Food Allergy: Common Causes, Diagnosis, and Treatment

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Abstract

Food allergy is a growing concern, and recognition of symptoms, knowledge of common food allergens, and management of reactions are important for patients and practitioners. Symptoms of a classic IgE-mediated food allergy vary in severity and can include any combination of laryngeal edema, wheezing, nausea, vomiting, diarrhea, urticaria, angioedema, and hypotension. Many foods can induce an allergic reaction, but the most commonly implicated foods include cow's milk, egg, peanut, tree nut, soy, wheat, fish, and shellfish. Milk and egg allergy generally develop and are outgrown in childhood. Peanut and tree nut allergy can occur during childhood or adulthood, are less likely to be outgrown, and tend to cause more fatal reactions. Given the possibility of life-threatening reactions, it is important to recognize the potential for cross-reactivity among food groups. Diagnosis of food allergy includes skin prick testing, specific serum IgE testing, and oral food challenges. Management is centered on avoidance of allergenic and cross-reacting foods and early recognition and immediate treatment of reactions. Treatment protocols to desensitize patients to food are currently under investigation.

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GENERAL OVERVIEW

Epidemiology

Food allergy is a public health concern that can impair quality of life and has the potential to induce life-threatening reactions. The prevalence of food allergy is increasing,[1] although an accurate prediction of prevalence is difficult given the imprecise diagnoses of food allergy.[2] A systematic review reported that food allergy affects between 2% and 10% of the population.[3] According to the National Health and Nutrition Examination Survey (NHANES)

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self-reported food allergy data from 2007-2010, the prevalence of food allergy was 8.96%, with a prevalence of 6.53% in children and 9.72% in adults.[4]

Risk Factors

Atopic dermatitis, a family history of atopy, and asthma are the primary risk factors for development of a food allergy.[5] These risk factors have been corroborated by studies suggesting that breakdown of the skin barrier in atopic dermatitis can result in epicutaneous sensitization to foods resulting in food allergy. Numerous other factors including vitamin D deficiency and obesity have been associated with food allergy, although these factors need further exploration.

Early Exposure Can Be Preventive—Lessons From a Peanut Allergy Population

In the past, it had been generally recommended that children avoid allergenic foods to reduce the likelihood of development of allergies. However, in a recent study, high-risk infants (those with atopic dermatitis, egg allergy, or both) were randomized to ingest or avoid peanut products from 4 to 11 months of age (depending on age at enrollment) until 5 years of age. The investigators found that high-risk children who regularly consumed peanut protein (in the form of peanut butter or peanut-flavored snacks) were far less likely (70%-86% reduction) to have development of a peanut allergy.[6] This marked reduction in development of allergy may impact new food allergy guidelines in the near future.

Common Food Allergens and Natural History

Although 170 foods have been identified as allergenic, only a small number of these foods are responsible for a majority of reactions.[1] Cow's milk, egg, peanut, tree nut, soy, wheat, fish, and shellfish are the most commonly allergenic foods. Allergy to egg, milk, soy, and wheat tends to occur most commonly during childhood (before 1-2 years of age),[7] while fish, peanut, and tree nut allergies can occur during any phase of life. In general, children are more likely to outgrow a wheat, soy, milk, and egg allergy and are less likely to outgrow peanut, tree nut, fish, or shellfish allergy.[8] Certain foods are more likely to produce a more severe reaction than others. In studies of food allergy fatalities, over 90% of fatal reactions were attributed to either peanuts or tree nuts.[9,10]

Classic Symptoms of Food Allergy and Intolerance

A food allergy is an IgE-mediated reaction. Symptoms may involve the respiratory tract, gastrointestinal tract, skin, and/or cardiovascular system. Respiratory symptoms include sneezing, congestion, rhinorrhea, wheezing, and laryngeal edema. Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea. Cutaneous findings include urticaria, angioedema, flushing, or pruritus. Cardiovascular findings include tachycardia, hypotension, or syncope. Symptoms are usually seen within minutes of ingesting a food but may not appear for up to 2 hours and can vary in severity from pruritus alone to anaphylactic shock.[1]

