

Childhood Food Allergies: Current Diagnosis, Treatment, and Management Strategies

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Abstract

Food allergy is a growing public health concern in the United States that affects an estimated 8% of children. Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a specific food. Nearly 40% of children with food allergy have a history of severe reactions that if not treated immediately with proper medication can lead to hospitalization or even death. The National Institute of Allergy and Infectious Diseases (NIAID) convened an expert panel in 2010 to develop guidelines outlining evidence-based practices in diagnosing and managing food allergy. The purpose of this review is to aid clinicians in translating the NIAID guidelines into primary care practice and includes the following content domains: (1) the definition and mechanism of childhood food allergy, (2) differences between food allergy and food intolerance, (3) the epidemiology of childhood food allergy in the United States, (4) best practices derived from the NIAID guidelines focused on primary care clinicians' management of childhood food allergy, (5) emerging food allergy treatments, and (6) future directions in food allergy research and practice. Articles focused on childhood food allergy were considered for inclusion in this review. Studies were restricted to the English language and to those published within the past 40 years. A cross-listed combination of the following words, phrases, and MeSH terms was searched in PubMed and Google Scholar to identify relevant articles: *food allergy*, *food hypersensitivity*, *child*, *pediatric*, *prevalence*, and *epidemiology*. Additional sources were identified through the bibliographies of the retrieved articles.

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Food allergy is a growing public health concern in the United States that affects an estimated 8% of children.^{1,2} Nearly 40% of children with food allergy have a history of severe reactions that if not treated immediately with proper medication can lead to hospitalization or even death.² Because of the ubiquity of food throughout our lives, providing food-allergic children and their caregivers with the proper guidance to successfully manage their food allergy remains essential for protection against adverse health outcomes. Therefore, adequate clinician training on the proper diagnosis and comprehensive management of childhood food allergy is essential.

Previous research suggests that primary care clinicians in the United States have many misconceptions regarding the diagnosis and management of food allergy.³ Specifically, some clinicians were unaware of the most common food allergens and unable to instruct families in the appropriate administration of lifesaving medication (ie, epinephrine).³ In addition, physicians

expressed concern regarding their ability to manage food allergy effectively because of inadequate training in residency. Lack of quality studies and heterogeneity in accepted diagnostic practices have resulted in wide variations among clinicians' food allergy management practices.⁴ In response to this variation, the National Institute of Allergy and Infectious Diseases (NIAID) convened an expert panel in 2010 to develop guidelines outlining evidence-based practices in diagnosing and managing food allergy.⁵ However, these guidelines have yet to be translated into clinical practice for specific subpopulations of physicians and affected patients.

The purpose of this review is to provide primary care clinicians with relevant background on the current scientific literature, best practices, and emerging issues facing children with food allergies. To this end, the review includes the following content domains: (1) the definition and mechanism of childhood food allergy, (2) differences between food allergy and food intolerance, (3) the epidemiology of childhood food

allergy in the United States, (4) best practices derived from the NIAID guidelines focused on primary care clinicians' management of childhood food allergy, (5) emerging food allergy treatments, and (6) future directions in food allergy research and practice. Articles focused on childhood food allergy were considered for inclusion in this review. Studies were restricted to the English language and to those published within the past 40 years. A cross-listed combination of the following words, phrases, and MeSH terms was searched in PubMed and Google Scholar to identify relevant articles: *food allergy*, *food hypersensitivity*, *child*, *pediatric*, *prevalence*, and *epidemiology*. Additional sources were identified through the bibliographies of the retrieved articles.

DEFINITION AND MECHANISM OF FOOD ALLERGY

An adverse reaction to a food can encompass a broad array of events that occur after ingestion. Food allergy is a specific type of adverse event in which a pathologic immune-mediated (IgE) reaction to a specific allergen results after the item is exposed to the skin or a mucosal surface of the body, which is typically the gastrointestinal tract.⁶ Food allergies can be attributed to several factors including genetic predisposition and environmental exposure.⁷

