecting the Skin

Acute Urticaria

Urticaria, or hives, are characterized by pruritic, transient, erythematous raised lesions with central clearing and a surrounding area of erythema. The rash should leave no residual lesions after resolution. Hives may sometimes be accompanied by localized swellng (angioedema). Although there are many causes of acute urticaria, food allergy accounts for up to 20% of episodes.[22] The immediate onset of hives is mediated by specific IgE to food protein. Lesions usually occur within an hour of ingestion or skin contact with the causal food.[23]

Chronic Urticaria

This disorder of longstanding hives lasting over six weeks is rarely associated with food allergy. Only 1.4% of chronic/persistent urticaria is caused by food allergy, so a search for a causative food in the initial evaluation of this illness is often futile.[24]

Contact Urticaria

In some cases, topical exposure to a food (e.g., on the skin of the face) can cause a local reaction either through irritation or through specific immune mechanisms.[25]

Atopic Dermatitis (AD)

This rash usually begins in early infancy. It is characterized by a typical distribution on the extensor surfaces and faces of infants, or creases in older children and adults, with

extreme pruritis and a chronic and relapsing course.[26] Atopic dermatitis is frequently associated with allergic disorders (asthma, allergic rhinitis) and with a family history of allergy.[27] Evidence suggests that, particularly in children, IgE-mediated food allergy plays a pathogenic role,[27] although non-IgE-mediated food allergy has also been implicated.[28] Clinical studies utilizing double-blind, placebo-controlled food challenges (DBPCFCs) have shown a prevalence rate of food allergy in 33 to 37% of children with moderate to severe AD.[29,30] Studies of dietary elimination have repeatedly shown improvement in AD symptoms.[12,31,32] The more severe the rash, the more likely that food allergy is associated;[33] however, AD is rarely associated with food allergy in adults.[34,35]

Dermatitis Herpetiformis (DH)

DH is a chronic papulovesicular skin disorder with lesions distributed over the extensor surfaces of the elbows, knees, and buttocks.[36] Immunohistologic examination of the lesions reveals the deposition of granular IgA antibody at the dermoepidermal junction.[37] The disorder is associated with a specific non-IgE-mediated immune response to gluten (a protein found in grains such as wheat, barley, and rye). Although related to celiac disease, there may be no associated gastrointestinal complaints; however, up to 72% may show villus atrophy on intestinal biopsy.[37] The rash abates with elimination of gluten from the diet.

Disorders Affecting the Gastrointestinal Tract

Immediate Gastrointestinal Hypersensitivity

In this syndrome, ingestion of the causal protein results in immediate (minutes to up to one to two hours) gastrointestinal symptoms that may include nausea, vomiting, abdominal pain, and diarrhea. Considered here as a distinct syndrome, it is more commonly associated with reactions in other organ systems, such as during systemic anaphylaxis in patients with other atopic diseases. For example, children with atopic dermatitis undergoing oral food challenges with foods to which they have specific IgE antibody will sometimes manifest only gastrointestinal symptoms.[13,38]

Oral Allergy Syndrome

Symptoms include pruritus and angioedema of the lips, tongue, and palate, and are of rapid onset, typically while eating certain fresh fruits and vegetables.[39] The reaction occurs primarily in adults with pollen allergy (hay fever) sensitized to crossreacting proteins in particular fruits and vegetables as shown in Table 41.4. Up to 71% of adults with pollen allergy experience these symptoms.[40] The proteins are labile, and cooked forms of the fruits and vegetables generally do not induce symptoms.

Dietary Protein-Induced Proctitis/Proctocolitis of Infancy

Food allergy is the most common cause of rectal bleeding due to colitis in infants.[41] Infants with this disorder are typically healthy, but have streaks of blood mixed with mucus in their stool. The most common causal food is cow's milk or soy, and even breastfed infants can develop this reaction from small amounts of protein passed through breast milk in mothers ingesting the causal protein.[42] Although peripheral eosinophilia and positive radioallergosorbent tests (RASTs; serum tests to determine specific IgE antibody) to milk have been reported, they are not consistent findings.[41,43-45] In cow's milk- or soy formula-fed infants, substitution with a protein hydrolysate formula generally leads to cessation

TABLE 41.4

Cross-Reactions Due to Proteins Shared by Pollens and Foods Leading to Symptoms of the Oral Allergy Syndrome[39,146,147,150]