Food allergy and food intolerances are different diagnoses and are commonly confused by patients. In childhood, intolerance syndromes, such as food protein–induced enterocolitis syndrome, can be severe and cause hypotension due to third spacing. Food protein–induced enterocolitis syndrome is triggered by milk, soy, oat, rice, and rarely meat and manifests with emesis, diarrhea, and lethargy.[1] Food protein–induced enteropathy presents as a milder reaction with diarrhea and less commonly with vomiting.[11] Food protein–induced allergic proctocolitis is a benign condition manifesting as bloody stools in well-appearing infants and is usually caused by milk or soy passed through breast milk or contained in formula.[11]

In adults, food intolerance usually presents with gastrointestinal symptoms including bloating, flatulence, diarrhea, abdominal pain, or nausea and generally does not cause life-threatening reactions. Symptoms of a food allergy occur reliably and reproducibly with exposure to a specific food, which is not always the case with food intolerances in adults. Food intolerances can include lactose intolerance, fructose intolerance, or irritable bowel syndrome that may or may not be associated with certain foods.

Other nonimmunologic conditions include histamine intolerance, which can be seen with high histamine containing and releasing foods (including alcoholic beverages, ripe cheese, tomato, and smoked or processed meats),

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TABLE. Specific food-induced allergic conditions

Pathology	Disorder	Key features	Most common causal foods
IgE mediated (acute onset)	Acute urticaria/angioedema	Food commonly causes acute (20%) but rarely chronic urticaria.	Primarily "major allergens" (see text)
	Contact urticaria	Direct skin contact results in lesions. Rarely this is due to direct histamine release (nonimmunologic).	Multiple
	Anaphylaxis	Rapidly progressive, multiple organ system reaction can include cardiovascular collapse.	Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg
	Food-associated, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise.	Wheat, shellfish, and celery most often described
	Oral allergy syndrome (pollen-associated food allergy syndrome)	Pruritus and mild edema are confined to oral cavity and uncommonly progress beyond the mouth (~7%) and rarely to anaphylaxis (1% to 2%). Might increase after pollen season.	Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)
	Immediate gastrointestinal hypersensitivity	Immediate vomiting, pain	Major allergens
Combined IgE and cell mediated (delayed onset/chronic)	Atopic dermatitis	Associated with food allergy in ~35% of children with moderate-to-severe rash	Major allergens, particularly egg, milk
	Eosinophilic esophagitis	Symptoms might include feeding disorders, reflux symptoms, vomiting, dysphagia, and food impaction.	Multiple
	Eosinophilic gastroenteritis	Vary on site(s)/degree of eosinophilic inflammation; might include ascites, weight loss, edema, obstruction	Multiple
Cell mediated (delayed onset/chronic)	Food protein–induced enterocolitis syndrome	Primarily affects infants; chronic exposure: emesis, diarrhea, poor growth, lethargy; re-exposure after restriction: emesis, diarrhea, hypotension (15%) 2 hours after ingestion	Cow's milk, soy, rice, oat, meat
	Food protein–induced allergic proctocolitis	Mucus-laden, bloody stools in infants	Milk (through breast-feeding)
	Allergic contact dermatitis	Often occupational because of chemical moieties, oleoresins. Systemic contact dermatitis is a rare variant because of ingestion	Spices, fruits, vegetables
	Heiner syndrome	Pulmonary infiltrates, failure to thrive, iron deficiency anemia	Cow's milk

Adapted from *J Allergy Clin Immunol*,[1] with permission.

and scombroid poisoning, which manifests as flushing, urticaria, diarrhea, or headache and occasionally with bronchospasm and hypotension due to excess histamine in fish as a result of improper storage.

