NCC Pediatrics Continuity Clinic Curriculum:
Food Allergies
Faculty Guide

Goals & Objectives:

- Know the common presenting signs of and foods associated with food allergies in children.
- Know how to distinguish anaphylaxis from oral-allergy syndrome.
- Demonstrate proper administration of an Epipen.
- Know the indications for food allergy testing and how it is performed.

Pre-Meeting Preparation:

Please read the following enclosures:

- "Clinical Management of Food Allergy" *(Pediatric Clinics of North America, 2015)*
- "Food Allergy" *(NEJM, 2017)*

Conference Agenda:

- **Group Exercise:** Practice giving epinephrine using an EpiPen Tester
- *Review* Food Allergies Quiz
- Complete Food Allergies Discussion Questions & Cases

Post-Conference: *Board Review Q&A*

Extra-Credit:

- Food Allergies *(PIR, 2020) alternate review article*
- The Learning Early About Peanut Allergy Study: The Benefits of Early Peanut Introduction and a New Horizon in Fighting the Food Allergy Epidemic *(Pediatric Clinics of NA, 2015)*
- Diagnosis of Food Allergy *(Pediatric Clinics of North America, 2015)*
- AAP Section on Allergy & Immunology—provider & parent resources
- Peanut oral immunotherapy in very young children *(Lancet, 2022)*

Hot Topics Video (7 min)

- **Resources for Patients/Parents:**
  - www.acaai.org – American College of Allergy, Asthma & Immunology
  - www.healthychildren.org – articles about allergies under "Health Issues", food allergy handout
  - www.foodallergy.org/ - The Food Allergy & Anaphylaxis Network
  - www.kidswithfoodallergies.org/ - largest online support community
  - www.teamsoaar.com/videos/food-allergy-management/ - educational videos

Clinical Management of Food Allergy

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KEYWORDS

• Food allergy • Treatment • Management

KEY POINTS

- There are no proactive treatments currently available for food allergy.
- Severe life-threatening reactions typically only occur following oral ingestion.
- Identifying the potential food trigger is critical, and diagnostic testing along with clinical history is needed for diagnosis, with a food challenge being confirmative.
- Providers should teach recognition and treatment of allergic reactions and provide an emergency action plan.
- Children with food allergies should be seen annually to assess for interval ingestions, provide education, and monitor for tolerance.

INTRODUCTION

Food allergy affects approximately 8% of children in the United States.[1] Of those children with food allergies, 38.7% have experienced a severe reaction.[1] At present there are no proactive treatments available for food allergy; consequently, the mainstay of therapy is education and avoidance.[2] Often pediatricians are the first physicians encountered by patients with food allergies; therefore, it is critical that pediatricians are trained in the principles of proper diagnosis, management, and referral. This article reviews the 5 main steps of food allergy management in a primary care clinic: (1) clinical history and physical examination, (2) appropriate use of diagnostic testing, (3) medication, (4) counseling/education for patients and families, and (5) referral to an allergist.

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CLINICAL HISTORY

A pertinent clinical history is the single most important tool a physician should use in the diagnosis of pediatric food allergy. Many patients may report symptoms related to food ingestion, but key historical elements can distinguish food allergies from other food-related disorders. All allergic disorders have their roots in inappropriate immune responses, from immunoglobulin E (IgE)-mediated immediate hypersensitivity (eg, anaphylaxis) to non–IgE-mediated conditions.

Differential Diagnosis

The differential diagnosis of food allergy is broad, and encompasses immune-mediated and non–immune-mediated processes. **Table 1** details the differential diagnosis of adverse reactions to foods.[3]

Allergy Versus Intolerance

Food allergies are often mistakenly defined as any adverse reaction owing to ingestion of specific foods or types of food. A true food allergy is an immunologic reaction leading to effector cell (ie, mast cell, basophil, T cell) activation, which results in a

Table 1
Differential diagnosis of adverse food reactions

Mechanism	Disorder	Example
Immune mediated	Celiac disease	Wheat ingestion results in abdominal pain, diarrhea, vomiting, and weight loss
	Eosinophilic gastrointestinal disorders	Ingestion of dairy products causes eosinophilic esophagitis manifesting as failure to thrive, vomiting, dysphagia, or food impaction
	Food protein-induced enterocolitis syndromes	Severe vomiting and hypotension hours after rice ingestion
	IgE-mediated food allergy	Severe anaphylaxis caused by peanut ingestion
	Milk protein allergy	Milk ingestion leads to bloody stools, diarrhea, and failure to thrive during the first few months of life
	Pollen-food allergy syndrome	Sensitization to birch pollens results in oropharyngeal symptom following consumption of raw apple or carrots
Non–immune mediated	Auriculotemporal (Frey) syndrome	Gustatory flushing caused by foods
	Chemical effects	Gustatory rhinitis caused by hot/spicy foods
	Food intolerance/aversion	Nonspecific symptoms resulting in unwillingness to ingest a particular food
	Metabolic disorders	Lactose intolerance characterized by abdominal pain, distension, and diarrhea following milk ingestion
	Pharmacologic reactions	Adverse effects related to caffeine, tryptamine, or alcohol consumption.
	Toxic reactions	Scromboid fish toxin, food poisoning

stereotypic clinical presentation (see later discussion). Many patients and some clinicians may attribute disorders such as celiac disease or irritable bowel syndrome to food allergies. Although some of these disorders certainly have immunologic underpinnings, they can largely be distinguished from hypersensitivity reactions based on key findings in the clinical history such as timing, reproducibility, and symptom complex. For example, a teenage patient who newly develops abdominal pain and diarrhea alone 6 hours after drinking a glass of milk is more likely to have lactose intolerance than an IgE-mediated milk allergy. Adverse reactions such as these should be labeled as intolerances and managed appropriately. Described here are salient clinical features that will assist in distinguishing IgE-mediated food allergies from other adverse reactions to foods.

Suspected Triggers

Although children can be allergic to any food, the 8 most common pediatric food allergens are peanut, cow's milk, shellfish, tree nuts, egg, fin fish, wheat, and soy.[1] Often families may be unsure of the exact food that precipitates a reaction. Common food allergens are usually explicitly stated on food labels. However, in cases where a trigger is not obvious, clinicians must assess the potential for cross-contamination, which commonly occurs in bakeries, buffets, ethnic restaurants, and ice cream parlors, among other locations.

The pathogenesis of IgE-mediated food allergies requires antigen exposure for sensitization to occur. Of note, most childhood food allergies are detected when the child is first introduced to the food.[4] Recent evidence suggests that cutaneous exposure in the context of barrier disruption (ie, atopic dermatitis), presumably early in life, may lead to food sensitization.[5,6] This aspect has important implications for food allergy prevention, as recent literature suggests that early oral exposures may be important for inducing tolerance.[7] In a landmark study, Du Toit and colleagues[8] demonstrated that children 4 to 11 months of age randomized to early oral exposure to peanut versus avoidance had an 86% reduction in the incidence of peanut allergy by 5 years of age. Previous guidelines to avoid potentially allergenic foods during the first few years of life are no longer recommended,[9] and may actually lead to food sensitization.

Type of Reaction

IgE-mediated reactions are distinguished by rapid onset (usually within 2 hours of ingestion) and typically resolve within 24 hours. Characteristic symptoms may include any of the following alone or in combination: hives, swelling/angioedema, vomiting, respiratory compromise, and anaphylaxis.[10] Less common symptoms may include eczematous rash (late onset), rhinorrhea, diarrhea, or abdominal pain. Clinicians should note which medications (antihistamines, epinephrine) were administered and the type of medical care that was given. Additional factors such as alcohol ingestion, exercise, concurrent fever, and use of nonsteroidal anti-inflammatory drugs may serve to augment food-induced reactions[11] and should be noted in the patient's clinical history.

Although most patients will have rapid symptoms that resolve relatively quickly, a significant minority will have biphasic reactions, defined as a recurrence of symptoms within 72 hours of an initial reaction.[12,13] An even smaller number of patients may develop refractory or persistent anaphylaxis requiring volume resuscitation and inotropic support.

Current Diet

In addition to classifying food-induced reactions, it is also important to determine which foods a child is currently avoiding. For example, if a patient suspects a distant

episode of hives was due to a peanut allergy, the clinician should ask about ingestion of peanut-containing foods since the time of reaction. In cases where the food was previously tolerated and is currently incorporated into the diet, no further testing is warranted. It is noteworthy that some children with food allergies to milk or egg proteins are able to tolerate these foods in extensively heated forms[14,15] because the IgE molecules in these individuals are likely specific for conformational epitopes, which are denatured during the heating process. As a result, some children may be able to tolerate egg in a muffin but not in an omelet. These children should continue to ingest the allergen in its baked form, as it may signal and hasten the development of oral tolerance.[16] By contrast, IgE to peanuts, tree nuts, and shellfish (among others) are specific for linear epitopes, which are not denatured with heating, and these allergies tend to persist.[17]

Physical Examination

Physical examination of the patient should focus on the signs of an allergic reaction in addition to other atopic disorders commonly associated with food allergies.[10] For example, many patients have comorbid atopic dermatitis.[18] Others may have a history of asthma, which coupled with food allergy increases the risk of mortality from childhood asthma[19] and anaphylaxis.[20–22] Photographs of acute reactions, if available, may also be helpful. The physical examination may prove useful in distinguishing other conditions with specific findings. It is also important to assess growth parameters in children with food allergy, as this is an established risk factor for growth impairment.[23–25] Children at special risk include those allergic to milk and/or multiple foods. Consultation with an experienced nutritionist may be considered for all children with food allergy, especially those with poor growth. Speech and feeding therapists may also be called upon to evaluate food-allergic children who may demonstrate dysfunctional feeding behavior.

