

Food Allergy

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Food allergy appears to be increasing in prevalence and is estimated to affect >2% and possibly up to 10% of the population. Food allergies are defined by an immune response triggered by food proteins. Emerging data suggest that carbohydrate moieties on food proteins, specifically mammalian meats, may

also elicit allergic responses. Food is the most common trigger of anaphylaxis in the community, which can be fatal. The underlying mechanisms of food allergy usually involve food-specific immunoglobulin E antibodies, but cell-mediated disorders account for a variety of chronic or subacute skin and gastrointestinal reactions. Eosinophilic esophagitis is an emerging food-related chronic disorder. The diagnosis of food allergy is complicated by the observation that detection of food-specific immunoglobulin E (sensitization) does not necessarily indicate clinical allergy. Diagnosis requires a careful medical history, laboratory studies, and, in many cases, oral food challenges to confirm a diagnosis. Novel diagnostic methods, many of which rely upon evaluating immune responses to specific food proteins or epitopes, may improve diagnosis and prognosis in the future. Current management relies upon allergen avoidance and preparation to promptly treat severe reactions with epinephrine. Studies suggest that some children with milk or egg allergy might tolerate extensively heated forms, for example milk or egg baked into muffins, without symptoms and possibly with some immunotherapeutic benefits. Novel therapeutic strategies are under study, including oral and sublingual immunotherapy, Chinese herbal medicine, anti-immunoglobulin E antibodies, and modified vaccines. *Mt Sinai J Med* 78:683–696, 2011. © 2011 Mount Sinai School of Medicine

Key Words: allergy, anaphylaxis, avoidance diets, food allergy, immunotherapy.

Adverse reactions to foods may result from immunologic (food allergy) or nonimmunologic responses.¹ Food allergy has recently been defined by an expert panel as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”² A meta-analysis of epidemiology studies on food allergy estimated that 12%–13% of individuals perceive that they have a food allergy.³ However, studies that include specific testing indicate prevalence

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rates in the range of 3%–5%.⁴ It is not clear whether the discordance of self-perceived allergy compared with true allergy is the result of lay misperceptions regarding any adverse response to a food being an “allergy,” or simply incorrect self-diagnosis. However, the discordance underscores an important role for the physician in addressing perceived allergies because the perceived culprit food can often be ingested safely. Importantly, true food allergies can be severe and potentially fatal,⁵ also indicating the need for careful diagnostic assessments.

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There are a number of adverse reactions to foods that are not true allergies. Toxins or pharmacologically active components of the diet account for a number of nonimmune adverse reactions, such as food poisoning or exaggerated tachycardia from caffeine. Nonimmune reactions include food intolerance. A common example is lactose intolerance caused by lactase insufficiency. Symptoms include abdominal discomfort, bloating, and loose stools from a reduced ability to digest lactose. Examples of adverse reactions to foods are shown in Table 1. This review addresses all forms of food allergy, but focuses primarily on immunoglobulin E (IgE)-mediated reactions.

Table 1. *Examples of Adverse Reactions to Foods.*

Intolerance
Lactose intolerance (lactase deficiency)
Alcohol
Caffeine (jitteriness)
Tyramine in aged cheeses (migraine)
Toxins
Bacterial food poisoning
Scombroid (in dark-meat fish, may mimic allergy)
Food allergy (immune responses)
IgE-mediated
Non-IgE-associated
Mixed IgE/non-IgE (eosinophilic gastrointestinal disease, atopic dermatitis)
Neurologic and psychological/psychiatric
Auriculotemporal syndrome (facial flush with salivation)
Gustatory rhinitis (rhinorrhea from spicy foods)
Anorexia nervosa and food aversions

Abbreviations: IgE, immunoglobulin E.

PATHOPHYSIOLOGY

Immune responses to foods are a normal phenomenon leading to a state of oral tolerance.^{6,7} In contrast, aberrant immune responses to food proteins can result in food allergies. It is conceptually and diagnostically helpful to consider food allergic disorders by immunopathology, among those that are or are not associated with detectable food-specific IgE

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antibodies. Disorders with an acute onset of symptoms following ingestion are typically mediated by IgE antibodies. Food-specific IgE antibodies bind to high-affinity IgE receptors on tissue mast cells and blood basophils, a state termed sensitization. Upon food re-exposure, the causal proteins bind to the food allergen-specific IgE antibodies, cross-linking them and initiating signal transduction pathways that result in the release of mediators such as histamine. The release of mediators then results in symptoms that may affect the skin, gastrointestinal (GI) tract, respiratory tract, and cardiovascular system. Another group of food allergic disorders, affecting primarily the GI tract, are subacute or chronic and are mediated primarily by T cells. A third group of chronic disorders that may be associated with food allergy, atopic dermatitis and eosinophilic GI disorders are variably associated with detectable IgE antibody (IgE associated/cell-mediated disorders).