Food intolerances cannot be detected by traditional allergy testing, which includes in vitro IgE testing or skin prick testing (SPT). However, this testing is often pursued in patients with eosinophilic esophagitis to identify a subset of patients who have concurrent IgE-mediated food allergy.[12]

This article focuses on classic food allergy. Other immunologic and nonimmunologic reactions to food (many discussed in the preceding sections) are summarized in the Table.

COMMON ALLERGENS

Cow's Milk

Cow's milk allergy is the most common food allergy. Its prevalence is higher in children (prevalence of 2.64% in the NHANES population)

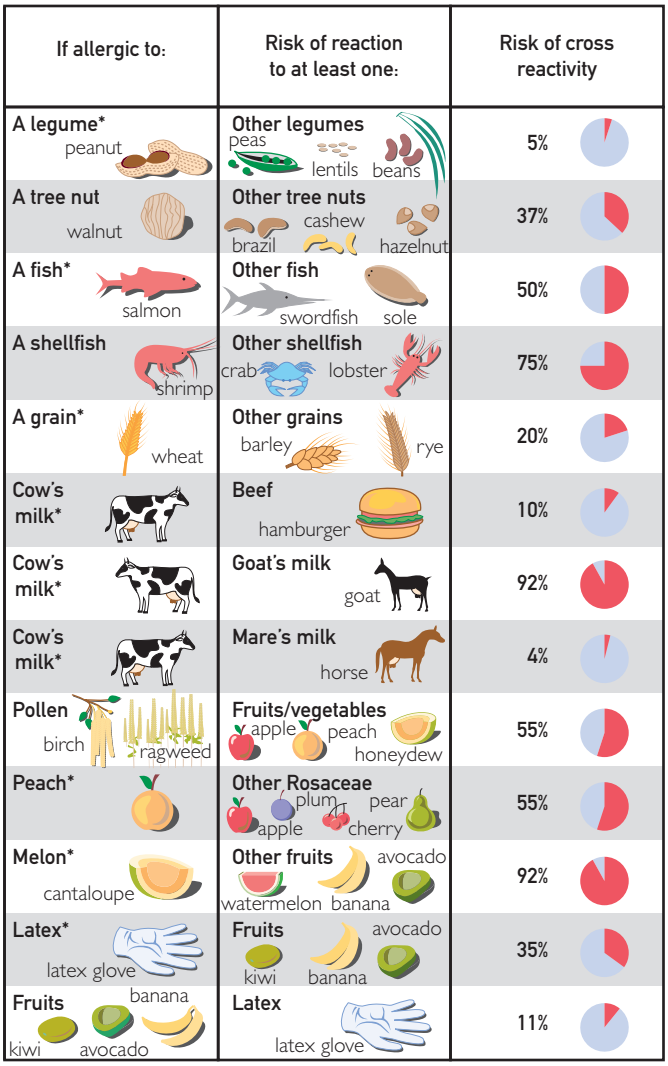

FIGURE. Approximate rate of clinical reactivity to at least one other related food. The probability of reacting to related foods varies, depending on numerous factors. *Data derived from studies with double blind, placebo-controlled food challenges. From *J Allergy Clin Immunol*,[14] with permission.

than in adults (prevalence of 1.94%).[4] Milk allergy usually develops in childhood and is outgrown by school age in most children.[13] Predictors of outgrowing a milk allergy include a lower milk-specific IgE level, a smaller wheal size on milk SPT, and milder atopic dermatitis.[13] In a study by Wood et al,[13] children with milk allergy with an IgE level of less than 2 kU/L had a 5.74-fold higher likelihood of tolerating milk at 66 months compared with children with a level of 10 kU/L. Clinical reactivity between cow's milk and goat's milk is 92%,[14] and therefore, patients with reactions to cow's milk should also avoid goat's milk and sheep's milk.[8] Clinical cross-reactivity between cow's milk and beef is 10%, and cooking beef further decreases its allergenicity; therefore, avoiding beef is generally not recommended in patients with a milk allergy[14] (Figure).