Immunoglobulin E Mediated Versus Non–Immunoglobulin E Mediated

Although IgE-mediated food allergies are the most common, additional immune-mediated food sensitivities known as eosinophilic gastrointestinal disorders have become increasingly prevalent.[26] Eosinophilic esophagitis (EoE), a disorder characterized by eosinophilic infiltration of the esophageal lining, has emerged as a closely related disease state.[27] In contrast to the rapid symptoms of IgE-mediated food reactions, EoE is defined by a more insidious course resulting in failure to thrive, vomiting, reflux, and food aversion. Constant inflammation of the esophagus may eventually lead to dysphagia, stricture formation, and food impaction in adolescents and adults. Eosinophilic gastrointestinal disorders, however, are not confined to the esophagus and may also involve other segments of the gastrointestinal tract.

DIAGNOSTIC TESTING

Several tools are currently used to assist in the diagnosis of food allergy. **Table 2** lists available tools and the settings in which they may be utilized.

Pediatric Clinic

Specific Immunoglobulin E (ImmunoCAP)

Allergen-specific IgE (sIgE) testing measures the presence of allergic antibody to a particular antigen. This blood test can be performed at any age and is not limited by concurrent antihistamine use. As in many other clinical situations, the detection of an antibody by a highly sensitive but nonspecific immunoassay does not necessarily

Table 2
Food allergy diagnostic testing

Test	Primary Care Clinic	Allergy Clinic
sIgE	X	X
Full protein	X	X
Component[a]	X	X
Skin-prick test	—	X
Oral food challenge	—	X

[a] The utility of component testing in diagnosing food allergy is still under investigation.

equate to disease. The presence of sIgE simply denotes allergic sensitization to a particular food protein. Many individuals, especially children with atopic dermatitis, may be sensitized but not clinically allergic. Although sIgE is not routinely recommended for the diagnosis of food allergies,[10] a pediatrician may consider targeted sIgE testing to likely triggers. It is important that this testing be based on a supportive clinical history after ingestion (eg, a high pretest probability of clinical food allergy) and not be ordered indiscriminately. Bird and colleagues[28] recently demonstrated that bulk testing to multiple food antigens with food allergy panels leads to unnecessary cost and dietary restriction. Therefore, if a child tolerates a particular food in his or her diet regularly without clear evidence of allergic disease, sIgE testing should not be ordered. sIgE testing should also not generally be used to screen patients for food allergies before the first ingestion.[10] The application of serologic IgE testing in the diagnosis and management of food allergy patients by primary care physicians has been recently reviewed elsewhere.[29,30]

Traditionally sIgE has been assessed for an entire food molecule composed of multiple component proteins. Recently, component-resolved diagnostics (CRD) have become available, potentially increasing the sensitivity and specificity of IgE measurements,[31] although this is still being studied. Although CRD for milk, egg, peanut, tree nuts, fish, and shellfish are commercially available, their use is not routinely recommended in food allergy diagnostic guidelines, and many such tests are not covered by insurance carriers. Most of the data supporting CRD come from English and European studies of component IgE testing in peanut-allergic patients, a topic that has been recently reviewed elsewhere.[32]

Allergy Clinic

Skin-prick testing

In addition to sIgE, skin-prick testing (SPT) may be useful in confirming clinical food allergy. SPT is an in vivo assessment of mast cell activation whereby a small amount of allergen is placed in the epidermis. Sensitized patients usually develop a wheal and flare reaction at the site of antigen placement within minutes. Skin reactions are then compared with positive and negative controls, as recent antihistamine use or dermatographism may result in false-negative or false-positive results, respectively. This approach is a safe, rapid, and relatively inexpensive way to assess for food sensitization. In general, SPT has an excellent negative predictive value (NPV; ~95%) but a poor positive predictive value (PPV; ~50%).[33]

For those patients who successfully avoid culprit foods and for whom the persistence of food allergy remains uncertain, serial sIgE and SPT may be used to determine whether an oral food challenge is warranted to definitively establish ongoing allergy or tolerance.[3] **Table 3** gives general recommendations for the frequency of laboratory

Table 3
General recommendations for the frequency of testing patients with food allergy

Allergen	Test	≤5 y Old	>5 y Old
Milk, egg, wheat, soy, peanut	sIgE, SPT	Every 12–18 mo	Every 2–3 y
Tree nuts, fish, shellfish	sIgE, SPT	Every 2–4 y	Every 2–4 y

Data from Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. J Allergy Clin Immunol 2012;129:906–20.

monitoring and SPT in children with food allergies. Interpretation of SPT and sIgE must be performed in the appropriate clinical context. Regardless of test values, patients with a recent history of anaphylaxis within the past year should not undergo oral food challenge. Conversely, children who have incorporated a food into their diet without symptoms do not require further testing.

Oral food challenge

The double-blinded placebo-controlled food challenge is the gold standard for the diagnosis of food allergy or confirming its persistence.[10] Because of its labor-intensive and time-intensive nature, open food challenges with commercially available food products are usually used in clinical practice. Before performing an oral food challenge (OFC), the patient should understand the risks associated with the procedure and also display an interest in eating the food afterward if he or she passes the challenge. Well-accepted protocols for OFCs have been published[34] but, in general, gradually increasing amounts of a food allergen are administered over successive intervals under close clinical observation. Once a designated quantity is safely consumed, a patient is allowed to incorporate the food into the diet.

Interpretation of test results

Challenge thresholds for interpretation of sIgE and SPT have been established.[3,35] **Table 4** provides the decision points used by many allergists in deciding whether to perform an OFC. These recommendations provide 95% PPV and 50% NPV for reactions to OFCs. A challenge is usually not recommended when sIgE and SPT are greater than 95% PPV. Conversely, a challenge may be considered when the sIgE and SPT are less than 50% NPV. Positive and negative predictive thresholds do not

Table 4
Predictive value of SPT and sIgE in positive or negative OFC results

	>95% Positive		~50% Negative	
Food	SPT	sIgE	SPT	sIgE
Egg white	≥7	≥7 ≥2 if age <2 y	≤3	≤2
Cow's milk	≥8	≥15 ≥5 if age <1 y	—	≤2
Peanut	≥8	≥14	≤3	≤2 (history of prior reaction) ≤5 (no history of prior reaction)
Fish	—	≥20	—	—

Data from Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004; 113:805–19; [quiz: 20]; and Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. J Allergy Clin Immunol 2014;134(5):1016–25.e43.

exist for many food allergens, and those listed cannot be extrapolated to antigens such as wheat and soy. These foods typically have much higher sIgE reaction thresholds. It should be noted that most predictive cutoffs were developed using the ImmunoCAP system in children with a high pretest probability of food allergy presenting to a tertiary care allergy subspecialty clinic[36]; therefore, values generated using other testing platforms cannot be reliably compared with these thresholds.[37] In addition, population-based estimates have shown that these cutoffs may be much higher if testing is performed indiscriminately or in the general population,[38] whereby the tests may detect sensitization more readily than clinical allergy.

MEDICATIONS

Prescription of Epinephrine

As a provider it is important to identify those patients most likely to develop fatal or near-fatal anaphylaxis and to prescribe injectable epinephrine.[10] **Box 1** presents clinical scenarios known to represent increased risk, although it is well established that allergic reactions to food are inherently unpredictable, making risk stratification difficult. Therefore, epinephrine prescription may be considered in any patient with IgE-mediated food allergy, as the severity of subsequent reactions cannot be predicted. Additional factors to consider, in addition to those listed in **Box 1**, include the age of the patient (adolescents and young adults at higher risk for fatality) and the distance from the patient's home to an appropriate medical facility.[33] Dosing of available autoinjector devices is detailed in **Table 5**.

First-line treatment of anaphylaxis is always epinephrine.[2] Second-line medications such as albuterol or antihistamines may also be prescribed for treatment of mild symptoms or adjunctive therapy, but unlike epinephrine they have no direct effect on the mast cells or basophils themselves. Prompt treatment with epinephrine is encouraged, as this may slow or halt progression of severe anaphylaxis. Furthermore, most fatalities from food-induced anaphylaxis are associated with delayed administration of epinephrine[22]; however, despite this knowledge there is a persistent and well-established underutilization of epinephrine in the treatment of anaphylaxis. When an epinephrine autoinjector is prescribed, families should be taught how and when to administer it. Written anaphylaxis action plans are encouraged, listing medications and their doses, and detailing emergency follow-up procedures including activation of emergency medical services.

Box 1
Guidelines for prescription of an epinephrine autoinjector

Prescribe epinephrine if a child has any one of the following:

- History of anaphylaxis
- Prior history of systemic allergic reaction
- History of food allergy and asthma
- Known food allergy to peanut, tree nuts, fish, and crustacean shellfish (ie, allergens known to be associated with more fatal and near-fatal allergic reactions)

[a] Consider epinephrine prescription in any child with a history of IgE-mediated food allergy.

Data from Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol 2010;126:1105–18.