FOOD ALLERGENS

Foods are composed of multiple proteins, and these may behave differently with regard to their potential to sensitize and in their interaction with the immune system. Most of the identified relevant food allergens are water-soluble glycoproteins that are 10–70 kD in size and fairly stable to heat, acid, and proteases. Examples include proteins in milk (caseins, β -lactoglobulin), peanut (vicillins, conglutin), egg (ovomucoid, ovalbumin), fish (parvalbumin), shellfish (tropomyosin), and nonspecific lipid transfer proteins found, for example,

in peach (Pru p 3). The labile proteins are less likely to trigger severe reactions; for example, the major allergen of birch (Bet v 1) may induce sensitization through the respiratory route and result in oral symptoms of pruritus to homologous proteins in raw apple (Mal d 1). The phenotypic expression of an allergy can vary according to the immune response to particular proteins in the food. For example, major allergens in peanut, Ara h 1, 2, and 3, are associated with severe peanut allergy, whereas Ara h 8 is a Bet v 1 homologue, similar to pollen protein, and is less likely to be associated with severe clinical reactions.

Not only may an individual mount immune responses to various proteins in a specific food, but the responses may be directed to any of multiple areas (epitopes) on a single protein. The exact repertoire of binding may, in fact, correlate with expression of disease. It has been suggested that IgE that recognizes epitopes that are dependent upon tertiary allergen structure is associated with transient childhood allergy, whereas expression of IgE that recognizes epitopes that are not dependant on complex protein folding (ie, linear epitopes), is associated with persistent allergy.^{8,9} These and additional factors such as heating a food and the food matrix (eg, egg protein baked into a matrix of wheat proteins) can influence disease outcomes.¹⁰ Although proteins are the typical component of food that trigger immune responses, carbohydrate moieties on the proteins have recently been identified as allergens causing delayed anaphylaxis to mammalian meats.¹¹

Although many botanically related proteins or animal proteins from similar species share regions of homology and may show cross-reactivity on allergy testing, clinical evidence of cross-reactivity is not as common.¹² For example, peanut is a legume, and most persons with a peanut allergy have IgE antibodies that recognize proteins in other legumes, such as peas and string beans. This phenomenon leads to positive tests. However, 95% of persons with a peanut allergy tolerate most other beans. The rate of clinically relevant cross-reactivity varies by food, with high rates of allergy among fish and among shellfish (>50%), and low rates of cross-reactivity among grains (<20%).

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Certain food additives are derived from natural sources and contain proteins that have been associated with allergic reactions.¹³ These include colors derived from turmeric, paprika, seeds (annatto), and insects (carmine/cochineal). Chemical additives are not likely to cause IgE-associated allergic reactions, but some may have drug effects that cause adverse reactions, including symptoms that are allergy-like, or may invoke immune responses. Tartrazine (Yellow #5) is a synthetic color that has been extensively investigated because of concerns that it may trigger hives, allergic reactions, and asthma. However, well-conducted studies have generally not validated these concerns. Like tartrazine, many other synthetic colors have not been proven to cause allergic reactions; however, some of these chemicals have rarely been associated with rashes. Sulfites are added to foods as a preservative, anti-browning agent, or for a bleaching effect. Sulfites can, in sensitive persons, induce asthma, and very rarely cause more significant allergic-like responses.

PREVALENCE

A recent comprehensive review of the literature estimated that food allergy affects >1%–2% but <10% of the population.¹⁴ This wide range belies more specific observations from many studies that generally show that food allergy is more common in children than adults, appears to be increasing in prevalence, and varies widely in rate and for specific triggers worldwide.⁴

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For diagnostic purposes, it is helpful to appreciate that some food allergies are more common in children and others in adults. For example, egg, cow's milk, wheat, and soy allergies are most often encountered in children and often resolve. Peanut, tree nut, fish, and shellfish allergies may develop in childhood and are more likely to persist. Tree nut and shellfish allergies are more likely to present in young adulthood.¹⁵ Seed allergies are being increasingly recognized.

There is some evidence that food allergies may be increasing; a pediatric study recently suggested an 18% increase over a decade.¹⁶ Studies of peanut allergy in children suggest almost a tripling in

prevalence in just over a decade,¹⁷ with multiple studies worldwide indicating >1% of school-aged children are now affected by peanut allergy.^{18–21} The reasons for the increase remain elusive, but theories include changes in food processing; timing of introduction of foods, either too early or too late; alterations in other components of the diet, such as fats or vitamins; and the “hygiene hypothesis” that lack of farm living and control of infection have resulted in immune dysregulation.^{4,22,23} Genetic risk factors for food allergy include a family or personal history of atopic disorders (asthma, atopic dermatitis, allergic rhinitis, food allergy). The influence of food

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allergy on specific disease states varies by the type of disease and age group affected.² Anaphylaxis in the community setting is attributed to food allergy in 35%–55% of episodes, and common offenders are peanuts, nuts, and seafood. Food allergy is also a common cause of acute urticaria (20%) and is associated with atopic dermatitis for nearly 40% of children with mild to moderate disease, most commonly associated with milk and egg allergy. However, food allergy is not a common cause of chronic isolated respiratory symptoms, chronic urticaria, or atopic dermatitis in adults.