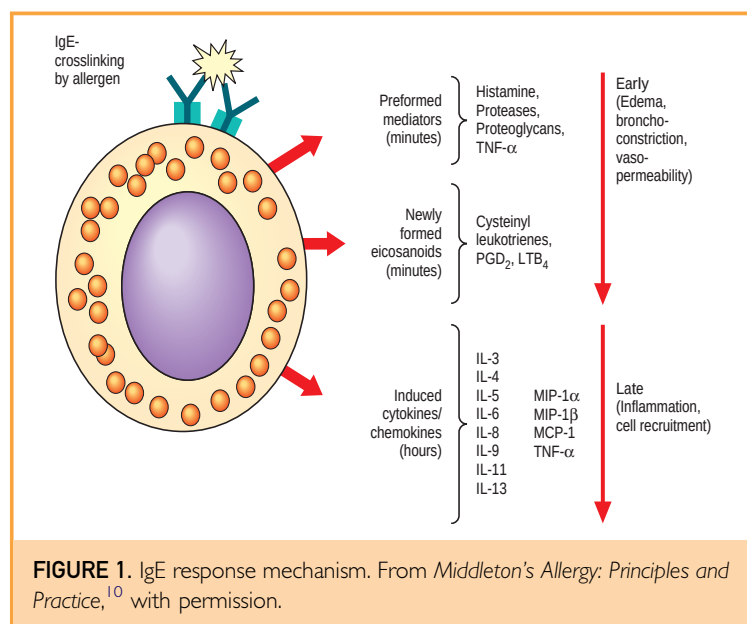
Most immunologic reactions to food allergies are IgE-mediated and target one or more specific proteins within a food called epitopes. Epitopes are the binding site for specific IgE or T cells. Most allergens are comprised of several different epitopes, and certain epitopes are homologous among food items and have been conserved through evolution (eg, peanut, tree nut, birch pollen).⁸

Although the focus of this review is on IgE-mediated food allergy, it is important to recognize that a growing subset of food-allergic children suffer from non-IgE-mediated food allergy. A small percentage of food allergies is non-IgE mediated and involves T-cell-mediated immunity to certain food proteins. The major types of non-IgE-mediated food allergy are food protein-induced enterocolitis syndrome (FPIES), dietary protein intolerance (eg, milk protein allergy), protein enteropathy, and mixed IgE/non-IgE syndromes such as eosinophilic esophagitis (EoE). Celiac disease is an immune-mediated gastroenteropathy triggered by gluten, but this is not considered a food allergy.

ARTICLE HIGHLIGHTS

- The prevalence of childhood food allergy in the United States is approximately 8% and has increased during the past decade. The most common food allergens are milk, egg, wheat, soy, peanut, tree nut, finfish, and shellfish.
- Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a specific food. Symptoms typically present within minutes to hours after ingestion. In contrast, food intolerance is not immune mediated and occurs because of pharmacologic, toxic, or metabolic properties of the food or the host.
- Food allergy diagnosis requires documentation of a clinical history of a food allergic reaction. After ingestion of a specific food, a child may have mild symptoms (eg, a few hives, mild nausea/discomfort) and/or severe symptoms (eg, diffuse hives, shortness of breath, any respiratory symptom, obstructive swelling of tongue and/or lips that interferes with breathing, or circulatory symptoms).
- Testing includes a food-specific IgE test and/or skin prick tests. A positive allergy test result in the absence of clinical symptoms is not adequate to make a diagnosis of food allergy.
- All food-allergic patients should be prescribed antihistamines (mild reactions) and an epinephrine autoinjector device (severe reactions).
- Comprehensive counseling regarding food allergy includes (1) food avoidance and appropriate nutritional monitoring, (2) label reading, (3) recognition of the signs and symptoms of anaphylaxis, (4) how and when to use the epinephrine autoinjector, (5) appropriate follow-up, and (6) documentation for school (eg, action plan).
- Current research focuses on finding a treatment for food allergy. Several potential therapeutic modalities are being investigated and include oral immunotherapy, sublingual immunotherapy, and Chinese herbal medicine.