Table 5
Dosing of available epinephrine autoinjectors

Brand	Dose
Adrenaclick (generic)	0.15 mg (for children 15–30 kg), 0.3 mg (for children ≥30 kg)
Auvi-Q	0.15 mg (for children 15–30 kg), 0.3 mg (for children ≥30 kg)
EpiPen	0.15 mg (for children 15–30 kg), 0.3 mg (for children ≥30 kg)

Ensure that the child has 2 autoinjectors accessible at all times

Other Medications: Antihistamines, Albuterol, and Steroids

Antihistamines such as diphenhydramine and cetirizine are commonly given for mild food-induced reactions. Although these medications may be useful in relieving symptoms, such as itch, they do not halt the progression of an allergic reaction, and are best considered an adjunctive therapy. Albuterol should be used as adjunctive therapy for respiratory symptoms, especially in patients with a history of bronchospasm or asthma. Asthmatic individuals experiencing lower respiratory symptoms such as cough or wheeze during an allergic reaction to food should always receive epinephrine. Corticosteroids have a delayed onset of effect, making them unhelpful in immediate management. Although commonly used in this context, there is little evidence supporting their effectiveness.

COUNSELING AND EDUCATION

Despite their best efforts, most patients with food allergies will be exposed to culprit foods.[39,40] Therefore it is incumbent on health care providers to prepare families to recognize and treat anaphylaxis.[3] Food-induced reactions may be subtle, and it is useful to teach patients that anaphylaxis may present anywhere on a spectrum of symptoms ranging from a few hives and throat clearing to respiratory failure and cardiac arrest. Because anaphylaxis may progress rapidly, early detection and action is a critical step in successful management. Patients and families should be encouraged to inject epinephrine at the first sign of anaphylaxis, even if relatively mild. More educational and counseling food allergy resources for providers and caregivers can be found at http://www.ruchigupta.com/i-will-thrive-video/.

Epinephrine Use

Patients, or their caregivers, should immediately inject epinephrine for any obvious signs of a potentially severe systemic reaction, including: cardiovascular collapse (lethargy, pallor, behavioral changes); respiratory distress (wheezing, coughing, increased work of breathing); or laryngeal edema (drooling, difficulty swallowing, throat tightness). It is important to convey to affected individuals and caregivers that anaphylaxis may not present with such potentially life-threatening symptoms at the onset. Operationally, a generalized allergic reaction involving symptoms affecting more than 1 organ system can be identified as anaphylaxis. For example, a child experiencing urticaria and vomiting after a likely or confirmed allergen exposure can be considered as having anaphylaxis, and such a child should receive epinephrine even if symptoms are not considered to be immediately life-threatening. More specific indications can be individualized based on the patient's medical history.

Use of an epinephrine autoinjector first requires removal of the safety lock. Once removed, the epinephrine should be injected into the lateral thigh. Clothing need not be removed, as the needle of the autoinjector should pass through without difficulty.

The autoinjector should be held in place for at least 10 seconds to ensure complete dose delivery. One removed from the thigh, a protective sheath will cover the needle. If symptoms do not resolve within 5 to 15 minutes, patients experiencing anaphylaxis should be given a second dose. The patient should be placed in the recumbent position with the lower extremities elevated.[41] Patients and families should be instructed to call the emergency services once epinephrine has been administered. Trainer devices from several manufacturers are available for demonstration and testing of proficiency.

Emergency Action Plan

Once a provider is comfortable with a patient's and caregiver's competency using the device, its indications for use should be discussed. Formulating an emergency action plan may facilitate this. Personalized action plan forms are available in English and Spanish through the American Academy of Allergy, Asthma and Immunology (www.aaaai.org) and Food Allergy Research and Education (www.foodallergy.org) Web sites. These forms list patients' food triggers and provide guidelines for treatment.

Avoidance

Strict avoidance of allergens is the only sure way to prevent food-induced reactions. Relatively small amounts of food can trigger acute reactions in highly sensitized individuals.[42] However, reactions may vary considerably depending on the patient and the allergen,[43] resulting in misdiagnosis or a false sense of security if small amounts of food can be ingested without symptoms. One must be aware that the severity of a food-induced reaction does not predict the severity of future reactions; therefore, a child with a peanut allergy who only develops hives after an initial ingestion might develop life-threatening anaphylaxis following subsequent exposure.

Although patients may be exposed to food antigens through a variety of routes (cutaneous, respiratory, oral), typically only oral ingestion causes severe reactions. Investigators have examined the potential for food-induced reactions through casual contact.[44,45] In 2003, Simonte and colleagues[44] performed a randomized, double-blind, placebo-controlled trial of 30 children with significant peanut allergy. Subjects underwent cutaneous and inhalation challenge with peanut, and none experienced a systemic or respiratory reaction. Mild cutaneous symptoms were noted in a minority of patients. A notable exception is that in children with asthma and food allergy, bronchial challenge with aerosolized food allergens can provoke respiratory symptoms, particularly in those with allergy to fish or crustacea.[46] For symptoms to occur, protein antigens must be vigorously aerosolized during food preparation (eg, cooking seafood in a rolling boil) and come in direct contact with the respiratory mucosa. An important distinction is that the smell of foods produced by volatile organic compounds does not cause clinical reactions.

Food Labeling

To properly adhere to recommended elimination diets, patients and families should be instructed to pay careful attention to ingredient lists and food labels.[3] The Food Allergen Labeling and Consumer Protection Act (FALCPA)[47] of 2004 was passed in an effort to make food labels more accurate and understandable for consumers with food allergies. This legislation requires manufactures to label in plain English foods containing any of the 8 major food allergens (peanut, milk, crustacean shellfish, tree nuts, egg, fin fish, wheat, and soy). Major implications of this law are listed in **Box 2**.

In addition to those foods listed containing allergens, patients should also be counseled to avoid products that are processed in a facility where other food allergens are

Box 2
Major implications of the Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004

1. Food allergens in products must be declared in plain English by one of the following:
   a. Placing the word "Contains" followed by the name of food source from which the allergen is derived. (ie, "Contains milk, egg, peanut")
   b. Including the common or usual name in parentheses next to food source in the ingredient list (ie, "albumin [eggs]")
2. Manufacturers are subject to penalties in the Federal Food, Drug and Cosmetic Act if food allergens do not appear on labels
3. FALCPA does not establish standards for the use of "May Contain" statements
4. FALCPA only applies to packaged foods sold in the United States (Except meat, poultry, certain egg products, and alcoholic beverages)
5. Companies may receive exemptions from labeling requirements if the allergen satisfies one of the following requirements:
   a. Highly refined oils are exempt (ie, peanut oil)
   b. Scientific evidence establishes that the food ingredient does not contain the allergenic protein
   c. The Food and Drug Administration determines that the food allergen does not elicit an allergic response in sensitized individuals

processed, causing cross-contamination. It should be noted that use of the phrases "may contain," "may contain traces of," and "manufactured in a facility that also processes" are voluntary; therefore, families must be aware of the potential for cross-contamination. A recent study in Canada[48] found that 17% of accidental exposures resulted from unintentional cross-contamination during manufacturing or packaging, with no precautionary statement being provided. Unfortunately, widespread and inconsistent use of these phrases has also resulted in a devaluation of this warning; consequently, up to 40% of individuals ignore "may contain" statements and consume foods with potential food allergens.[49] Helpful patient information to assist with food allergen avoidance is available through the Food Allergy Research and Education Network (www.foodallergy.org) and the Consortium of Food Allergy Research (www.cofargroup.org).

Different Environments

Although most food-induced reactions occur in the home,[50] many families find that eating out at a restaurant or a friend's home can be difficult. At home, ingredient lists can be screened and meals carefully prepared to prevent cross-contamination, but eating away from home may pose unique challenges. Studies suggest that 40% to 100% of fatalities from food-induced reactions are due to food prepared or catered outside the home.[33] Although risks can be mitigated with advance planning, it is important to identify high-risk situations. Ice cream parlors, ethnic restaurants, bakeries (peanut, egg, milk, and tree nuts), and buffets (all foods) are common places where cross-contamination or occult exposure may occur.[51] Such environments seem to pose a special risk to adolescents and young adults,[20,21] who may be relatively inexperienced in self-management and have been shown to willfully engage in risk-taking behavior pertaining to food allergen exposure.[52]

REFERRAL TO AN ALLERGIST

If a food allergy is suspected or diagnosed, the patient should be referred to an allergist. As mentioned previously, allergists can provide additional diagnostic testing (ie, SPT, OFC) and are equipped to manage anaphylaxis in the clinic. In addition to assisting with diagnosis, allergists can monitor and assess for the development of tolerance and can help manage the comorbid conditions commonly encountered in food-allergic children, such as atopic dermatitis and asthma.