CLINICAL DISORDERS

The clinical manifestations of food allergy are diverse, and result from the underlying immune mechanisms and their impact on particular target organs.^{1,24,25} Food allergy may present as an acute reaction, with a sudden onset of stereotypical symptoms, such as hives or respiratory compromise; as an increase in chronic symptoms, such as exacerbation of atopic

Table 2. *Clinical Disorders According to Pathophysiology.*

Immunopathology/Disorder
IgE antibody-associated
Urticaria/angioedema
Oral allergy syndrome (pollen-related)
Anaphylaxis
Food-associated, exercise-induced anaphylaxis
Onset of isolated symptoms (eg, wheeze, abdominal pain, vomiting)
IgE antibody-associated/cell-mediated, chronic
Atopic dermatitis
Eosinophilic gastroenteropathies
Non-IgE-associated
Dietary protein enterocolitis
Dietary protein proctitis
Dietary protein enteropathy
Dermatitis herpetiformis
Contact dermatitis
Pulmonary hemosiderosis

dermatitis; or as a chronic disease where recognition of symptom patterns suggests a food allergy should be considered. Specific disorders are summarized by pathophysiology in Table 2. Disorders and symptoms such as behavioral problems, arthritis, and headache have not been convincingly or commonly linked to food allergy. Reflux, infantile colic, and recalcitrant constipation have been attributed to food allergy in a subset of pediatric patients.

Immunoglobulin E–Associated Food Allergies

Immunoglobulin E–mediated food-allergic reactions typically occur within minutes and rarely beyond an hour following ingestion of a triggering food. The organ system(s) affected and the specific symptoms additionally define these reactions. Urticaria and/or angioedema, pruritis, and flushing are common skin manifestations of food allergy, either alone or in combination with other symptoms. Contact urticaria describes lesions that occur at the site of direct contact with the food that may not induce a reaction when ingested.

Pollen-Food Syndrome (Oral Allergy Syndrome)

Oral allergy syndrome is a form of allergy confined primarily to direct contact with raw fruits and vegetables in the oropharynx.²⁶ Initial sensitization to pollen proteins may result in symptoms when homologous proteins in particular fruits/vegetables are ingested, as described above. This type of allergy is probably the most common of all food allergies.⁴ Symptoms are usually limited to the oropharynx with

pruritus and mild angioedema, but progression to a systemic reaction may occur. Causal proteins are presumably heat-labile, as cooking the food typically abolishes reactions. The foods causing this oral syndrome may induce systemic reactions in persons reactive to stable proteins in them (eg, lipid transfer proteins).

Although chronic asthma and allergic rhinitis are not typically solely attributable to food allergy, the same symptoms may accompany acute systemic food-allergic reactions. Inhalation of airborne allergenic food proteins may also induce respiratory reactions in occupational settings (eg, baker's asthma from wheat) or when stable proteins become aerosolized during cooking or processing.

Food-Induced Anaphylaxis

Food-induced anaphylaxis is a serious systemic allergic reaction that is rapid in onset and may cause death.²⁷ Symptoms vary and may affect any combination of organ systems among the skin, respiratory tract, GI tract, and cardiovascular system. Symptoms may include an aura of "impending doom." Life-threatening symptoms include laryngeal edema, severe asthma, and cardiovascular compromise. Serum tryptase elevation is often not detected during food-associated anaphylaxis. Reactions may follow a biphasic course where severe symptoms recur 1–2 hours later, or longer, after acute initial symptoms wane.

Food-Associated, Exercise-Induced Anaphylaxis

Food-associated, exercise-induced anaphylaxis is a syndrome where anaphylaxis only occurs if exercise follows ingestion of a causal food that is otherwise tolerated. Fatal reactions appear to be more common in teenagers and young adults who typically have a diagnosed food allergy and asthma, and who delay treatment with epinephrine despite significant symptoms during a reaction.⁵

Mixed Immunoglobulin E- and Non-Immunoglobulin E-Associated Allergies: Atopic Dermatitis and Eosinophilic Gastrointestinal Disease

Studies using double-blind, placebo-controlled oral food challenges (DBPCFC) show that approximately 1 in 3 young children with moderate to severe atopic dermatitis has food allergy.²⁸ There is controversy about the role of foods in the chronic rash. There is

agreement that children with moderate to severe atopic dermatitis are at increased risk to have immediate-type food-allergic reactions. When there is food-responsive dermatitis, studies reveal that food-specific IgE antibody is usually detectable to the trigger foods.²⁹ However, food-responsive disease has also been documented in children without detectable IgE to the causal food; therefore, cell-mediated mechanisms are likely involved. Because of the chronic nature of the disorder, and its waxing and waning course, it is difficult to associate symptoms with particular foods by history. Studies in children identify that >90% of reactions are attributed to "major" allergens including milk, egg, wheat, and soy.³⁰ It is less common to verify a role for meats, fruits, or vegetables.