It is important to recognize these conditions as distinct from IgE-mediated food allergy for the following diagnostic and therapeutic reasons: (1) to understand that standard allergy skin prick testing and serologic IgE testing (ImmunoCAP or other similar systems) will not detect these conditions and that these are largely clinical diagnoses and (2) to understand that epinephrine and antihistamine will not treat these conditions.⁵



Before discussing how the body responds to a food allergen, it is necessary to distinguish two processes that are easily confused: sensitization and allergy. Sensitization implies that the body makes allergen-specific IgE, which is detected in the blood or through skin testing. In contrast, allergy is defined by sensitization in conjunction with clinical symptoms in response to a trigger (eg, food allergen). Although food allergies are often associated with high levels of allergen-specific IgE levels, it is fundamental to understand that sensitization is not pathognomonic for food allergy. Sensitization can exist without a clinical response to the allergenic food. Therefore, isolated sensitization alone should not be used to diagnose food allergy.⁵

In food-allergic individuals, it is widely believed that a normal mechanism of immune suppression occurs when exposure to an oral antigen fails within the gut. This process results in the loss of tolerance. It is believed that the structure of an allergenic protein resists breakdown or conformational change once it comes into contact with digestive enzymes, which allows it to retain its allergenicity. Failure of the digestive system to degrade proteins into smaller fragments results in the transluminal absorption of large, immunologically intact proteins. Once absorbed, antigen-presenting cells are able to bind these allergens and present them in association with major histocompatibility complex class II antigens for presentation to T cells within

the lymph tissue. This is the first step of a complex cascade that results in the production of antigen-specific IgE antibodies or reactive T cells.

In the case of IgE-mediated allergy, the antigen-specific IgE antibodies are produced and bind to the surface of mast cells. Bound IgE can then become cross-linked on recognition and binding of an allergen. These steps lead to degranulation, which is the process by which preformed chemicals (eg, histamine) are released from the mast cell and cause the symptoms we associate with an allergic reaction (Figure 1).^{5,9}

FOOD ALLERGY VS FOOD INTOLERANCE

Food allergy is an immune-mediated response most commonly associated with IgE; food intolerance is a nonimmunologic response to a particular type of food. Food allergies are commonly due to egg, cow's milk, wheat, soy, shellfish, fish, peanuts, and tree nuts whereas food intolerance may be attributable to food additives (eg, sulfates), lactose, and gluten.¹¹ Furthermore, food intolerance may be of a pharmacologic, toxic, or metabolic etiology, which includes lactase deficiency, impaired complex carbohydrate digestion, inhibition of diamine oxidase to metabolize histamine, and gluten sensitivity.^{9,11,12}

For example, children with cow's milk allergy may potentially experience hives and impaired breathing after allergen exposure. Conversely, children who are lactose intolerant lack the enzyme lactase. Clinically, this translates into the child being unable to metabolize milk, which can result in bloating, flatulence, and diarrhea. Moreover, gluten-associated disorders can be categorized into 3 types: (1) a person can have a nonimmunologic gluten intolerance, (2) a person can have a gluten food allergy that elicits an IgE response, and (3) a person can have celiac disease. Celiac disease differs from a food allergy because the reactions do involve the immune system but are relegated to the small intestine. Often, reactions can be confusing and require a clinician's evaluation to determine if the reaction is a food allergy or food intolerance.

EPIDEMIOLOGY OF CHILDHOOD FOOD ALLERGY

Prevalence

Food allergy is a rapidly emerging public health issue that affects an estimated 8% of

US children.² In 2007, data from the National Health Interview Survey indicated that childhood food allergy prevalence had increased by 18% over the previous decade.¹ According to the National Hospital Ambulatory Medical Care Survey, the increase in prevalence of pediatric food allergy parallels a rise in ambulatory care visits and food allergy–related hospitalizations.¹ Furthermore, the rate of anaphylactic reactions requiring hospitalizations has substantially increased among young persons, with food-induced reactions being the most common cause.¹³ The 8 most common pediatric food allergens are peanut, tree nut, cow's milk, shellfish, fin fish, egg, wheat, and soy.^{2,5} Food allergy can be diagnosed in infants, children, and adolescents. Although allergies to certain foods can be triggered through food protein in the breast milk, food allergies are often detected and diagnosed as a child is being introduced to foods.