Birch Pollen	Ragweed Pollen	Grass Pollen
Apple	Melons	Peach
Carrot		Potato
Cherry		Tomato
Apricot		Cherry
Plum		
Celery		

of obvious bleeding within 72 hours. The majority of infants who develop this condition while ingesting protein hydrolysate formulas will experience resolution of bleeding with substitution of an amino acid-based formula.[46]

Dietary (Food) Protein-Induced Enteropathy

This disorder affects primarily infants and young children and is characterized by failure to thrive, diarrhea, emesis, and hypoproteinemia usually related to an immunologic reaction to cow's milk protein.[47-50] The syndrome may also occur following infectious gastroenteritis in infants.[48,51] Patchy villous atrophy with cellular infiltrate on biopsy is characteristic. Diagnosis is based upon the combined findings from endoscopy/biopsy, allergen elimination, and challenge. While this syndrome resembles celiac disease, resolution generally occurs in one to two years.[48]

Dietary (Food) Protein-Induced Enterocolitis Syndrome (FPIES)

FPIES as defined by Powell[52,53] describes a symptom complex of profuse vomiting and diarrhea diagnosed in infancy during chronic ingestion of the causal food protein — usually cow's milk or soy. Since both the small and large bowel are involved, the term enterocolitis is used. When the causal protein is reintroduced acutely after a period of avoidance with resolution of symptoms, symptoms characteristically develop after a delay of two hours, with profuse vomiting and later diarrhea.[53,54] There is also an accompanying increase in the peripheral polymorphonuclear leukocyte count and, in some cases, severe acidosis and dehydration.[54,55] Confirmation of the allergy included a negative search for other causes, improvement when not ingesting the causal protein, and a positive oral challenge resulting in the characteristic symptoms/signs. Approximately 50% of the infants react to both cow's milk and soy. Sensitivity to milk is lost in 60% and to soy in 25% of the patients after two years from the time of presentation.[54,56] Treatment with a hydrolyzed cow's milk formula is advised, although some patients may react to the residual peptides in these formulas, requiring an amino acid-based formula.[57]

Allergic Eosinophilic Gastroenteritis (AEG)/Allergic Eosinophilic Esophagitis (AEE)

These disorders are characterized by infiltration of the esophagus (AEE), gastric, and/or intestinal walls (AEG) with eosinophils, peripheral eosinophilia (in 50 to 75%) and absence of vasculitis.[58] Patients with AEG present with postprandial nausea, abdominal pain, vomiting, diarrhea, protein-losing enteropathy, and weight loss, and depending upon the obstruction ascites can also develop.[59,60] Those with AEE may present with symptoms of severe reflux disease.[61] The diagnosis rests upon biopsy showing eosinophilic infiltration, although there may be patchy disease and infiltration may be missed.[62] Formal trials of

food elimination in adults have had mixed success, but large groups have not been evaluated for depth of infiltration and abdominal bloating,[60,63,64] and those studied clearly represent a heterogeneous group. In children with AEE, significant success from dietary elimination has been achieved.[61] AEE was associated with positive tests for food-specific IgE antibody in some of the children, but most with this disorder do not have IgE-mediated food allergy.

Celiac Disease

Celiac disease is a dietary protein enteropathy characterized by an extensive loss of absorptive villi and hyperplasia of the crypts leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. As the disease represents an immune response to a food protein, it may be considered a food allergic disorder.[65] Patients with celiac disease are sensitive to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley. Endoscopy typically reveals total villous atrophy and extensive cellular infiltrate. The prevalence of Celiac disease has been reported between 1:3700 and 1:300.[66] Chronic ingestion of gluten-containing grains in Celiac patients is associated with increased risk of malignancy, especially T-cell lymphoma.[67]

Other Disorders Possibly Associated with Food Allergy

Gastroesophageal Reflux (GER)

GER has been associated with cow's milk allergy (CMA) in infants. Forget and Arenda[68] demonstrated that infants who appear to have GER but do not respond to medical therapy may have CMA. Cavataio, Iacono, and colleagues[69-71] have investigated these issues in several prospective controlled trials. They have demonstrated that up to 42% of infants under one year of age with GER also have CMA.

Constipation

Constipation has also been associated with cow's milk allergy in young children.[72,73] Investigators have demonstrated the presence of eosinophilic proctitis in children with chronic constipation, resolution of constipation after withdrawal of cow's milk from the diet (and substitution with soy-based formula), and recurrence upon reintroduction of cow's milk.