Allergic eosinophilic esophagitis/gastroenteritis is a group of disorders characterized by eosinophilic inflammation in the GI tract. Symptoms overlap those of other GI disorders and may include dysphagia, vomiting, diarrhea, obstruction, and malabsorption. Studies in children indicate that almost all patients are food-responsive, although implicated foods may or may not be associated with evidence of IgE antibody.^{31–33}

Non-Immunoglobulin E-Associated Disorders

Similar to the IgE-associated disorders, these disorders may also affect various target organs.^{2,8} In regard to skin manifestations, contact dermatitis, a type IV hypersensitivity response, may occur from contact with foods in occupational handling. Fixed raised, erythematous eruptions, similar to fixed drug eruptions, have rarely been attributed to ingested foods. Dermatitis herpetiformis a papulovesicular skin rash associated with celiac disease caused by an immune response to gluten.

A rare pulmonary disorder affecting infants, Heiner's syndrome or milk-induced pulmonary hemosiderosis, is associated with precipitating (immunoglobulin G; IgG) antibodies to cow's milk. Symptoms include anemia, pulmonary infiltrates, recurrent pneumonia, and growth failure, which resolve with milk elimination.

Several non-IgE-mediated disorders of the GI tract affect primarily infants.²⁵ Food protein-induced proctocolitis is characterized by mucus and blood in stools. Patients are usually breast-fed infants and the bleeding usually resolves with maternal exclusion of cow's milk. Foods other than milk are sometimes implicated. Empiric dietary exclusion is commonly instituted. If rectal biopsy is performed, an

eosinophilic inflammation is observed. The disorder is not associated with detectable IgE antibody to milk and resolves by age 1 to 2 years.³⁴ Infants with food protein-induced enteropathy experience diarrhea, poor growth, and edema due to hypoproteinemia caused by malabsorption when ingesting the causal food. Enteropathy syndromes attributed to cow's milk protein usually resolve in 1–2 years. A dramatic form of non-IgE-mediated GI food allergy is food protein-induced enterocolitis syndrome. The onset is usually in infancy and is characterized by a symptom complex of profuse vomiting and hemepositive diarrhea, leading to failure to thrive, and potentially dehydration and shock during chronic ingestion of the causal protein.³⁵ These infants also may develop acidemia and methemoglobinemia and present with a sepsis-like picture including an elevated peripheral polymorphonuclear leukocyte count. Cow's milk and soy are most often responsible, but grains such as rice and oat, and poultry, are increasingly recognized triggers.³⁶ Ingestion of the causal protein after resolution of symptoms may lead to a delayed (about 2-hour) recurrence of symptoms that may be severe and include shock. Resolution usually occurs in 2–3 years.

DIAGNOSIS

The clinical evaluation of an adverse reaction to food requires a careful history and physical examination to determine the type of adverse response, whether potentially IgE-associated or not.^{1,37} Important factors

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to consider include the types of symptoms, their chronicity and reproducibility, and alternative reasons for symptoms. If symptoms indicate a nonimmune etiology, additional evaluation can be directed to the specific suspicion. For example, lactose intolerance may be confirmed through breath hydrogen testing. For chronic disorders such as atopic dermatitis and eosinophilic gastroenteritis, the identification of suspect foods is difficult, because food is ingested throughout the day and symptoms are often chronic with a waxing and waning course.

Symptom diaries are helpful but rarely diagnostic. In addition, individuals with these disorders often test positive to multiple foods that may not be causing illness. Care in selecting and interpreting the tests is paramount, and consideration of the previously reviewed epidemiology and pathophysiology of food allergies is helpful for test selection and interpretation.

Following a history, tests for food-specific IgE antibodies may be performed. The test modalities include skin prick tests (SPTs), performed using a probe to introduce food protein to the superficial skin layer, or serum tests. The tests have similar performance characteristics.¹⁴ They are generally very sensitive (~75%–95%) and modestly specific (~30%–60%).¹ Skin prick tests are used on rash-free skin while the patient is avoiding antihistamines; intradermal skin tests should not be used. Though commercial extracts are available for performing SPTs for many foods, fresh extracts, particularly when testing fruits and vegetables whose proteins are prone to degradation, may be more sensitive. If IgE antibody specific for the food protein is present, a wheal and flare will occur that is compared with positive (histamine) and negative (saline) controls. The test is available to allergists, and has advantages of immediate results and low cost.