Egg

Egg allergy also tends to occur in childhood, and most children outgrow egg allergy by late childhood.[15] The prevalence of egg allergy in the NHANES population was 0.65% in children and 0.51% in adults.[4] A retrospective study found resolution of egg allergy in 4% of children by age 4 years, 12% by 6 years, 37% by 10 years, and 68% by 16 years. Patients who did not have resolution of their allergy had higher egg-specific IgE levels.[15]

Influenza Vaccination and Egg Allergy

Egg allergy has generated considerable interest because of concern regarding the safety of the influenza vaccine in patients with this allergy. The inactivated influenza vaccine and the live attenuated vaccines are produced by growing the influenza virus in chicken eggs, and therefore, these vaccines contain small quantities of ovalbumin. Many studies have found that these vaccines can be safely given to egg-allergic individuals including those with severe allergic reactions such as anaphylaxis.[16] Egg-allergic patients may receive the vaccine as a single dose or a 2-step challenge (10% of the dose followed by 90% of the dose), but these individuals should be monitored for 30 minutes after vaccination.[17] Therefore, egg allergy, even in those with egg-induced anaphylaxis, may not be a contraindication to receiving the influenza vaccine. Alternatively, the recombinant influenza vaccine Flublok (Protein Sciences Corporation), which was first approved by the US Food and Drug Administration in January 2013, does not contain any egg protein and is also an option for patients with egg allergy.

Baked Egg and Milk

High-temperature cooking and processing of food can increase or decrease food allergenicity, depending on the particular food. For example, dry roasting of peanuts can increase the allergenicity of peanuts by strengthening bonds and forming new

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epitopes.[18] However, with extensive heating of some foods, conformational epitopes can be denatured and combine with other food components forming a matrix, thereby making them unrecognizable to the immune system. Some proteins in egg and milk lose their allergenicity when cooked.[18] Most patients with egg and milk allergy will tolerate the baked forms of these foods. In one study, 75% of milk-allergic children tolerated products with heated milk.[19] In another study performed in Australia, 80% of egg-allergic patients tolerated baked egg.[20]

Baked egg and milk may tolerize the immune system to these foods and can have an effect comparable to immunotherapy. In one study, children eating baked egg products regularly were 14.6 times more likely to be tolerant to regular egg and achieved tolerance sooner (50 months vs 78.7 months) than patients not ingesting baked egg.[21] Similarly, in a study evaluating baked cow's milk, patients who regularly ingested baked milk were 16 times more likely to become tolerant to unheated milk than patients who were not consuming baked milk.[22] If patients have already incorporated baked egg and milk products into their diets, they should continue to ingest these foods regularly. If not, an oral food challenge with the baked food should be performed before consumption of the unbaked product.[8] Incorporation of baked products not only hastens tolerance to regular milk and egg but also improves quality of life in these patients and therefore should be considered for egg- and milk-allergic patients.

Peanut (Legumes)

Peanut allergy is of particular concern given that it leads to fatal reactions more commonly than other foods.[9,10] In a study evaluating fatal food reactions, 62.5% of fatalities were thought to be due to peanut.[9,10] Peanut allergy can develop in adulthood or childhood and is not as likely to be outgrown. A recent prospective study found that a lower peanut-specific IgE level and a smaller wheal size on peanut SPT predicted a higher rate of resolution of peanut allergy.[23] In this study, an SPT threshold of 8 mm or a peanut-specific IgE level of 2.1 kU/L or greater at age 4 years had a 95% positive predictive value for persistent peanut allergy.[23] Only 22% of children with a peanut allergy diagnosed at age 1 year had resolution of their allergy by age 4 years.[23] Legumes (which include peanut and soy) have a high rate of cross-sensitization on testing, but clinical cross-reactions between foods in the legume family occur infrequently.[14] From limited data from double-blind, placebo-controlled trials, the rate of clinical reactivity to another food within the legume family is 5% (Figure).