Occult Blood Loss from the Gastrointestinal Tract/Iron Deficiency Anemia

Ingestion of whole cow's milk by infants less than six months of age may lead to occult blood loss from the gastrointestinal tract and iron deficiency anemia.[74] The use of infant formulas generally results in resolution of symptoms.

Infantile Colic

There is limited evidence that infantile colic is associated with food (cow's milk) allergy in a subset of patients (sometimes on an IgE-mediated basis), but more studies are needed to define the relationship.[75-77]

Inflammatory Bowel Disease

A role for food allergy in inflammatory bowel disease has been suggested because elemental diets have been shown to induce remission in Crohn's disease. [78,79] However, meta-analyses of elemental diets for Crohn's disease have demonstrated that they are inferior to steroids at inducing and maintaining remission, despite their popularity in some countries.[80-82]

TABLE 41.5

Gastrointestinal Diseases Associated with Food Allergy

Disorder	Age Onset	Duration	Symptoms/Features	Foods
Food protein-induced enterocolitis syndrome [53,54]	1 day-9 months	Usually 1-3 years	Vomiting, diarrhea, failure to thrive, villus injury, dehydration, acidosis	Cow's milk, soybean, (rare grains, poultry)
Enteropathy [15,48]	2-18 months	Usually 1-3 years	Failure to thrive, edema, diarrhea, villus injury, malabsorption	Cow's milk, soy
Celiac disease[152]	Any	Lifelong	Villus injury, malabsorption	Gluten
Proctocolitis [42]	Infants	1 year	Bloody stools	Cow's milk, soybean
Allergic eosinophilic gastroenteritis/ esophagitis[59,61]	Any	Long-lived	Vomiting, abdominal pain, diarrhea, eosinophilic infiltration of gut	Multiple foods

Irritable Bowel Syndrome

The relationship of irritable bowel syndrome to food allergy has not been systematically studied.[83-85] A summary of the gastrointestinal diseases associated with food allergy is given in Table 41.5.

Disorders Affecting the Respiratory Tract

Allergic Rhinitis

Symptoms of congestion, rhinorrhea, and nasal pruritus are usually associated with hypersensitivity to airborne allergens, not foods. Rarely, isolated nasal symptoms may occur as a result of an IgE-mediated allergy to ingested food proteins.[86] The prevalence of this illness, even among patients referred to allergy clinics, appears to be under 1%. On the other hand, 25 to 80% of patients with documented IgE-mediated food allergy experience nasal symptoms during oral food challenges that result in systemic symptoms.[86] In contrast to immune-mediated rhinitis, *gustatory rhinitis* refers to rhinorrhea caused by spicy foods. This reaction is mediated by neurologic mechanisms.[87]

Asthma

Lower airway symptoms of wheezing, cough, and dyspnea induced by lower airway inflammation and bronchoconstriction can be related to food allergy. Reactions may occur based upon IgE-mediated reactions from ingestion of the causative food or from inhalation of vapors released during cooking or in occupational settings.[88-90] The prevalence of food-related asthma in the general population is unknown, but studies utilizing DBPCFCs report a prevalence of 5.7% among children with asthma,[91] 11% among children with atopic dermatitis,[88] and 24% among children with a history of food-induced wheezing.[89] The prevalence of food-induced wheezing among adults with asthma is under 2%.[92]

Heiner's Syndrome

This is a rare, non-IgE-mediated adverse pulmonary response to food, affecting infants. The disorder is characterized by an immune reaction to cow's milk proteins with precip-

TABLE 41.6

Symptoms Occurring in Anaphylaxis[14,15,94,96]

Organ System	Symptoms
Respiratory	Throat tightness, wheezing, repetitive coughing, nasal congestion rhinitis, hypoxia/cyanosis
Gastrointestinal	Obstructive tongue edema, nausea, vomiting, diarrhea, abdominal pain, oral pruritus, lip edema
Skin	Pruritus, urticaria, angioedema, morbiliform rash
Cardiovascular	Hypotension, syncope, dysrhythmia
Other	Sense of "impending doom," uterine contractions

itating antibodies (IgG) to cow's milk protein resulting in pulmonary infiltrates, pulmonary hemosiderosis, anemia, failure to thrive, and recurrent pneumonias.[93] Elimination of cow's milk protein is curative.