A more widely available test is a serum test for food-specific IgE antibodies. There are 3 commercial manufacturers of the test.³⁸ The analyzers use nonisotopic anti-IgE-detection reagents, a common calibration strategy and analytical sensitivity, and have computer-driven autoanalyzers that report IgE antibody levels in quantitative units. Although the 3 systems are similar, exact results between them vary, probably because the reagents have slight differences in the proteins displayed by the tests.³⁹ This may also account for differences in results that sometimes occur between SPTs and serum tests. Previous-generation tests used radioactivity (radioallergosorbent test, RAST), but the term RAST is now antiquated.

A positive SPT or serum IgE test merely indicates that food-specific IgE is present, a state termed sensitization. Sensitization does not confirm an allergy.² Increasingly larger wheal diameters or increasing concentrations of IgE antibodies are associated with increasingly higher probability that the test reflects clinical allergy. In a limited number of studies of a few foods in infants and/or children, diagnostic values associated with very high ($\geq 95\%$) predictive values for reactions have been determined, though not universally confirmed. A study using SPTs in young children revealed that when wheals were particularly large (≥ 8 mm for milk and peanut and

≥ 7 mm for egg), clinical reactions were virtually certain.⁴⁰ Studies determining the concentration of specific IgE antibody measured using a particular method (ImmunoCAP, reported in units kU_A/L) showed food-specific IgE concentrations of $\geq 7 \text{ kU}_A/\text{L}$ to egg, ≥ 15 to milk, and ≥ 14 to peanut were 95% predictive for a reaction among 5-year-old children.⁴¹ For children aged <2 years, the values where most reacted were lower (eg, $\geq 2 \text{ kU}_A/\text{L}$ for egg or milk). These results have not been universally confirmed.^{1,24} It must be emphasized that diagnostic concentrations are undetermined for other foods, allergic disorders, or age groups.

Food-specific IgE may be detected despite tolerance of a food, or may remain detectable but typically decline, as a food allergy resolves. Obtaining “panels” of food allergy tests without consideration of the history is not a good practice, because numerous irrelevant positive results may result, creating confusion and anxiety. The history is crucial

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because tests are expected to be negative when the pathophysiology of the response is consistent with non-IgE-mediated reactions. However, acute anaphylactic reactions may also occasionally occur despite a negative test,^{42,43} so caution is needed when evaluating a patient with a convincing history despite a negative test. Neither the size of the SPT nor level of IgE in serum usefully predicts the type or severity of reaction. The atopy patch test, which is performed by placing the food allergen on the skin under occlusion for 48 hours and assessing for a delayed rash at 24–72 hours, shows some promise for non-IgE-mediated disorders, but more studies are needed to determine utility.¹ There are tests that have been touted for the diagnosis of food allergy but have never been found useful in blinded studies. These tests, which are not recommended, include measurement of IgG₄ antibody, provocation-neutralization (drops placed under the tongue or injected to diagnose and treat various symptoms), and applied kinesiology (muscle strength testing).²

For evaluation of chronic diseases such as atopic dermatitis and eosinophilic esophagitis, improvement of symptoms during dietary elimination of suspected

foods provides presumptive evidence of causality. Elimination diets can be undertaken by removing foods suspected to be causing symptoms, removing all but a selected group of foods that are rarely allergenic (oligoantigenic diet), or by giving an elemental diet consisting only of a hypoallergenic extensively hydrolyzed formula or a nonallergenic amino acid–based formula. The elemental diet provides the most definitive trial, but is difficult to follow. The type of elimination diet selected will depend upon the clinical scenario, a priori reasoning concerning offending foods based upon history and epidemiology, and, when appropriate, the results of tests for IgE antibody. The length of trial depends upon the type of symptoms, but 1–6 weeks is usually the range required. A dietitian may be needed to ensure nutritional sufficiency of trial diets. For breast-fed infants, maternal dietary elimination is required. When a food to which IgE has been demonstrated is removed from the diet for a prolonged period during a chronic disorder, it is possible for reintroduction to induce severe reactions.⁴⁴ Thus, guidance from an allergist is prudent.

When history and IgE testing have not confirmed an allergy, or when the development of tolerance is suspected, an oral food challenge (OFC) may be required to confirm clinical allergy.^{1,2} An OFC is

When history and immunoglobulin E testing have not confirmed an allergy, or when the development of tolerance is suspected, an oral food challenge may be required to confirm clinical allergy.

performed by feeding gradually increasing amounts of the suspected food under medical observation.⁴⁵ Oral food challenges are performed either openly, where the patient and physician know the food being tested is being ingested, or blinded, by camouflaging the food in a carrier food or opaque capsules. The DBPCFC is least prone to bias and is considered the “gold standard.” Briefly, this format of OFC has a third party develop 2 feedings that are identical in taste/texture, but only 1 has the test allergen. The OFC is randomized such that true or placebo doses are given, for example on separate days, and the patient and observer are not aware of the content. The OFC can be used to evaluate any type of adverse response. For non-IgE-mediated reactions, the OFC is usually the only means of diagnosis. Feeding tests, particularly in IgE-mediated

reactions and enterocolitis syndrome, can induce severe reactions. The supervising clinician, usually an allergist, must have medications and supplies for resuscitation immediately available to manage reactions. Negative challenges should always be followed by a supervised open feeding of a relevant portion of the tested food in its commonly prepared state. More details about undertaking OFCs are provided in a recent report.⁴⁵