Monitoring for Tolerance

An OFC, performed in the allergist's office, is the gold-standard test to determine whether tolerance has occurred. Serial measurements indicating a decline in the patient's allergen-specific IgE level often provide useful predictive power that a patient is outgrowing a food allergy, and that a challenge is indicated. IgE-based online calculators developed by the Consortium of Food Allergy Research are available for public use to generate individualized probabilities for outgrowing milk and egg allergies.[53] Often the patient's interval history can provide important clues; for example, a child may accidentally be exposed to a trigger food without developing symptoms. If a significant quantity of the food has been tolerated several times without ill effect, the food allergy has likely resolved. Acquisition of tolerance is more likely to occur in younger children, who are allergic to foods such as wheat, soy, milk, or egg.[54,55] By contrast, allergies to nuts including peanut, fish, and shellfish are much less commonly outgrown.[17]

Tolerance of Extensively Heated Allergens

As mentioned previously, some children with milk or egg allergy may be able to tolerate these allergens in their baked forms.[14,15] Researchers hypothesize that this is due to sensitization to conformational epitopes that are unable to cross-link surface IgE molecules when extensively heated.[56] Some data suggest that tolerance to baked milk or egg may be an early intermediate step in the development of immunologic tolerance to the food antigen, and that consumption of baked allergens may actually hasten the resolution of clinical allergy.[16] OFCs with products containing baked milk or egg are routinely performed in the allergist's office.

Routine Follow-Up

A specialist in allergy and immunology should see patients with food allergies at least annually. Periodic visits allow for the following:

- Assessment of interval progress including a history of accidental ingestions
- Renewal of epinephrine prescription
- Renewal and revision of emergency action plans
- Additional education regarding avoidance and recognition/treatment of anaphylaxis, and transition to self-management for teenagers
- Assessment of nutritional status
- Monitoring of coexisting conditions, such as asthma or atopic dermatitis
- Monitoring for development of tolerance to food antigens

Allergen-specific immunotherapy as a proactive treatment strategy for food allergy is currently being developed in phase II/III clinical trials.[57] Its use is not recommended outside of research settings at present,[10] but allergists may be able to routinely provide this life-changing clinical treatment in coming years (Appendices 1 and 2).

SUMMARY

Successful diagnosis and management of food allergies is complex, and demands collaboration from both pediatricians and board-certified allergists, in addition to skilled nurses, nutritionists, and occasionally other team members such as psychologists and feeding therapists. It is hoped that these 5 steps for primary care providers will provide a more straightforward approach: (1) clinical history and physical examination, (2) diagnostic testing, (3) medication, (4) counseling/education for patients and families, and (5) referral to an allergist. Although some clinical trials of interventional food allergy treatments have generated promising preliminary data,[58] the standard of care continues to focus on prescribing the proper elimination diet, education, and training in the recognition and management of accidental allergic reactions.

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CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Food Allergy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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An 18-year-old basketball player with a known peanut allergy and moderate, persistent, controlled asthma has just played in a collegiate game. Cough, shortness of breath, and sneezing develop 10 minutes after he ingests a homemade sugar cookie at a party after the game. He immediately takes 50 mg of diphenhydramine, but hoarseness, throat tightness, worsening shortness of breath, rhinorrhea with copious clear mucus, and repetitive emesis continue to progress. He then administers 0.30 mg of epinephrine with the use of an autoinjector into his upper lateral thigh and four actuations of an albuterol inhaler (at a dose of 90 μg per actuation). The use of these agents results in immediate relief of the throat tightness and full resolution of the other symptoms within 15 minutes. What would you advise at this point? Could his symptoms have been prevented?

THE CLINICAL PROBLEM

IgE-mediated food allergy is a global health problem that affects millions of persons and multiple aspects of a person's life.[1,2] Prevalence rates are uncertain, but food allergy is estimated to affect 15 million Americans — approximately 4% of children and 1% of adults — and studies suggest an increased prevalence in the past two decades.[1-4] Food allergy probably results from a breakdown of or a delay in the development of oral tolerance, or a lack of clinical reactivity to a food substance, in persons who are genetically and possibly environmentally predisposed to the development of atopic disease.[5] Eight foods (milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish) are the most common food allergens in the United States.[1] Peanut allergy is typically lifelong; fewer than 20% of persons who receive a diagnosis in childhood outgrow the allergy. In contrast, milk and egg allergy is typically outgrown by school age.[8]

An audio version of this article is available at NEJM.org

Peanut allergy, which affects approximately 1% of persons in the United States, is the leading cause of fatal and near-fatal anaphylaxis.[6,7] Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death[9]; it involves multiple organ systems, including the respiratory tract, gastrointestinal tract, and skin (Table 1).[9] Risk factors that are most strongly associated with fatal or near-fatal anaphylaxis (Table 2) include the type of allergenic food, adolescence or young adulthood, the presence of concomitant asthma, and the delayed use of or lack of access to an epinephrine autoinjector.[6,9] In addition, several factors, including exercise, viral infections, menses, emotional stress, and alcohol consumption, place some persons at increased risk by lowering the reaction threshold after exposure to an allergen.[11]

KEY CLINICAL POINTS

FOOD ALLERGY

- Food allergy, which affects 15 million Americans, has a substantial effect on many aspects of daily living.
- Peanuts are the most common food allergen associated with fatal and near-fatal anaphylaxis.
- Obtaining an appropriate medical history and collaborating with an allergist to interpret the results of clinical tests are important for the diagnosis and management of food allergy.
- Medical management currently focuses on the following: recognition of signs and symptoms of anaphylaxis; ready availability of an epinephrine autoinjector, with early use when signs or symptoms of anaphylaxis are present, followed by immediate evaluation in an emergency facility for monitoring after use; strict avoidance of culprit food allergens; and education about safe food products.
- Early introduction of peanuts in the first year of life in many children reduces the risk of peanut allergy considerably.

Table 1. Diagnostic Criteria for Anaphylaxis.*

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
Criterion 1
Onset of an illness within minutes to several hours after possible exposure to an allergen, with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, or swollen lips, tongue, or uvula) and at least one of the following signs or symptoms:
Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia or collapse, syncope, or incontinence)
Criterion 2
Two or more of the following signs or symptoms that occur rapidly (within minutes to several hours) after exposure to a likely allergen:
Involvement of the skin or mucosal tissue (e.g., generalized hives, itching or flushing, or swollen lips, tongue, or uvula)
Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
Reduced blood pressure or associated symptoms of hypotension (e.g., hypotonia or collapse, syncope, or incontinence)
Persistent gastrointestinal symptoms (e.g., crampy abdominal pain or vomiting)
Criterion 3
Reduced blood pressure within minutes to several hours after exposure to a known allergen:
Infants and children: low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure
Adults: systolic blood pressure of <90 mm Hg or >30% decrease from the person's baseline blood pressure

* Data are from Berin.[10]

Food allergy–associated anaphylaxis is an IgE-mediated reaction. In a previously sensitized person with food-specific IgE on mast cells and basophils, the food allergen is ingested and absorbed into the local tissue and then cross-links IgE, resulting in immediate release of preformed mediators.[1,10,12] This immune response is rapid; the onset of symptoms typically occurs within 5 to 60 minutes after exposure to the food.

An anaphylactic reaction requires the involvement of multiple organ systems (Table 1), and it may rapidly progress to severe symptoms (e.g., hypotension or respiratory collapse) and death.[9] Although cutaneous manifestations such as hives and pruritus are the most common, they are absent in 20% of persons who have anaphylaxis. Thus, a high index of suspicion is required when other signs and symptoms such as cough, wheezing, laryngeal edema, vomiting, diarrhea, and hypotension are present.

STRATEGIES AND EVIDENCE

EVALUATION

The most important step in diagnosing a food allergy is obtaining a thorough medical history

Table 2. Risk Factors for Food-Induced Anaphylaxis.

Risks associated with fatal and near-fatal food-induced anaphylaxis
Most common risk factors
Delayed treatment with epinephrine
Allergy to peanuts, tree nuts, fish, or shellfish
Adolescence or young adulthood
Asthma
Other risk factors
Cardiovascular disease in middle or older age
Pregnancy
Absence of skin symptoms during reaction
Coexisting conditions and factors associated with increased risk of food-induced anaphylaxis or increased severity of reaction
Asthma
Chronic lung disease
Systemic mastocytosis
Use of beta-adrenergic blocker, angiotensin-converting–enzyme inhibitor, or alpha-adrenergic blocker

that includes the type of food ingested, the type of symptoms, and the timing of the reaction.[1,13] Testing typically includes a skin-prick test for allergen-specific IgE, in vitro allergen-specific IgE tests, or both. If used alone and without a medical history, these tests have a greater than 90% negative predictive value but an approximately 50% positive predictive value.

Oral food challenges are indicated when the clinical history and testing do not indicate a high likelihood that the person has a food allergy. Since many food allergies are outgrown later in life, food challenges are most often used to establish that the person is no longer allergic to the culprit food.

PREVENTION

The Learning Early About Peanut Allergy (LEAP) trial and follow-up studies tested the hypothesis that regular consumption of peanut-containing products, when started during infancy, would elicit a protective immune response (instead of an allergic immune reaction) that would be sustained over time.[14,15] In the LEAP trial, 640 children who were 4 to 11 months of age and who were at high risk for peanut allergy (i.e., those who had severe atopic dermatitis, egg allergy, or both) were randomly assigned to consume peanuts or to avoid them until 5 years of age. Children in the consumption group ate a food containing peanuts at least three times weekly.