Tree Nuts

Tree nuts include but are not limited to walnut, almond, hazelnut, cashew, pecan, pistachio, and Brazil nut. Tree nut allergy may develop in adulthood or childhood. The prevalence in childhood is 0.52%, and the prevalence in adulthood is 0.87%.[4] As with peanuts, tree nuts can also lead to fatal reactions. In a study assessing food allergy fatalities, 31% of fatal reactions were attributed to tree nuts.[9,10] Another important point with tree nuts is the potential for cross-reactivity. Cross-reactivity between tree nuts has been reported at 37%, although comprehensive studies have not been performed given the potentially fatal and relatively frequent reactions to tree nuts.[14]

Peanut and Tree Nut Cross-Reactivity

The rate of clinical reactivity between peanuts and tree nuts is unknown but is reported to be between 23% and 50% in atopic patients and is likely lower in the general population.[14] Given the severity of reactions that can occur with tree nuts and peanuts and misidentification between these foods, avoidance of all tree nuts and peanuts should be considered in allergic patients, especially children.

Shellfish

Shellfish allergy has a prevalence of 0.87% in children and 2.04% in adults. Shellfish allergy commonly develops during adulthood. There is no established relationship between iodine allergy or radiocontrast reactions with shellfish or fish allergy.[8] Clinical cross-reactivity between shellfish is 75%.[14] Tropomyosin is the identified allergen and has a high rate of conserving its sequence among different crustaceans including shrimp, crab, and lobster; mollusks including oyster, scallop, and squid; and insects such as cockroach, grasshopper, and dust mite.[14] Given the severity of shellfish reactions and cross-reactivity between shellfish, all shellfish should

be avoided unless a challenge can prove tolerance.

Fish

As with shellfish, fish allergy can develop in adulthood. Clinical cross-reactivity between fish is 50%[24]; therefore, all fish should be avoided unless an oral challenge confirms tolerance to specific fish. Most patients with fish allergy are able to tolerate shellfish and vice versa.

Wheat

Wheat allergy most commonly develops in childhood and is usually outgrown before adulthood.[8] Cross-reactivity between grains is 20%.[14] Elimination of all grains in a patient with wheat allergy may be nutritionally harmful and therefore is not recommended.[8] If there is concern about allergies to other grains, an oral challenge may be performed.

Celiac disease is a non—IgE-mediated small-bowel immunologic reaction to gluten in genetically susceptible individuals. Patients present with symptoms of malabsorption including diarrhea, bloating, weight loss, and growth failure in children. Laboratory testing can reveal anemia and vitamin deficiencies. Testing for celiac disease should take into account whether a patient is consuming a gluten-free diet and the probability of disease. Testing may include small-bowel biopsy and serum anti—tissue transglutaminase antibody measurement (both of which should be done while the patient consumes a gluten-rich diet) and/or HLA-DQ2/DQ8 testing. Treatment is gluten avoidance.

OTHER FORMS OF FOOD ALLERGY

Oral Allergy Syndrome

Oral allergy syndrome (also known as *pollen food allergy syndrome*) is caused by allergen proteins that share homology between environmental pollens and fruits, vegetables, and tree nuts. Patients are usually sensitized to the environmental allergen and then experience reactions when ingesting a food that contains the closely related protein. For example, the Bet v 1 protein in birch pollen shares homology with the Mal d 1 protein in apple and the Ara h 8 protein in peanut, resulting in clinical cross-reactivity in oral allergy syndrome. Symptoms are usually localized to the oropharynx and consist of itching, tingling, and mild swelling of the lips, tongue, oral mucosa, or throat. Systemic symptoms such as urticaria, asthma, or anaphylaxis are rare but can occur. In one study, 8.7% of patients with oral allergy syndrome had systemic symptoms.[25] These cross-reactive proteins are generally heat labile, and therefore, symptoms seen with ingestion of the raw food do not occur when the food has been cooked or processed.