FUTURE DIAGNOSTICS

Current diagnostics described above are not able to accurately identify clinical allergy. They are affected by cross-reactive proteins without clinical relevance, lack ability to predict severity, and do not reflect prognosis. Exploration of the interaction of humoral immune responses to particular food proteins (component resolved diagnostics) or to binding regions on the proteins (epitopes) is an active avenue of investigation to improve diagnostic accuracy.^{46–48} Component-resolved diagnosis evaluating binding to specific proteins was explored in several recent studies. Nicolaou *et al.*²¹ evaluated this strategy for peanut using primarily a population-based cohort and testing with Ara h 1–3 and 8; binding to Ara h 2 provided the best discrimination of clinical reactivity. Additional examples of improved diagnostics through component analysis was demonstrated for kiwi⁴⁹ and shrimp.⁵⁰ However, more studies are needed to prospectively evaluate these approaches, as limitations are already evident.⁵¹

A series of studies evaluated IgE binding to epitopes on proteins to determine improved diagnostic or prognostic insights.^{9,52–54} Several studies evaluated milk allergy.^{9,54,55} Savilahti *et al.*⁵⁴ compared the progression of epitope binding of milk proteins in children with resolved or persisting cow's milk allergy. Binding patterns were stable over time for those with persistent allergy, but among those with early recovery, IgG₄ epitope binding increased while corresponding IgE epitope binding decreased. Distinct epitope binding patterns were noted to differentiate clinical phenotypes of cow's milk allergy⁹: a wider diversity of IgE epitope binding was noted for those with persisting milk allergy and for those with more severe reactions. The same pattern was seen in children who could not tolerate extensively heated forms of milk (eg, in muffins) compared with those who could. Additional studies are evaluating the diagnostic accuracy of lymphocyte tests, basophil activation, atopy patch tests, and other modalities.²

CURRENT TREATMENT

Dietary Avoidance

The mainstay of treatment is avoidance of the food and preparation for treatment in the event of an accidental ingestion leading to an allergic reaction. Dietary management of food allergy is

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fraught with nutritional and other pitfalls. In most countries, manufacturing and labeling deficiencies make it difficult to identify allergens in commercial food products. In the United States, labeling laws require plain-English disclosure of the “major” food allergens: milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish. The specific type of food is required to be named for categorical types (eg, tuna, shrimp, pecan). It is notable that currently several potent allergens, such as sesame, are not included in the laws. Additionally, advisory labels such as “may contain peanut” are not regulated, are increasingly common, and reflect variable risks.^{56,57} Strict avoidance therefore requires concern to avoid products with advisory labeling. Cross-contamination and errors in packaged food and restaurants are an additional obstacle, so it is imperative that individuals notify and discuss their allergy with restaurant personnel who may need some coaching about situations where foods may become contaminated with allergens, such as in fryers, shared bowls and cutting boards.^{58,59} For children, dietary management in schools can be difficult, because food-sharing, school projects using foods, parties, lack of on-site medical personnel, and other issues arise.⁶⁰ Ingestion, rather than skin or air exposure, is the primary concern for avoidance,⁶¹ although attention should be paid to avoid fumes of allergens (eg, boiling milk, steaming shellfish) and passionate kissing when a partner recently consumed the allergen.⁶²

Although strict avoidance is generally advised, there is a growing body of literature indicating that in select cases this may not be necessary.⁶³ About 70% of children with allergic reactions to milk products or egg can tolerate these foods when they are heated extensively, for example baked into muffins or breads.^{9,10,64} Some children may tolerate larger amounts of less-heated forms, such as cheese

on pizza. It is presumed that heating results in conformational changes in the proteins, allowing ingestion for persons with a milder form of the allergy, probably a phenotype that is also more likely to resolve the allergy. Adding such foods to the diet can improve quality of life and nutrition, but the impact on the natural course of allergy is not well studied. Early evidence suggests that immune responses to addition of these foods are similar to those seen during successful active immunotherapy, for example an increase in food-specific IgG antibodies is noted and some suppression of IgE responses is also observed. However, caution remains with this approach, as some children experience anaphylaxis to the heated products.