Multisystem Disorders

Anaphylaxis

Clinically, anaphylaxis refers to a dramatic, severe multi-organ systemic allergic reaction associated with IgE-mediated hypersensitivity that may be life-threatening. Anaphylaxis has been defined technically as an immediate, systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from mast cells and basophils.[94] Food is the most common cause of out-of-hospital anaphylaxis.[95-97] Symptoms may affect the skin, respiratory tract, and gastrointestinal tract (Table 41.6). Symptoms can be severe, progressive, and potentially fatal. Fatal food-induced anaphylaxis appears to be more common among teenage patients with underlying asthma.[14,15] In addition, patients who experienced fatal or near fatal anaphylaxis were unaware that they had ingested the incriminated food, had almost immediate symptoms, had a delay in receiving adrenaline, and in about half of the cases there was a period of quiescence prior to a respiratory decompensation.[14] The foods most often responsible for food-induced anaphylaxis are peanut, tree nuts, and shellfish.[14,15,98,99]

Food-Associated, Exercise-Induced Anaphylaxis

This uncommon disorder refers to patients who are able to ingest a particular food or exercise without a reaction. However, when exercise follows the ingestion of a particular food, anaphylaxis results.[100-102] In some cases, exercise after any meal results in a reaction. Treatment depends upon elimination of the causal food for 12 hours prior to exercise.

Disorders not Clearly Related to Food Allergy

Patients may relate a variety of ailments to food allergy (headaches, seizures, behavioral disorders, fatigue, arthritis, etc.), but many of these are either false associations or adverse

reactions that are not immunologic in nature. Food allergy may play a role in a minority of patients with migraine headaches,[103] although the pharmacologic activity of certain chemicals that are found in some foods (i.e., tyramine in cheeses) is more often responsible. The role of food allergy in childhood behavioral disorders is also controversial. Although a small subset of patients with behavioral disorders may be affected by food dyes, there is no convincing evidence that food allergy plays a direct role in these disorders,[104,105] and children are not allergic to "sugar." On the other hand, for individuals with these ailments who also have bona fide allergies, treatment to relieve symptoms of asthma, atopic dermatitis, and hay fever should be pursued in parallel to treatment directed at the unrelated disorder.

Diagnostic Approach to Food Allergic Disorders

The diagnosis of food allergy often rests simply upon a history of an acute onset of typical symptoms, such as hives and wheezing, following the isolated ingestion of a suspected food, with confirmatory laboratory studies indicating the presence of specific IgE antibody to the suspected food. However, the diagnosis is more complicated when multiple foods are implicated or when chronic diseases such as asthma[106] or atopic dermatitis[107] are evaluated. The diagnosis of food allergy and identification of the particular foods responsible is also problematic when reactions are not mediated by IgE antibody, as is the case with a number of gastrointestinal food allergies.[54] In these latter circumstances, well-devised elimination diets followed by physician-supervised oral food challenges are critical in the identification and proper treatment of these disorders.

General Approach to Diagnosis

The history and physical examination must review general medical concerns to exclude nonimmunologic adverse reactions to foods or to consider other allergic causes for symptoms (e.g., cat allergy causing asthma). In relation to foods, a careful history should focus upon the symptoms attributed to food ingestion (type, acute versus chronic), the food(s) involved, consistency of reactions, quantity of food required to elicit symptoms, timing between ingestion and onset of symptoms, the most recent reaction/patterns of reactivity, and any ancillary associated activity that may play a role (i.e., exercise, alcohol ingestion). The information gathered is used to determine the best mode of diagnosis, or may lead to dismissal of the problem based upon the history alone.

For acute reactions after isolated ingestion of a particular food, such as acute urticaria or anaphylaxis, the history may clearly implicate a particular food, and a positive test for specific IgE antibody would be confirmatory. If the ingestion was of mixed foods and the causal food was uncertain (e.g., fruit salad), the history may help to eliminate some of the foods (those frequently ingested without symptoms), and specific tests for IgE may help to further narrow the possibilities. In chronic disorders such as atopic dermatitis or asthma, it is more difficult to pinpoint causal food(s).[107] The approach to diagnosis in these chronic disorders usually requires elimination diets and oral food challenges to confirm suspected associations. This is particularly the case for the non-IgE-mediated reactions or those attributed to food dyes/preservatives in which ancillary laboratory testing is not helpful.