Delayed Anaphylaxis Due to Red Meat and Association With Cetuximab Reactions

Recently, a delayed reaction of 3 to 6 hours after ingestion of mammalian red meat has been identified. Identification of this phenomenon occurred after hypersensitivity reactions were reported to cetuximab, predominantly in patients in Southern states. Further investigations noted that these patients had an IgE antibody to galactose-α-1,3-galactose (alpha-gal), a carbohydrate moiety in cetuximab that is also present in mammalian red meat.[26] It was later noted that the distribution of cetuximab reactions and delayed red meat reactions overlapped with the geographic distribution of *Amblyomma americanum* (the Lone Star tick). When questioned, patients who presented with delayed meat reactions and IgE antibodies to alpha-gal recalled recent tick bites.

An IgE reaction to alpha-gal should be suspected in patients who may have been exposed to the Lone Star tick and present with repeated episodes of urticaria, angioedema, or anaphylaxis without a known trigger. The association with red meat may not be readily apparent given the delayed nature of these reactions. Patients often report reactions in the middle of the night after consuming mammalian red meat for dinner. Implicated meats include beef, lamb, pork, venison, goat, and bison. The diagnosis is made through history and detection of elevated serum IgE antibodies to alpha-gal on a commercially available test. Skin prick testing has variable utility in diagnosis.[27] Affected patients should avoid all mammalian meat.[8]

Cofactors in Food-Induced Anaphylaxis

Some patients experience allergic reactions to food only in the presence of a cofactor. Exercise, nonsteroidal anti-inflammatory drugs, asthma, infections, and alcohol are well-known cofactors that induce food-related

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reactions.[28] Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a well-identified phenomenon. In a study of adult patients with anaphylaxis, over half of those with anaphylaxis due to wheat had WDEIA[28].Wheat-dependent exercise-induced anaphylaxis can manifest as urticarial or gastrointestinal, respiratory, or cardiovascular symptoms 1 to 4 hours after ingestion of wheat, although cases with symptoms occurring 10 or more hours after ingestion have been reported.[29] Patients with WDEIA should avoid exercise for at least 6 hours after wheat ingestion. Several case reports of anaphylaxis after celery ingestion and exercise have also been published.[30] Other foods such as nuts and shellfish can also be implicated in food-dependent exercise anaphylaxis. Identifying this association is important in advising against exercise after ingestion of these foods.

DIAGNOSIS

Diagnosis of food allergy is based on a suggestive history, allergen-specific IgE (sIgE), SPT, and/or a food challenge. A positive SPT or sIgE result suggests sensitization, and therefore, a history of a reaction or a positive food challenge result is additionally needed to make a diagnosis of a clinical allergy.

Skin prick testing has a high sensitivity and a negative predictive value of more than 90%,[31] although specificity is lower. The accuracy of SPT depends on the commercial food extract used because such extracts are not standardized. In some instances, an SPT with fresh fruits and vegetables may be more accurate than using commercial extracts given the lability of allergenic proteins. A reaction 3 mm greater than the negative control is generally considered positive, although this standard can vary among facilities.

Wheal size on SPT and sIgE levels correlate with the likelihood of a reaction and in some foods the probability of outgrowing an allergy, and therefore patients can be followed up over time to evaluate for tolerance.[1] For example, an sIgE for egg of 2 kU/L predicts a 95% probability of reaction to egg in children younger than 2 years of age. However, for children older than 2 years of age, an sIgE of 7 kU/L has a 95% probability of reaction to egg.[2]

An open oral food challenge is commonly used to confirm tolerance to a food after SPT and/or sIgE testing is negative for allergy in the setting of a questionable history and to confirm the development of tolerance in a previously allergic patient. An oral challenge should only be performed in a setting that is equipped to handle severe allergic reactions.