Medical Management

In the event of an allergic reaction, antihistamines may be required to reduce itching/rash. However, for patients experiencing more severe symptoms of anaphylaxis, with respiratory and/or cardiovascular symptoms, additional therapies are required.² Self-injectable epinephrine should be prescribed for those at risk of anaphylaxis.²⁷ Guidelines for determining

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those who should have access to this medication are under scrutiny, but candidates include food-allergic patients with previous severe reactions, allergy to foods commonly causing severe reactions, and food-allergic patients with underlying asthma.^{65,66} It is essential to periodically review the indications and technique of administration of self-injectable epinephrine because mistakes are common. Patients must be instructed that, following the administration of the medications, prompt transportation to an emergency facility (by ambulance) should be sought, with prolonged observation (>4 hours) because recurrence of severe symptoms is possible. Individuals with potential shock should remain prone with legs raised; rising upright without proper treatment has rarely been reported to result in death due to "empty ventricle syndrome."⁶⁷ Patients should obtain medical jewelry identifying their allergy, and be reminded to update expired epinephrine injectors. For children, an important component of the school management of food allergy is to have a clear written emergency plan in place, medications readily available, and school personnel trained in

recognizing and treating reactions.⁶⁸ Teenagers are at special risk of fatal reactions,⁵ probably due to risk-taking behaviors.⁶⁹ It is therefore important to encourage education of the school staff, the affected teenager, and their friends about the allergy and when to treat with epinephrine.

The emotional toll of living with food allergy should not be neglected. Various studies have identified a serious impact on quality of life, and increased anxiety.^{70–74} Children with food allergies may be subjected to bullying as well.⁷⁵ Therefore, discussion of the psychosocial factors involved with management, ensuring that families are coping appropriately and not overly isolating themselves, and considering mental health referral are important components of management.

NATURAL HISTORY

Most (~85%) children lose their allergy to most allergenic foods (egg, milk, wheat, soy) within the first 3–5 years of life.⁷⁶ Recent studies from a referral center indicate that the rate of resolution may be slowing, but is still usually achieved prior to adolescence.^{77,78} In contrast, adults with food allergy may have long-lived allergy. Allergy to peanut, tree nuts, and seafood is rarely lost. The notion that peanut and tree nut allergy is permanent derives, in part, from the observation that it is an allergy that affects adults; however, it has become apparent that about 20% of peanut-allergic children aged <2 years, and about 9% of those with tree nut allergy, may achieve tolerance by school age.^{79,80}

PREVENTION

Early approaches for prevention of food allergy focused upon having infants avoid allergenic foods.⁸¹ This approach is partly based upon studies showing that infants ingesting hypoallergenic forms of cow's milk formula had less atopic dermatitis than those randomized to ingest whole-protein cow's milk.⁸² However, extensive delays in introducing potentially allergenic foods to otherwise well but "at-risk" infants, based upon their family history of atopy, have not been well studied. Concerns have arisen that such delays may not be preventive. In fact, there are studies suggesting that delayed ingestion may allow more time for sensitization by routes such as skin or air exposure, while mechanisms of oral tolerance are circumvented for lack of ingestion exposure. This concept has support in

the observation that the degree of family-member peanut ingestion was associated with a child's peanut allergy⁸³ whereas maternal ingestion was not, and that use of peanut-containing skin creams was a risk factor for peanut allergy in young children.⁸⁴ Recent guidelines suggest a beneficial role for exclusive breast-feeding infants at high risk for atopic disease for the first 3–6 months of life, and for avoiding supplementation with cow's milk or soy formulas in favor of hypoallergenic formulas if breast-feeding is not possible, but no additional dietary restrictions.⁸⁵ Some conflicting studies have maintained this as a very active area of investigation.⁸⁶ Primary prevention must be distinguished from secondary prevention; once a child has demonstrated allergies, for example to milk, there is an increased risk there will be or are concomitant food allergies to foods such as egg or peanut.⁸⁷

FUTURE THERAPEUTICS

Although allergen avoidance has been the mainstay of therapy, and no cure has been discovered, numerous approaches for more definitive management are being investigated.^{88,89} The use of an

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anti-IgE monoclonal antibody reduced the reaction threshold for a subset of individuals in a study of peanut allergy,⁹⁰ but routine use has not come to fruition, in part for the lack of clarity on the degree of protection. Another form of treatment that is not directed to a specific food is a Chinese herbal preparation termed Food Allergy Herbal Formula (version 2).^{91–93} This potential treatment appears to affect several mechanisms of the allergic response, passed a phase I trial and is undergoing additional testing. Prior allergen-specific food immunotherapies were aimed at injections of whole proteins, similar to immunotherapy used to treat insect-venom allergy or environmental allergies. However, there were serious side effects that stopped development.⁹⁴ More recently, food-allergen immunotherapy has aimed to avoid side effects through gradual oral or sublingual administration.^{95–98} Such studies have