Tests for Specific IGE Antibody

In the evaluation of IgE-mediated food allergy, specific tests can help to identify or exclude responsible foods. One method to determine the presence of specific IgE antibody is prick-puncture skin testing. While the patient is not taking antihistamines, a device such as a bifurcated needle or lancet is used to puncture the skin through a glycerinated extract of a food and appropriate positive (histamine) and negative (saline-glycerine) controls. A local wheal and flare response indicates the presence of food-specific IgE antibody (a wheal >3 mm is considered positive). Prick skin tests are most valuable when they are negative, since the negative predictive value of the tests is very high (over 95%).[108,109] Unfortunately, the positive predictive value is on the order of only 50%.[108,109] Thus, a positive skin test in isolation cannot be considered proof of clinically relevant hypersensitivity. Intradermal allergy skin tests with food extracts give an unacceptably high false-positive rate, have been associated with systemic reactions including fatal anaphylactic reactions, and should not be used.[109] An additional issue is that the protein in commercial extracts of some fruits and vegetables are prone to degradation, so fresh extracts of these foods are more reliable[110] and the "prick-prick" manner of testing may be indicated, where the probe is used to first pierce the food being tested (to obtain liquid) and then the skin of the patient.

RASTs

In vitro tests for specific IgE (RASTs) are also helpful in the evaluation of IgE-mediated food allergy.[111] Unlike skin tests, RASTs can be used while the patient is taking antihistamines and does not depend on having an area of rash-free skin for testing. Like skin tests, a negative result is very reliable in ruling out an IgE-mediated reaction to a particular food, but a positive result has low specificity. Recent studies have been evaluating improved RASTs that may have added predictive value for clinical reactivity.[111-113]

In addition to the high false positive rate of tests for food-specific IgE antibodies, several other issues complicate interpretation. It is not uncommon for patients to have positive skin tests and RASTs to several members of a botanical family or animal species. This usually represents immunologic cross-reactivity but may not represent clinical reactivity. For example, most peanut-allergic patients will have positive skin tests to at least a few of the other members of the legume family, but only 5% will have clinical reactions to more than one legume.[114] Further testing with oral challenges, if the history does not resolve the issue, would be required. More importantly, the foods selected for testing should be carefully selected to include only those suspected to be at issue in order to avoid false positive tests that inappropriately lead to questions about foods that have been previously tolerated. Lastly, one should be wary of tests such as measurement of IgG_4 antibody, provocation-neutralization, cytotoxicity, applied kinesiology, among other unproved methods.[115]

Food Elimination Diets

As an adjunct to testing, the first step in proving a cause-and-effect relationship with a particular illness and food allergy (whether IgE-mediated or not) is to show resolution of symptoms with elimination of the suspected food(s). In many cases, one or several foods are eliminated, which may be the obvious course of action when an isolated food ingestion

(i.e., peanut) causes a sudden acute reaction and there is a positive test for IgE to the food. This would also represent a therapeutic intervention. However, eliminating one or a few suspected foods from the diet when the diagnosis is not so clear (asthma, atopic dermatitis, chronic urticaria) can be a crucial step in determining whether food is causal in the disease process. If symptoms persist, the eliminated food(s) is (are) excluded as a cause of symptoms. Alternatively, and as is more likely the case for evaluating chronic disorders without acute reactions, eliminating a large number of foods suspected to cause a chronic problem (usually including those that are common causes of food-allergic reactions as described above) and giving a list of "allowed foods" may be the preferred approach. The primary disadvantage of this approach is that if symptoms persist, the cause could still be attributed to foods left in the diet. Thus, a third type of elimination diet is an elemental diet in which calories are obtained from a hydrolyzed formula, or preferably from an amino acid-based formula. A variation is to include a few foods likely to be tolerated (but, again this adds the possibility that persistent symptoms are caused by these foods). This diet is extremely difficult to maintain in patients beyond infancy. In extreme cases, nasogastric feeding of the amino acid-based formula can be achieved, although some patients can tolerate the taste of these formulas with the use of flavoring agents provided by the manufacturers. This diet may be required when the diets mentioned above fail to resolve symptoms, but suspicion for food-related illness remains high. It is also required in disorders associated with multiple food allergies such as allergic eosinophilic gastroenteritis. With AEG, prolonged dietary elimination for three to six weeks is sometimes needed to determine whether resolution of symptoms will occur.[61]