Component-resolved diagnostics (CRD) is a relatively new testing option, and its utility has been studied principally in peanut allergy. Whereas traditionally used sIgE tests evaluate for IgE associated with the whole food, component testing can identify IgE for specific components of the food, differentiating between components that are clinically important in allergy and those that are not. Studies of component testing for Ara h 2 (a component of peanut) have reported greater diagnostic accuracy with this method than with evaluating IgE for whole peanut.[32] The utility of CRD testing for other foods is variable, and increased specificity results in decreased sensitivity. Although CRD is promising, it should be studied further before it is widely used.

Intradermal testing and patch testing should not be performed for diagnosis of food allergy.[5] IgG testing is available commercially but is not recommended for diagnosis of food allergy.

TREATMENT

Diet and Education

Unfortunately, there are no Food and Drug Administration—approved treatment options for food allergy. Management at this time is centered on strict avoidance of foods and immediate management of a reaction. Patients should be prescribed a targeted allergen avoidance diet including relevant cross-reactive foods. It is crucial that patients and parents of children with food allergy are educated on reading food labels and are aware of the potential for cross-contamination of foods at restaurants, parties, and other locations. Avoidance of foods that contain the labels "this product may contain trace amounts of allergen" or "manufactured on equipment with" may be prudent.[8] The Food Allergy Research and Education website provides valuable and practical information for patients, including common products containing allergens and information on reading food labels. An epinephrine autoinjector should be provided to patients with food allergy, as well as a written emergency action plan for reactions. Patients

should be followed up regularly by a physician to discuss accidental exposures or reactions and to evaluate for tolerance. Repeated SPT, sIgE testing, and oral challenges may be performed periodically depending on the natural history of the allergenic food.[1]

A question that is occasionally raised is whether patients with food allergy can donate blood products. Although case reports have documented the transfer of a specific allergy via transfusions,[33] such transmission is extremely rare. At this time, the presence of a food allergy does not automatically exclude an individual from donating blood products.

Oral Immunotherapy and Sublingual Immunotherapy for Food Allergy

Oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) are methods of inducing tolerance to an allergenic food by gradually increasing the dose of the allergen extract. Oral immunotherapy is ingested, whereas allergen extract is placed under the tongue with SLIT. The effectiveness of OIT for peanut, egg, and milk allergy has been investigated in randomized double-blind, placebo-controlled studies, which have reported that patients receiving OIT were more tolerant of the allergenic food in oral food challenges than patients receiving placebo.[34-36] However, local gastrointestinal reactions and systemic reactions requiring epinephrine have been reported with OIT, and further study is needed.[37]

Studies on SLIT have also documented effectiveness with foods including peanut,[38] hazelnut,[39] and milk.[40] In general, limited data suggest that OIT is more effective than SLIT in developing tolerance to an allergenic food, although SLIT has an improved safety profile.[41] Oral immunotherapy and SLIT hold promise as future treatment options for food allergy, but additional studies confirming safety and efficacy should be performed before these therapies can be widely implemented.

CONCLUSION

A classic food allergy is an IgE-mediated reaction manifesting as any combination of respiratory, cutaneous, gastrointestinal, cardiovascular, or pulmonary symptoms. The most commonly implicated foods include cow's milk, egg, peanut, tree nut, soy, wheat, shellfish, and fish. Factors that should be considered in a patient presenting with food allergy include the possibility of food cross-contamination and cross-reactivity, cofactors contributing to a reaction such as exercise or the use of nonsteroidal anti-inflammatory agents, and food preparation, which can either increase or decrease the allergenicity of a food. Food allergy can be diagnosed by blood or skin IgE testing or an oral challenge. At this time, treatment of a food allergy is centered on education, avoidance of allergenic foods, and management of acute reactions.

Abbreviations and Acronyms: **alpha-gal** = galactose-α-1,3-galactose; **CRD** = component-resolved diagnostics; **NHANES** = National Health and Nutrition Examination Survey; **OIT** = oral immunotherapy; **sIgE** = allergen-specific IgE; **SLIT** = sublingual immunotherapy; **SPT** = skin prick test; **WDEIA** = wheat-dependent exercise-induced anaphylaxis

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