The rate of peanut allergy by 5 years of age was only 1.9% among children who ate peanuts, as compared with 13.7% among those who avoided peanuts. Overall, sustained consumption of peanuts beginning in the first 11 months of life was highly effective in preventing the development of peanut allergy. On the basis of these results, new dietary guidelines recommend the introduction of peanuts in the first 4 to 6 months of life.[16]

MANAGEMENT

The current management of peanut allergy and other food allergies involves dietary and medical management, ongoing education, and scheduled follow-up (Table 3).[1] Strict avoidance of food allergens requires continual vigilance before ingestion. This vigilance includes reading and interpreting labels, avoiding cross-contamination, and communicating with other persons who are preparing foods (e.g., in restaurants and school cafeterias).[17]

Medical intervention is focused on the availability of epinephrine as the initial drug of choice for treatment of food-induced anaphylaxis.[1] Epinephrine is the most effective treatment to prevent death from anaphylaxis, but it has a short half-life (minutes) and often requires a second dose for treatment of persistent or recurrent symptoms.[18] Despite its recognized benefit in preventing fatal anaphylaxis, epinephrine continues to be vastly underprescribed and underutilized by health care providers and patients, whereas antihistamines are commonly overused in treating reactions.[18,19] The use of epinephrine earlier in the development of anaphylactic symptoms would most likely prevent more serious reactions and complications.[18] Medications such as antihistamines, glucocorticoids, and inhaled beta-agonists are considered to be adjunctive medications that are used to reduce symptoms, but they should not be used as first-line treatment for anaphylaxis.[1,20,21] The most common reason for morbidity in systemic allergic reactions is that epinephrine is not administered early in the course of the allergic reaction.

Guidelines for the management of food-induced anaphylaxis recommend activation of the local emergency medical services system for

Table 3. Management of Food Allergy.

Strategy	Standard Management	Additional Strategies
Diet	Strict avoidance of culprit foods	Some limited forms of food (e.g., baked products containing milk and egg) may be safely consumed, but this safety must be confirmed clinically with a medically observed feeding or food challenge
Medication	First-line treatment: epinephrine administered with the use of an autoinjector	Adjunctive treatment: antihistamines, beta-agonists, glucocorticoids
Education	Education on label reading, cross-contamination, cross-contact, access to safe foods, and use of medical-alert jewelry; creation of patient-specific action plan for food allergy anaphylaxis	Information provided in schools, workplaces, restaurants, and the food service industry; change in labeling laws for food industry
Scheduled clinical follow-up	Planned follow-up with provider who has experience in treating food allergies (may include allergist); ongoing education, including review of technique for administering epinephrine and use of anaphylaxis action plan; evaluation for resolution of allergy or change in disease with management of coexisting conditions; review of therapeutic plan	Review of emerging treatment options; consideration of participation in clinical trials if applicable

transport of the person to an emergency facility once anaphylaxis occurs, epinephrine is administered, or both. Owing to the potential for biphasic or protracted reactions that can occur 4 to 24 hours after the initial reaction in 10 to 15% of persons, immediate evaluation in an emergency medical facility, with close observation for 4 to 6 hours or longer according to the severity of the reaction or if additional symptoms develop, is recommended.[1]

Currently, no proactive specific treatment is available for persons with food allergy. However, during the past decade, substantial progress has been made toward the development of allergen-specific immunotherapy for food allergy.[22] Scientific investigation and recent clinical trials have focused on three major forms of treatment (oral, sublingual, and epicutaneous immunotherapy), each of which targets a different aspect of the mucosal surface. All these treatments remain experimental.[23] These therapies have a tremendous safety advantage over traditional subcutaneous immunotherapy[24,25] and newer forms of mucosal immunotherapy[26] that have been associated with high rates of serious side effects and have been dismissed as potential treatment options in their current forms.

In order to understand the effects of emerging therapies for food allergy, an understanding of the definitions of clinical desensitization, sustained unresponsiveness, and oral tolerance is essential.[23] "Desensitization" is defined as an increase in the reaction threshold to a food allergen during active therapy; this increase provides some protection from accidental ingestions. Desensitization is achieved after only months of therapy and requires ongoing therapy.

"Sustained unresponsiveness," which is defined as a lack of a clinical reaction to a food allergen after active therapy has been discontinued, requires some level of continued exposure to the allergen to maintain the unresponsive state. Achievement of sustained unresponsiveness requires years of therapy and has been seen only in subgroups of persons.[27,28]

"Oral tolerance," which is used to describe a specific type of immunologic response that does not produce any clinical reactivity after ingestion of a food allergen, typically occurs naturally early in life.[5] Current data suggest that true immunologic and clinical tolerance in patients who have received experimental immunotherapies for food allergy is unlikely to develop; this point is important in understanding the clinical outcomes and potential future implications of immunotherapy.

Table 4. Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Feature	Oral Immunotherapy	Sublingual Immunotherapy	Epicutaneous Immunotherapy
Form of study product (protein dose)	Allergen powder (300–4000 mg per day)	Allergen extract drops (2–7 mg per day)	Allergen patch (100–500 μg per day)
Clinical effect			
Desensitization	Large effect	Moderate-to-small effect	Variable effect
Sustained unresponsiveness	Occurs in subgroups of persons	Not known (studies under way)	Not known
Side effects	Oral or gastrointestinal; potential for anaphylaxis in persons with fever, infection, or menses and during exercise after receipt of a dose of oral immunotherapy	Oral or pharyngeal (local effects)	Skin (local effects)
Immune modulation: antibody and cellular changes	Substantial	Small or moderate	Small or moderate

Oral Immunotherapy

The use of oral immunotherapy (Table 4) against a variety of food allergens has been studied, but most randomized, controlled trials have focused on oral immunotherapy for the treatment of peanut, milk, and egg allergies.[22,28-35] This form of immunotherapy, which can be administered over a period of years, requires daily ingestion of an allergen powder (e.g., peanut protein) mixed with another food. The initial dose of peanut protein is measured in micrograms, building up to reach maintenance doses ranging from 300 to 4000 mg of peanut protein.

Oral immunotherapy has resulted in the highest rates of desensitization and sustained unresponsiveness of all therapies studied as of this writing, but it is also associated with a risk of serious adverse events, including episodic anaphylaxis, eosinophilic esophagitis (among <5% of participants in clinical trials of oral immunotherapy), and dose-limiting gastrointestinal side effects (among approximately 20% of the trial participants).[36,37] Oral immunotherapy may be associated with a higher risk of adverse events and a lower effectiveness in persons with seasonal allergies than in those with food allergies who do not have seasonal allergies.[38] In addition, in persons with a viral illness or menses and in those who exercise within minutes to 2 hours after receiving an oral dose of immunotherapy, reductions in the amounts of allergenic protein used in oral immunotherapy are frequently required to maintain safety.[11,30] Adjunctive therapy with omalizumab, a monoclonal anti-IgE antibody, during the induction stages of treatment has proved to be beneficial in reducing short-term side effects, but studies have not shown that the use of this agent has a major influence on eventual outcomes.[39-41]

Sublingual Immunotherapy

The use of sublingual immunotherapy has been evaluated in clinical trials for the treatment of peanut allergy and allergies to a few other foods. It requires the application of an allergen extract under the tongue on a daily basis for a period of years, with doses ranging from 2 to 7 mg of protein. Sublingual immunotherapy leads to clinical desensitization in most people after 1 year of treatment and to moderate immunologic changes; data are limited from longer-term studies of sustained unresponsiveness.[42-46] This form of immunotherapy has few side effects and minimal adverse effects, which are typically limited to oropharyngeal itching or tingling.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy, which has been investigated for the treatment of peanut and milk allergy, involves application of an allergen patch to the back or upper arm at 24-hour intervals, with doses ranging from 250 to 500 μg of protein. Therapy can continue over a period of years.[47-49] Epicutaneous immunotherapy for peanut allergy is associated with some benefit in clinical desensitization after 1 year of treatment in children, especially those who are 4 to 11 years of age. It has been associated with only modest

desensitization and immunologic changes, and it has not been associated with sustained unresponsiveness.[49] Epicutaneous immunotherapy is associated with minimal adverse effects, with only mild skin irritation at the patch site in most persons, and no systemic allergic reactions have been reported as of this writing.[48,49]

Of the three forms of immunotherapy, the greatest likelihood of clinical desensitization and also the highest frequency of adverse events occur with the use of oral immunotherapy. Sublingual immunotherapy is associated with a lower likelihood and frequency than oral immunotherapy. Epicutaneous immunotherapy is associated with the lowest likelihood of clinical desensitization and the lowest frequency of adverse events.[22,50]

AREAS OF UNCERTAINTY

A recent National Academy of Medicine report, "Finding a Path to Safety in Food Allergy," outlines the difficulties in stating the true prevalence of food allergy.[2] In studies in which participants report having received a diagnosis of food allergy, the prevalence of food allergy among adults is at least 15%, whereas in well-defined studies, the prevalence is 4% among children and 1% among adults. Although most physicians and public health and school administrators would attest to the increase in numbers of persons with food allergy, data are lacking from systematic studies with a sufficient sample size, and in various populations, to determine the true prevalence.[2]

The apparent increases in the prevalence of food allergy and overall allergic disease are unexplained. Changing practices in food manufacturing (e.g., alterations in the production of processed foods), decreases in microbial exposure early in life, and the changing microbiome are speculated to contribute to increases in the prevalence of allergic disease.[5,51,52]

Clear and accurate diagnostic testing in patients with food allergy remains a challenge. The emergence of recombinant testing such as allergen component testing or DNA testing has allowed for broader testing, but its role in clinical practice remains unclear owing to difficulty with interpretation of test results in persons with multiple allergic sensitivities (e.g., those with a pollen allergy or additional food allergies). Additional biomarkers of disease activity and severity are needed to improve diagnostic accuracy.