Associations

Although an explanation for the development of food allergy among certain children has not yet been clearly articulated, there are several known factors that are associated with food allergy, including specific demographic characteristics, existing atopic conditions, perinatal feeding habits, and infant diet.

Demographic Characteristics. Disparities may exist in food allergy prevalence and management. For example, previous research found that black and Asian children have significantly higher odds of food sensitization compared with white children; however, these children have significantly lower odds of receiving a formal physician diagnosis of food allergy.¹⁴ Similarly, a recent systematic review examining race and food allergy in the United States noted wide study heterogeneity and few quality studies evaluating these racial associations.¹⁵ This review noted that no study utilized food challenge to diagnose food allergy, and the included studies had very different definitions of what was considered food allergy. However, 10 studies included in the review have documented either increased odds of food sensitization in black children or a significantly higher proportion of reported food allergy or sensitization in black children compared with white children. Income may also have a significant role because the odds of confirmed food

allergy have been shown to be higher in households with incomes greater than \$50,000.²

Existing Atopic Conditions. *Atopy* is defined as the tendency to develop allergic diseases.¹⁶ Typically, patients with one atopic condition are predisposed to development of multiple allergic conditions.¹⁷ The *allergic march* is a theory that describes an often-observed triad of associated atopic conditions that progress from early into late childhood. The march starts in the first year of life with atopic dermatitis and progresses to allergic rhinitis, asthma, and food allergy.¹⁸ This march has been observed in several birth cohorts outside the United States.¹⁹

The presence of severe eczema within the first 6 months of life has long been associated with an increased risk of developing peanut, milk, and egg allergy.^{7,20} For children with asthma, there is an increased likelihood of food sensitization, and conversely, an increased likelihood of asthma has been noted in food-allergic individuals.^{13,21,22} Asthma has long been recognized as a moderating factor in severe allergic reactions.^{23,24} Children with food allergy have a 4 times higher odds of having asthma.¹ In addition, findings from a retrospective study indicate that 44% of children diagnosed as having asthma have an existing food allergy.²⁵

A recent study has also found that 30.4% of children with reported food allergy have multiple food allergies.² This could be due to a tendency for an individual's immune system to be hypersensitive, cross-reactive to structurally similar food allergens, or an artifact of having increased testing.

Perinatal/Postnatal Maternal Eating Habits.

There is insufficient evidence to formally recommend that pregnant women avoid allergenic foods throughout pregnancy and while breastfeeding.^{26,27} Neither the American Academy of Pediatrics (AAP) nor the American Academy of Allergy, Asthma, and Immunology guidelines advocate for perinatal allergen avoidance. Although a 2006 Cochrane review found no evidence to support perinatal allergen avoidance,²⁸ there is a need for additional research and further consideration of the current recommendations.⁵ Factors associated with avoidance, such as maternal quality of life (QoL), should also be considered in the overall risk-benefit analysis of perinatal dietary recommendations.

TABLE 1. Recommendations on Formula Choice by Food Allergy Condition

Formula choice	Condition				
	Milk allergy	Soy allergy	FPIES	Dietary protein intolerance	Colic or irritability
Cow milk formula	...	Best alternative if not milk allergic	...	...	Seek specialist evaluation if there is concern for milk allergy
Soy formula	Best alternative	...	May not be appropriate due to soy co-reactivity	May not be appropriate due to soy co-reactivity	Empiric switch for colic or irritability not recommended. Soy is an acceptable alternative for lactose intolerance
Extensively hydrolyzed casein formula	Good alternative	Good alternative	May not be appropriate for all milk-triggered FPIESs	Best alternative, although a small percentage still react to this	Empiric switch for colic or irritability not recommended
Elemental formula	Good alternative	Best alternative if both milk and soy allergic	Best alternative	Good alternative	Empiric switch for colic or irritability not recommended

FPIES = food protein–induced enterocolitis syndrome.