Food Challenges

An oral food challenge is performed by feeding the patient the suspected food under physician observation. There are several settings in which physician-supervised oral food challenges are required for diagnosis of food-allergic disease (Table 41.7). Because food challenges may elicit severe reactions, they are usually conducted under physician supervision, with emergency medications to treat anaphylaxis immediately available.[116] Challenges can be performed "openly" with the patient ingesting the food in its native form, "single-blind" with the food masked and the patient unaware if they are receiving the test food, or as DBPCFCs where neither patient nor physician knows which challenges contain the food being tested. While open and single-blind challenges are open to patient or observer bias, the DBPCFC is considered the gold standard for diagnosis, since bias is removed.[116]

In all of these challenges, the food is given in gradually increasing amounts that may be individualized both in dose and timing, depending on the patient's history. For most IgE-mediated reactions, experts suggest giving 8 to 10 grams of the dry food or 100 ml of wet food (double amount for meat/fish) at 10 to 15 minute intervals over about 90 minutes followed by a larger, meal-size portion of food a few hours later.[116] Starting doses may be a minute amount applied to the inner lip followed by 1% of the total challenge, followed by gradually increasing amounts (4, 10, 20%, etc.). However, challenges may be individ-

TABLE 41.7

Indications for Performing Physician-Supervised Oral Food Challenges

To confirm a food allergy when history is unclear and tests not confirmatory
To exclude a food allergy
To monitor for development of tolerance

ualized to parallel the clinical history (i.e., feeding over consecutive days for chronic disorders with delayed symptoms). Similarly, higher risk challenges may start at extremely low doses with very gradual increases over longer time intervals.

Symptoms are recorded and frequent assessments are made during the challenge for symptoms affecting the skin, gastrointestinal tract, and/or respiratory tract. Challenges are terminated when a reaction becomes apparent, and emergency medications are given as needed. Generally, antihistamines are given at the earliest sign of a reaction, with epinephrine and other treatments given if there is progression of symptoms or any potentially life-threatening symptoms.

The practical issues in preparing food challenges include palatability and masking foods in appropriate vehicles, with placebos for DBPCFCs. In many cases, dry forms of the food (flour, powdered egg whites, etc.) can be hidden in puddings or liquids. Bulkier foods may be hidden in pancakes or ground beef. Flavoring agents such as mint can be added for further masking. Hiding the food in opaque capsules is a convenient method to administer blinded challenges for patients who are able to ingest these capsules.

Non-IgE-mediated reactions (e.g., AEG, enterocolitis, etc.) are more difficult to diagnose since there are no specific laboratory tests to identify particular foods that may be responsible for these illnesses. In many cases, a biopsy may be needed (e.g., AEG) to establish an initial diagnosis. Elimination diets with gradual reintroduction of foods and supervised oral food challenges are often needed to identify whether diet plays a role in the disorder, and to identify the causal food(s). Specific challenge protocols have been advised for food-induced enterocolitis syndrome.[53] Oral challenges can be used to evaluate reactions to food additives (coloring and flavoring agents and preservatives) or virtually any complaint associated with foods. When used to evaluate behavioral disorders or other complaints not convincingly associated with food allergy, DBPCFCs are advised to avoid bias.

Treatment of Food Allergy

The mainstay of treatment for food allergy is dietary elimination of the offending food. The elimination of particular dietary food proteins is not a simple task. Table 41.8 lists a variety of possible pitfalls in dietary management of food allergy. A primary issue in avoidance is the ambiguity of food labeling practices. In a cow's milk-free diet, for example, patients must be instructed to not only avoid all cow's milk products, but also to read ingredient labels for key words which may indicate the presence of cow's milk protein. Terms such as casein, whey, lactalbumin, caramel color, "natural flavoring," and nougat may, for example, signify the presence of cow's milk protein. In many cases, the allergic individual must query companies for further product information, although product labeling is improving. Patients and parents must also be made aware that the food protein, as opposed to sugar or fat, is the ingredient being eliminated. For example, lactose-free cow's milk contains cow's milk protein, and many egg substitutes contain chicken egg proteins. Conversely, peanut and soy oil do not generally contain the food protein, unless the processing method is one in which the protein is not completely eliminated (as with cold pressed or "extruded" oil). Lay organizations such as The Food Allergy Network (800-929-4040; www.foodallergy.org) assist families and physicians in the difficult task of eliminating the allergenic foods. When multiple foods are eliminated from the diet, it is prudent to enlist the aid of a dietitian in formulating a nutritionally balanced diet.