Regulatory policies for food labeling, including statements such as "may contain" or "manufactured in the same plant as," which are intended to minimize acute allergic reactions, often produce more confusion and anxiety than benefit.[53,54] Efforts to define minimal reaction thresholds for food allergens are under way and may guide the development of improved policies for food manufacturing, preparation, and labeling.

Questions remain about the best management of food allergy, both in the short term and long term. With respect to epinephrine autoinjectors, there are few data on the potential for alternative routes of delivery (intramuscular vs. sublingual or inhaled), the need for the availability of additional doses (currently the doses in the United States are 0.15 mg and 0.30 mg), consideration of an alternative needle length or injection site for severely overweight or underweight persons, determination of best practice for the appropriate number of autoinjectors prescribed per patient, and clear guidelines regarding which persons should receive a prescription for an autoinjector.

Substantial knowledge gaps also remain with respect to the use of immunotherapy in the management of food allergy.[55,56] Most clinical trials have been small and have involved primarily homogeneous populations. Phase 3 clinical trials of oral and epicutaneous immunotherapy for the treatment of peanut allergy are ongoing. Longer-term data regarding the effectiveness of immunotherapy are limited to a small number of studies assessing sustained unresponsiveness after successful treatment with immunotherapy for peanut, egg, or milk allergy.[28,32]

Other forms of allergen-specific and allergen-nonspecific treatment have been studied or are in various stages of development, including Chinese herbal therapy; probiotic treatment, prebiotic treatment, or both; recombinant protein-based, peptide-based, or epitope-based immunotherapy; and anti-IgE therapy. If any of these immunotherapies is approved, clinicians will need to decide on an individual patient basis between careful avoidance (with the potential risk of inadvertent exposure) and the use of immunotherapy with potentially adverse effects and an

uncertain duration of effectiveness without ongoing treatment.[57]

GUIDELINES

Recommendations are outlined in the U.S.[1] and European[20] guidelines for the diagnosis and management of food allergy. Disease-specific practice guidelines and position statements regarding food allergy and anaphylaxis are also available.[9,21]

In addition, important findings noted above in the LEAP trial and follow-up studies in the United Kingdom[14,15] have resulted in the dissemination of updated dietary recommendations for the prevention of peanut allergy. These recommendations classify infants into three categories according to risk.[16] In infants with the highest risk — those with severe eczema, egg allergy, or both — allergy testing should be performed and, if appropriate according to their development and feeding abilities, peanuts then should be introduced in these infants at as early as 4 to 6 months of age. In infants with mild-to-moderate eczema, who are also at increased risk for peanut allergy, peanuts should be introduced at approximately 6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy. In infants without an increased risk (i.e., those who do not have eczema or a food allergy), peanuts can be introduced freely into the diet with other solid foods and in accordance with family preferences and cultural practices.

CONCLUSIONS AND RECOMMENDATIONS

The young man described in the vignette had an anaphylactic reaction after eating a cookie. He was at high risk for illness and death owing to his peanut allergy, age, risk-taking behavior (i.e., eating food without investigating its ingredients or cross-contamination), and concomitant asthma.

Persons with food allergy should be educated and reminded to ask about food ingredients and preparation to avoid cross-contamination and to avoid ingestion when this information is not known. They should be instructed regarding the immediate use of intramuscular epinephrine if symptoms or signs suggest an impending systemic anaphylactic reaction, and they should be informed about the need to immediately seek medical care after they administer epinephrine. If food-allergen immunotherapy is ultimately approved by the Food and Drug Administration, such treatment would warrant consideration in such persons, although there are limited data regarding long-term effectiveness.

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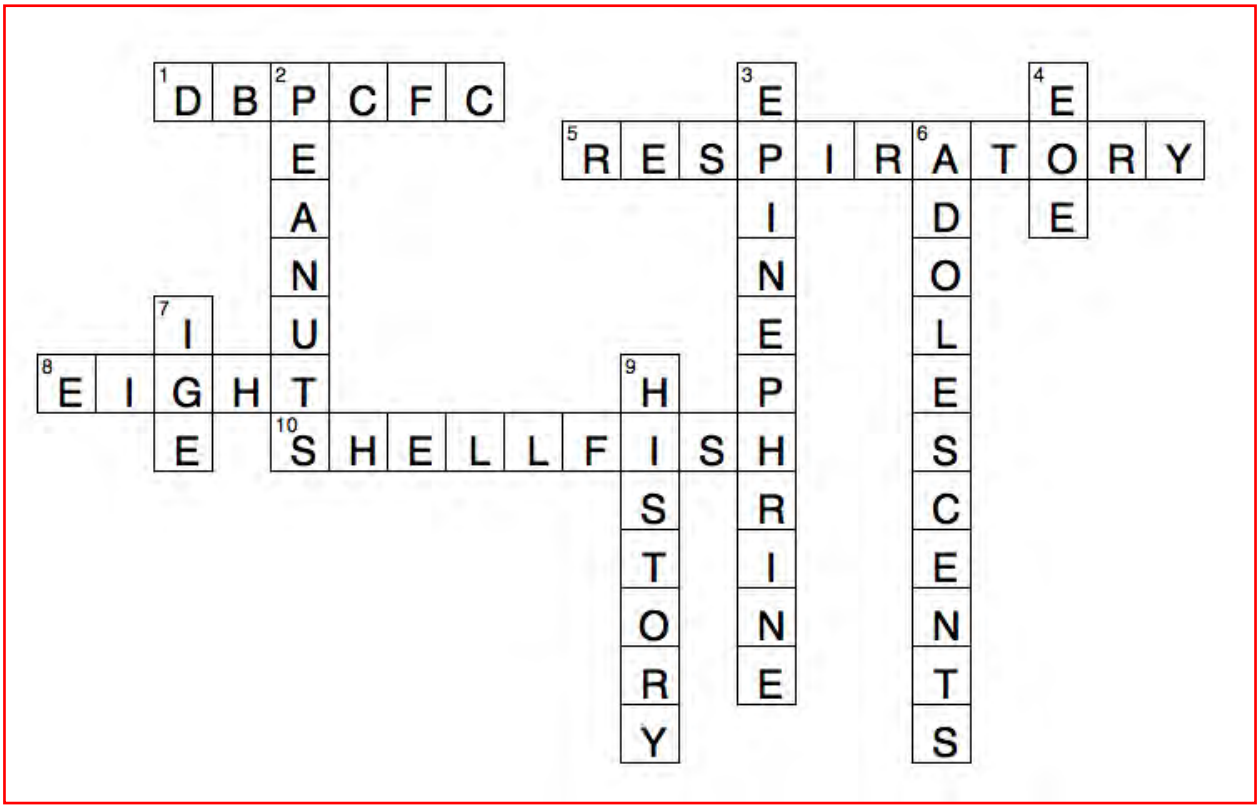
Food Allergies Quiz



ACROSS:

1. The gold standard test (abbreviation) for diagnosing a food allergy. double blinded placebo controlled food challenge
5. Anaphylaxis is characterized by the involvement of 2 or more of the following systems: the skin, GI tract and ___ system.
8. Up to ___ percent of children have food allergies.
10. The most common food allergy in adults.

DOWN:

2. Food allergies to tree nuts, seafood and ___ are unlikely to be outgrown.
3. Risk for a severe allergic reaction to food include a delay in administering this medication.
4. In children this condition may present with vomiting, reflux symptoms or feeding disorders.
6. This age group is at the most risk to have a fatal food allergic reaction.
7. Anaphylaxis is an ___-mediated reaction.
9. The most important element in diagnosing a food allergy.

Food Allergies Cases

Discussion Questions:
Does anyone have any patients with food allergies in the panel?
How did they present?
At well visits, do you normally check for accidental ingestions?
Or look for epinephrine expiration dates?

Case 1:
Bobby is a 2 year old boy who presents to the clinic with parental concern for food allergy. His mother reports that on two occasions in the past he has developed an itchy, raised rash over his face, chest and abdomen, lip swelling, and hoarseness after eating eggs. The last episode was yesterday. He ate roughly 1 cup of scrambled eggs and 40 minutes later developed symptoms. He did not have any vomiting, diarrhea, or labored breathing. Bobby's mother gave him a dose of diphenhydramine and his symptoms resolved after 1-2 hours. He eats baked goods containing eggs without developing similar reactions.

What additional history will you obtain?
- What other foods was he eating prior to the reactions?
- Past medical history, especially history of eczema, asthma or allergic rhinitis. Remember that asthma is a risk factor for more severe food allergy reactions.
- Family history of atopic disease
- Current medications and drug allergies

Bobby's mother reports that the only other foods he ate with the eggs were toast, butter, and orange juice. He has had all of these alone recently and tolerated them well. He had eczema as an infant, but only required frequent applications of Aquaphor. He was breastfed for 9 months and then switched to a cow's milk formula. Eggs were introduced first at 18 months of age. His mother had asthma as a child and one of Bobby's older sisters has allergic rhinitis. He is not currently taking any medications and does not have any medication allergies.

Are you concerned Bobby has an egg allergy? How will you further evaluate him?
- His history of respiratory symptoms (hoarseness), lip swelling, and hives as well as the timing of symptom onset is concerning for an egg allergy.