Table 3. *Selected Immunotherapeutic Strategies Under Investigation.*

Therapy	Rationale	Benefits	Observations to Date
Sublingual/oral immunotherapy	Antigen presentation to mucosal site may provide desensitization and may induce tolerance	Natural foods, reduced risk of systemic anaphylaxis compared with injections	Mounting evidence for desensitization and relative safety; unclear effect on tolerance
Modified protein vaccine	Reduced IgE activation by mutation, eliminating some IgE binding epitopes	Potentially safer form of immunotherapy compared with injection of native protein	Murine models show promise, human studies in phase I trial
Peptide vaccine (overlapping peptides)	Peptides are less likely to cross-link IgE, avoiding mast cell activation	No requirement for IgE epitope mapping/mutation	Limited
Conjugation of immune stimulatory sequences to allergen and additional adjuvant methods	Enhance Th2 response by activating innate immune receptors	Increased efficacy, possibly improved safety	Preclinical studies
Anti-IgE antibodies	Can inactivate IgE with reduced risk for activating mast cells	Not food-specific	Preliminary study showed improved threshold overall but not uniform protection
Chinese herbal medicine	Mechanism unknown; multiple pathways affected	Not food-specific	Murine models show efficacy; human safety studies underway
Cytokine/anti-cytokine (eg, anti-IL-5)	To interrupt inflammatory signals	May allow directed interruption of inflammatory processes without need for food restriction	Preliminary study shows benefit for eosinophilic esophagitis

Abbreviations: IgE, immunoglobulin E; IL, interleukin; Th2, T helper cell type 2.

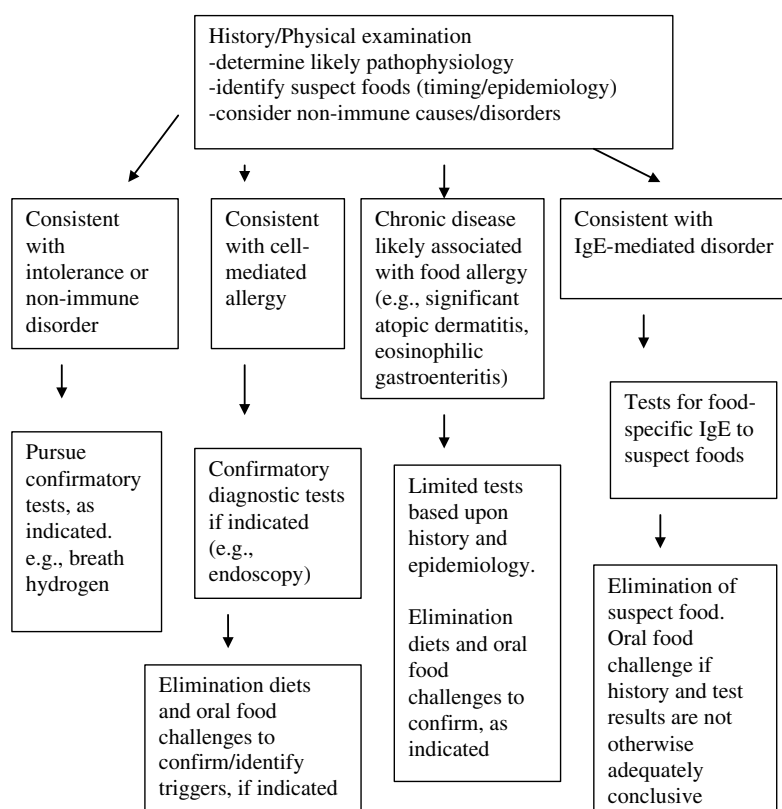


Fig 1. General diagnostic scheme. The history is the focus of determining potential triggers and the underlying pathophysiology of an adverse food reaction. This illustration provides a conceptual framework only; see text for additional explanations. **Abbreviations:** IgE, immunoglobulin E.

generally supported the notion that about 70%–80% of participants can be “desensitized” by gradual exposure and ingest larger amounts of the allergenic food. However, most participants experience allergic reactions from therapy, and it remains unclear if this treatment eventually effects a cure. For example, discontinuation of therapy for a period of time might result in loss of the desensitized state.⁹⁹ Thus, whether the therapy establishes permanent oral tolerance remains to be better explored.¹⁰⁰ Despite this caveat, oral immunotherapy remains a leading area of investigation. Additional approaches include combining therapies and additional treatments, as indicated in Table 3.

CONCLUSION

Food allergy is common and appears to be increasing. Recent US Guidelines supported by the National Institutes of Allergy and Infectious Diseases provide recommendations based upon a comprehensive literature review and expert panel advice. The guidelines underscore the importance of an accurate

diagnosis of food allergy and highlight the fact that tests for food-specific IgE have limitations, and that medically supervised OFCs may be needed for a definitive diagnosis. Rational use of the currently available diagnostic tests can result in a definitive diagnosis, and tests under development may facilitate the process. Although current management requires avoidance and reactionary treatment in the event of symptoms, studies are underway for more definitive therapies.

DISCLOSURES

Potential conflict of interest: Nothing to report.

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