TABLE 41.8

Pitfalls in Dietary Allergen Avoidance

Pitfall	Examples
Unfamiliar terms on food labels	Various terms indicating particular food proteins such as casein (milk), whey (milk), ovalbumin (egg)
Ambiguous terms on food labels	"Natural flavoring" may indicate cow's milk
Religious labels	"Pareve" may indicate non-dairy but does not guarantee absence of milk protein
Cross-contamination	In processing lines (e.g., milk protein found in juice boxes) or in the home setting (shared utensils)
Ingredient switching	Large size of a product may have different ingredients than a small size, despite similar packaging design
Hidden ingredients	Egg white to make a pretzel shiny, peanut butter to seal the end of egg rolls, peanut butter to thicken sauces

In addition to elimination of the offending food, an emergency plan must be in place to treat reactions caused by accidental ingestion. Injectable epinephrine and oral antihistamine should be readily available and administered without delay to treat patients at risk for severe reactions.[15,94,117] Caregivers must be familiarized with indications for the use and method of administration of these medications.

Natural History

Most children outgrow their allergies to milk, egg, wheat, and soy by age three years.[18] However, patients allergic to peanuts, tree nuts, fish, and shellfish are much less likely to lose their clinical reactivity,[14,96,118,121] and these sensitivities may persist into adulthood. Approximately one-third of children with AD and food allergy "lost" (or "outgrew") their clinical reactivity over one to three years with strict adherence to dietary elimination, believed to have aided in a more timely recovery.[12] Elevated concentrations of food-specific IgE may indicate a lower likelihood of developing tolerance in the subsequent few years.[113,122] However, tests for food-specific IgE antibody (prick skin tests, RAST) remain positive for years after the food allergy has resolved and cannot be followed as the sole indicator of tolerance.[12] Thus, it is recommended that patients with chronic disease such as atopic dermatitis be rechallenged intermittently (e.g., egg: every two to three years; milk, soy, wheat: every one to two years; peanuts, nuts, fish, and shellfish: if tolerance is suspected; other foods every one to two years) to determine whether their food allergy persists, so that restriction diets may be discontinued as soon as possible.

Prevention of Food Allergy

Dietary modification with the goal of allergy prevention has been attempted during pregnancy, lactation, and early feeding of infants who are at risk for atopic disease based upon strong family histories of allergy. In several series, infants from atopic families whose mothers excluded highly allergenic foods from their diets during lactation had significantly

less AD and food allergy compared to infants whose mothers' diets were unrestricted.[123,126] However, the differences may not may not extend beyond early childhood.[126,127]

The delayed introduction of solid foods has also been associated with reduction in allergic disease. In a study of 1265 unselected neonates, the effect of solid food introduction was evaluated over a ten-year period.[128,129] A significant linear relationship was found between the number of solid foods introduced into the diet by four months of age and subsequent AD, with a threefold increase in recurrent eczema at ten years of age in infants receiving four or more solid foods compared to infants receiving no solid foods prior to four months of age. A prospective, nonrandomized study comparing breastfed infants who first received solid foods at three or six months of age revealed reduced AD and food allergy at one year of age in the group avoiding solids for the six-month period,[130] but no significant difference in these parameters at five years.[131] Since these series did not randomize patients, the studies must be considered suggestive until further randomized trials confirm the findings.

Future Therapies

Currently, strict avoidance of causal foods and treatment of accidental ingestion is the only available therapy for food allergy. Immunotherapy ("allergy shots") has not proven practical for treatment[132] except in the case of the oral allergy syndrome, in which immunotherapy with the pollens responsible for the cross-reactivity may provide relief.[133] Toward a goal of more definitive therapies for food allergic disorders, a multitude of experimental therapies is under investigation.

Humanized anti-IgE antibodies for injection into patients have been developed that are able to bind and remove free-floating IgE antibodies from the bloodstream and may reduce or abolish allergic responses. Anti-IgE may, therefore, provide treatment for many IgE-mediated allergic disorders (not just food allergy). More allergen-specific novel therapies include vaccination with proteins altered such that the epitopes that bind IgE are removed while areas of the protein are left intact so that T-cells can still mount a response leading, potentially, to tolerance.[134-137] Another approach to induce tolerance to specific food allergens is vaccination with DNA sequences that code for the production of food allergens,[138,139] and the use of immune modulators (cytokines, specific DNA sequences) that can direct the immune system away from allergic responses and toward tolerance of the proteins. It is hoped that these novel approaches will provide relief from chronic disease and prevent anaphylaxis for food allergic individuals.

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