- Options for further evaluation include:
    - **Immunocap, Egg-specific IgE**: The detection of an antibody by a highly sensitive, but nonspecific immunoassay does not necessarily equate to a particular food protein allergy. Some individuals, especially children with atopic dermatitis, may be sensitized but no clinical allergy. *SO, in general, food allergy panels should be avoided as there is a high false positive rate and positive results do not always correlate with clinical symptoms.* Can also see false negative results. A clinical history consistent with food allergy is the best indicator.
    - May refer to **Allergy & Immunology** where options for further evaluation may include skin testing or the gold standard, oral food challenge.

You discuss your concerns with Bobby's mother and put in a prescription for an Epipen Jr. **When and how should she administer the Epipen Jr? What can she expect after she injects the medication?**

- **Epinephrine** should be given if there is suspected egg intake and any clinical symptoms of anaphylaxis. *It is important to give epinephrine early!* In general, epinephrine should be given if the child has one of the following: history of anaphylaxis, prior history of systemic allergic reaction, history of food allergy and asthma, known food allergy to peanut, tree nut, fish, and crustacean shellfish (allergens known to be associated with fatal and near-fatal allergic reactions), or a child with a history of IgE-mediated food allergy.

- **Side effects** from epinephrine include tachycardia, flushing, anxiety, nausea, or vomiting. These symptoms can overlap with those of anaphylaxis.

- Can give an **antihistamine** as needed for cutaneous symptoms, some people recommend also giving an **H2 blocker**, however it is important to understand that theses do not replace epinephrine and do not treat anaphylaxis. **Albuterol** can be given as needed for wheezing; however, this has no direct effect on mast cells and basophils themselves and is second-line treatment.

- After administering epinephrine he should be taken to the **ER** for further support and monitoring. He could have a **late phase reaction 6-10 hours later** (6-20% of all anaphylaxis), so observation for a minimum of 4-8 hours following an episode of anaphylaxis is warranted.

As you're wrapping up Bobby's clinic visit you notice that he has not gotten his influenza vaccine this year. **Given your concerns for a food allergy to eggs, can Bobby get the influenza vaccine today? Bobby's mother also asks if he will always be allergic to eggs?**

- He may not be able to get the influenza vaccine today, but an **allergy to eggs is not a contraindication to give the influenza vaccine**.
- Allergies to egg, wheat, soy and milk are the most common allergies that improve by adulthood. Allergies to peanuts, tree nuts, shellfish and fish are most likely to persist.

Case 2:

You are seeing Isabella, a 4 month old previously healthy infant who presents for a routine well visit. Parental concern today is whether she can start eating complementary foods. She is showing interest in food during family meals. Family history includes asthma in her mother and an older sibling with a severe food allergy to peanuts and eggs. On your exam, she has good muscle strength/tone and is able to hold her head upright.

Isabella's mother asks what foods she should avoid to prevent Isabella from developing a food allergy. Mom is also planning returning to work and intends to stop breast feeding and wants to know what formula to switch to?

- Complementary foods including potential allergens **should not be restricted**. In fact, the newest recommendations include introduction of peanut no later than 4-6 months for children at highest risk of developing food allergies.

- Should encourage Isabella's mother to **continue breast-feeding** and pumping breast milk once she returns to work. If continuing breast feeding is not feasible, it is no longer recommended to switch to a **hydrolyzed formula**.

- Consider the results of the **LEAP trial**: 640 high-risk infants between 4-11 months of age were assigned randomly either to avoid peanut entirely or to regularly include at least 6g of peanut protein per week in their diets. Regimens were continued until 5 yrs of age. Found an overall **81% reduction of peanut allergy in children who began early, continuous consumption of peanut compared to those who avoided peanut.**

Case 3:

Lionel is a 10 year old boy with a history of allergic rhinitis who presents for a routine physical. His only concern today is that he gets tingling around his mouth after eating apples. He denies any other associated symptoms. The tingling self-resolves over 1 hour.

What additional questions will you ask?

- Timing of his symptoms, similar symptoms with other foods?
- Current medications, history of drug allergies?

Lionel reports that the tingling occurs within 30 minutes of eating apples. He has eaten apple pie without having symptoms. He reports he is a meat and potatoes guy and he does not like any other fruits. Besides allergic rhinitis he has been healthy. He currently takes fexofenadine daily as needed, when his allergic rhinitis symptoms flare. He does not have any known medication allergies.

What is the most likely cause of his symptoms. How will you evaluate him further and how will you treat him? What other foods may cause him to experience similar symptoms?

- History is consistent with **oral allergy syndrome** to apples due to a cross-reaction with birch
- Evaluation may include:
    - Measurement of **serum IgE** to birch pollens
    - **Allergy Immunology Referral** for further testing which may include:
        - Skin testing with raw apple or birch pollens
        - Oral food challenge
- Treatment:
    - Avoidance of apples and other fruits that cross-react with birch
    - **Cooking, microwaving or baking apples** prior to consuming, which may make them more tolerable.
    - **Antihistamines** as needed for symptoms
    - If he should develop systemic symptoms in the future, may recommend that he carry an Epipen at all times.
    - May be a candidate for **immunotherapy** against pollen allergens
- Other foods that cross-react with birch antigens = plums, peaches, nectarines, cherries, almonds, kiwi, celery, almond, hazelnut, watermelon.

Food Allergies Board Review

1. The parents of a 10-year-old boy who has a peanut and tree nut food allergy ask your advice on the treatment of food allergy reactions at school. They describe a scenario that occurred last year when their son started itching diffusely and having difficulty breathing during lunchtime after inadvertently eating some of his friend's chocolate candy bar that contained peanuts. At his current school, the child is allowed to carry his own self-injectable epinephrine. His current weight is 90 lb (41 kg).

Of the following, the BEST advice for the child, if a similar situation occurs, is to
A. have the school call emergency services, who should evaluate and administer epi if needed
B. have the school nurse observe the child for 10 to 15 minutes while calling his parents
C. immediately administer 0.15 mg of self-injectable epinephrine
D. immediately administer 0.30 mg of self-injectable epinephrine
E. take an oral antihistamine immediately

The boy described in the vignette experienced an anaphylactic reaction, a potentially life-threatening event. In children, the most commonly identified causes for anaphylaxis are food, insects, drugs, latex, and vaccines. Food allergy is the most common cause of anaphylaxis in the home or school setting and accounts for an estimated 50% of all pediatric cases annually.

Some 85% to 90% of allergic reactions to food in children are due to milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish. Peanuts and tree nuts account for most cases of fatal anaphylaxis from foods in the United States.

Recently, a panel of experts published a set of clinical criteria for diagnosing anaphylaxis. The skin and respiratory system are the most commonly affected systems in cases of food allergy-induced anaphylaxis, as described for the boy in the vignette. Fatal anaphylaxis almost always is due to airway edema and subsequent respiratory failure.

For a person experiencing anaphylaxis, epinephrine should be administered immediately and without delay. Observation of the child while calling his parents wastes precious time in this situation. In the school setting, self-injectable intramuscular epinephrine is used. Other methods of delivery, used primarily in the hospital setting, include intravenous, intraosseous, and via an endotracheal tube. Current epinephrine injectors are available in two strengths: 0.15 mg and 0.30 mg. The child in the vignette, who weighs more than 30 kg, should be given the 0.30-mg dose, preferably in the lateral thigh. Antihistamines may decrease pruritus or flushing, but their effect has a slow onset, and they are not recommended as the initial treatment for anaphylaxis. Because some children may require additional doses of epinephrine and observation, emergency services should be called, but waiting for them to arrive to make a decision regarding the initial dose of epinephrine is not recommended.

Caregivers of children who have experienced food-induced anaphylaxis should have epinephrine readily available, understand the indications for its use, have a written action plan, and understand the proper technique for use of self-injectable epinephrine devices.

2. You have been asked by a local school to provide recommendations about the use of self-injectable epinephrine for anaphylaxis. The school supervisor is concerned about the increased incidence of peanut and tree nut food allergy. School officials have requested that each child who has a diagnosis of "food allergy" have two self-injectable epinephrine devices at the school nurse's office.

Of the following, the BEST response regarding anaphylaxis is that

A. a patient should not receive a second dose of epinephrine unless a clinician is present

B. epi reaches higher peak plasma concentrations if injected into the thigh rather than arm

C. families should keep one epi autoinjector in the car in case a reaction occurs after school

D. skin manifestations (eg, flushing, itching, urticaria) are rare in severe anaphylaxis

E. subcutaneous injection of epinephrine is preferable to intramuscular injection

The prevalence of food allergies has continued to increase over the past 3 to 4 decades. Specifically, many children, parents, and school officials have been faced with the need to know about and understand how to recognize and appropriately treat food anaphylaxis in the school. Education and counseling of school officials and health-care clinicians is paramount to reduce morbidity and mortality from food anaphylaxis.

The most common antigenic triggers of anaphylaxis are foods, drugs, insect venom, radiocontrast media, and latex. After exposure to an antigenic trigger, symptoms generally develop within 5 to 30 minutes, although symptoms can occur up to several hours after the exposure. Severe allergic reactions usually occur after binding of specific immunoglobulin (Ig) E to the high-affinity IgE receptor, with subsequent cross-linking of receptors and mediator release (eg, histamine, tryptase) from mast cells and basophils.

Cutaneous manifestations such as urticaria, flushing, pruritus, and angioedema are the most common symptoms in anaphylaxis, occurring in 80% to 90% of episodes. Respiratory symptoms such as dyspnea, wheezing, shortness of breath, and cough are the next most frequent symptoms. Cardiovascular symptoms include cardiovascular collapse, tachycardia or relative bradycardia, and arrhythmias. Among the gastrointestinal manifestations are nausea, vomiting, diarrhea, abdominal pain, and cramping. Finally, many patients complain of either a metallic taste or "a sense of impending doom."

Appropriate treatment of anaphylaxis consists of early administration of epinephrine. Because anaphylaxis can occur in the absence of a health-care professional such as at school home, or a birthday party, children at risk always should have self-injectable epinephrine nearby.

Although parents or other adults may be reluctant to inject a child with epinephrine, this agent, not an antihistamine, is the drug of choice for anaphylaxis. In the past, outpatient administration of epinephrine was subcutaneous, but research has demonstrated that intramuscular injection, specifically in the thigh, is the preferred route and location due to higher and faster peak plasma concentration. If epinephrine is administered, parents or school personnel should follow an emergency action plan. This should involve calling emergency services to evaluate the child and transport him or her to the emergency department for further evaluation. The effects of a single dose of epinephrine typically last for 5 to 15 minutes; up to 20% of individuals experiencing anaphylaxis may require a second epinephrine dose. When symptoms persist, a second (or third) dose should be administered, even if the parent or school professional still is awaiting the ambulance. Although epinephrine always is the drug of choice in anaphylaxis, glucagon may be required in refractory cases for patients using beta blockers.

Self-injectable epinephrine should be available for all locations (ie, the patient usually carries one to two injectors), but leaving the device in the car is not recommended because extreme temperature changes can

decrease the efficacy. Recommended storage temperatures are 20° to 25°C at home and 15 to 30°C during trips outside the home, school, or workplace. Approximately 5% to 20% of patients who suffer initial anaphylactic events can experience a "late-phase" response 4 to 24 hours later in which symptoms such as flushing, pruritus, or airway obstruction recur. Such later symptoms result from the recruitment of inflammatory cells after the initial hypersensitivity response.

3. A 12-month-old girl presents with a 3-month history of a pruritic rash that involves her cheeks, neck, anterior trunk, and antecubital and popliteal areas. The rash improves after use of an over-the-counter topical steroid cream but still is present most days, and the infant often wakes up at night scratching. On physical examination, you observe a raised erythematous rash that has areas of lichenification.

Of the following, the MOST helpful intervention is to
A. eliminate fruit and acidic juices from the diet
B. eliminate milk, eggs, soy, and wheat from the diet
C. perform aeroallergen allergy testing
D. perform food allergy testing
E. recommend a skin biopsy

PREP2009 Answer: Some 30% to 40% of infants who have moderate-to-severe atopic dermatitis (AD), such as described for the infant in the vignette, may have an underlying immunoglobulin (Ig) E-mediated food allergy exacerbating the AD. For some infants, food ingestion may result in immediate worsening of AD severity, although most infants do not demonstrate this immediate reaction. Many foods have been implicated in AD, but 5 (milk, eggs, soy, wheat, and peanut) account for 90% of the causative allergens.

Both allergy skin testing and measurement of serum IgE concentrations to these foods can help to identify and eliminate likely triggers. Either a negative IgE blood test (<0.35 kU/L) or a negative skin test for a specific food provides a high negative predictive value. On the other hand, the positive predictive value for a skin or blood test may be only 50%.

Although the most commonly implicated foods often are eliminated from the diet, such an approach does not improve symptoms in most (60% to 70%) children because they do not have IgE-mediated AD. The unnecessary elimination of multiple foods can have an adverse effect on nutrition, and food avoidance should be guided by the dietary history, eczema severity, and skin or blood testing.

Frequently, children experience perioral rashes after drinking fruit juice. Such rashes typically are nonpruritic, limited to the area of contact, and resolve within a few hours. The mechanism of such rashes is unknown, but children generally outgrow such reactions by age 4 years. In cases involving more widespread cutaneous symptoms, such as described in the vignette, elimination of fruit or acidic juices is unnecessary.

Parents often request testing for environmental allergies. House dust mites have been implicated in some cases of AD, although they are less likely a cause for moderate-to-severe atopic dermatitis than food allergies. Climate changes such as cold, dry air or hot, humid weather can worsen AD, but specific seasonal allergens such as oak tree or ragweed are not associated with eczema in infants.

A skin biopsy can provide insight into the pathophysiology of chronic rashes or lesions. Generally, skin biopsies neither are advised nor provide insight into the causes of typical AD manifestations in infants, but atypical presentations or lack of expected improvement with appropriate therapy should prompt consideration of a dermatology referral.

4. A mother brings in her 11-month-old son after he broke out in "hives" today during breakfast. The infant had stayed home from child care with a low-grade fever, and the mother had let him eat eggs for the first time. Immediately after breakfast, the mother noted a diffuse erythematous, pruritic rash covering the boy's trunk and extremities. She is concerned that her son may have an egg allergy.

Of the following, the BEST statement regarding Ig-E-mediated egg food allergy is that
A. cooking the egg eliminates its allergic potential
B. egg is the most common food allergy in the first postnatal year
C. egg white is more allergenic than egg yolk
D. most children do not outgrow their egg allergy
E. the measles-mumps-rubella vaccine is contraindicated in children who have egg allergy

Immunoglobulin (Ig) E-mediated egg allergy is one of the more common childhood food allergies, affecting approximately 1% to 2% of children. As described in the vignette, cutaneous features are common, including atopic dermatitis, urticaria, and pruritus. Once the diagnosis of egg allergy is determined, patients generally are advised to avoid all egg food products with the hope that most children will outgrow their egg allergy within 3 to 5 years.

The primary allergenic egg protein is ovomucoid, a protein predominantly in the egg white. Approximately 50% of children may be able to tolerate small amounts of egg protein that has been heated extensively (eg, baked goods). Prolonged heating at high temperatures can denature proteins from a conformational form to a linear form. Some children who are allergic to eggs do not recognize the linear protein form as an allergen and, therefore, do not experience a reaction. Of note, the brief cooking used to make scrambled eggs will not denature heat-stable proteins.

The relationship between egg allergy and vaccination is a common question. The measles-mumps- rubella vaccine is safe for children who have egg allergy and should be administered without special precautions. The trivalent influenza and live attenuated influenza vaccines contain small amounts of egg protein and are contraindicated for patients who have egg allergy.

However, studies have supported a two-dose protocol for the administration of the influenza vaccine in egg-allergic patients. The two-dose protocol involves administering one tenth of the vaccine, observing the recipient for a period of time, and administering the rest of the vaccine, followed by a similar observation period.

In westernized countries, milk generally is regarded as the most common food allergen in infants, with an incidence of 2.5%, compared with an incidence of 1.5% for egg allergy.

5. A 10-year-old boy presents to the clinic complaining of tongue and mouth itching within a few minutes after eating apples. His mother states that he has not experienced these symptoms with other foods, but they occur every time he eats a fresh apple. He denies systemic symptoms, and the oral symptoms resolve within a few minutes. Other than allergic rhinitis in the spring months, he is healthy.

Of the following, you are MOST likely to advise his mother that

A. allergy skin testing to fresh apples probably will have negative results
B. cooking the apple will not alter its allergenicity
C. her son should avoid eating all fruits
D. her son should avoid milk products
E. her son's symptoms are related to his allergic rhinitis

The boy described in the vignette is exhibiting a common form of food allergy called food pollen syndrome or oral allergy syndrome (OAS). OAS is seen in 30% to 40% of children who have allergic rhinitis. Certain foods contain proteins that are similar to airborne allergens, and patients who are allergic to an aeroallergen are at risk of developing reactions to the cross-reacting food protein.

In most cases, symptoms are isolated to the oropharynx, where food comes in contact with a mucosal surface, and include lip, tongue, and oral mucosal pruritus; tingling; and occasionally angioedema. Interestingly, because these food proteins are heat-labile, cooking the food (eg, apple pie) negates its antigenic properties. Although symptoms typically are mild, there are reports of severe reactions. In one recent review involving 1,361 patients who had OAS, 8.7% experienced systemic symptoms outside the gastrointestinal tract, 3% experienced symptoms other than oral symptoms, and 1.7% experienced anaphylactic shock.

Because OAS is relatively specific to particular cross-reacting food(s), patients do not need to avoid other fruits or vegetables to which they have not experienced reactions. Avoidance of unrelated foods (eg, milk, eggs) is not recommended unless the history suggests a previous reaction. The decision to avoid causative foods can be based on the severity of reaction.

Referral to an allergist typically is reserved for situations when skin testing is desired or if the child has experienced systemic symptoms. Skin testing is performed using a commercial extract or the fresh fruit or vegetable. When using fresh food, the sensitivity of skin testing with a history of reproducible reactions is close to 90%, while the negative predictive value is more than 90%. The skin prick device is pressed into the food and then pressed in the skin (so-called "prick-prick" skin test).

Other immunoglobulin (Ig) E food reactions include atopic dermatitis, eosinophilic esophagitis, and specific food allergy. In the United States, 85% of specific food allergies are due to egg, milk, wheat, soy, peanuts, tree nuts, fish, and shellfish. Most children who have IgE food allergies react to only one or two causative foods, although children who have tree nut allergy, atopic dermatitis, and eosinophilic esophagitis often have IgE-mediated reactions to multiple foods.