Infant Diet. There is insufficient evidence to determine recommendations regarding the avoidance of allergenic foods in the early years of infancy or to encourage delaying introduction of solid foods. Thus, parents often elect to avoid feeding their children commonly allergenic foods for fear of inducing allergy due to premature exposure in a developing immune system.²⁰ Moreover, development of allergy in infants may be affected by both the timing and the quantity of exposure to allergenic foods.²⁹ The current AAP guidelines highlight one recommendation related to infant feeding: exclusively breastfeed the child for his or her first 4 to 6 months of life.²⁷ If there is strong suspicion for a milk or soy allergy, food protein–induced enterocolitis syndrome, or dietary protein intolerance, recommendations for formula change presented in Table 1 should be considered. Hopefully, further research in this area over the next several years will produce more clarity.

Tolerance

Tolerance develops at different rates according to food allergen. Factors that affect the development of tolerance include allergy to another food, tolerance to another food allergen, and other atopic conditions.³⁰ For example, the average time to development of tolerance to soy was increased from 1 to 5 years in children who had coexisting asthma, allergic rhinitis, eczema,

and other food allergies.³¹ Another potentially predictive factor may be the level of initial serum IgE response to the food allergen.^{5,30,32} For wheat, tree nut, egg, cow's milk, and soy allergy, lower initial and peak levels of antigen-specific IgE were associated with the development of tolerance.³⁰⁻³⁴ Lower peak IgE levels were also associated with more rapid development of tolerance for soy allergy.^{31,32}

Once tolerance has developed, recurrence of the allergy has been known to occur.³⁵ This phenomenon has been observed with peanut allergy and is more likely to occur with infrequent consumption of the allergenic food after it can be consumed safely.³⁶ Research has indicated that once tolerance is established, eating the allergenic food frequently may decrease the likelihood of recurrence.³⁶ In terms of long-term outcomes of having a food allergy, it remains unknown whether EoE is more likely to develop in formerly food-allergic individuals who develop tolerance; however, evidence of EoE development has been noted in oral immunotherapy (OIT) trials and may be related to long-term exposure in a formerly sensitive individual.^{37,38}

Severity

Allergic reactions to foods can result in a combination of cutaneous, gastrointestinal, and respiratory manifestations that can potentially be fatal.^{5,22,24,39} Predicting the severity of a

subsequent reaction is difficult because it may vary and is independent of previous reaction history or serum IgE levels.^{5,40} However, research on the natural history of peanut allergy suggests an association may exist between reaction severity and IgE level.⁴¹ In a recent study, 40% of children with a food allergy had already experienced a severe reaction.² Severe reactions are more likely to occur in adolescents aged 14-17 years and in youths who have multiple food allergies.^{2,42} Peanut, tree nut, and shellfish allergies are the most likely to result in severe reactions.^{2,23,24,39} Among tree nuts, cashews and walnuts account for the majority of severe reactions.³⁰ Severity is a purely clinical observation and cannot yet be predicted by the magnitude of results of skin or blood tests (eg, higher scores do not necessarily indicate a more severe allergy).⁵ In addition, severity of a reaction is also highly influenced by recognition and prompt treatment. Even a seemingly mild reaction has the potential to quickly progress to a severe reaction if not addressed quickly and monitored.

NIAID GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

Primary care clinicians are often the first resource for affected families and play a critical role in the diagnosis and management of childhood food allergy. Accordingly, recognition and proper management of food allergy in the primary care setting is critical and may be life-saving. To better equip primary care physicians in managing patients with food allergy, we have distilled the NIAID guidelines into the following 5 categories to ensure optimal management in the primary care setting: (1) clinical history of reactions, (2) diagnostic testing and test interpretation, (3) prescription of potentially lifesaving medications, (4) counseling and education for patients and caregivers, and (5) referral to an allergist (Figure 2).⁵ Common food allergy scenarios in the primary care setting are shown in Table 2. A resource list of reputable food allergy organizations has also been provided to help guide primary care physicians in the management of childhood food allergy (Supplemental Appendix, available online at <http://www.mayoclinicproceedings.org>).

Clinical History of Reactions

Primary care clinicians are often the first to assess a child with suspected new-onset food

allergy. Examples of mild to moderate food allergy symptomatology include angioedema of the lips, eyes, face, or other body parts, oropharyngeal symptoms, eczema, flushing, hives, pruritus, and vomiting.⁵ Examples of severe food allergy symptomatology include low blood pressure or syncope, dyspnea, wheezing or any respiratory difficulty, or multiple organ system involvement. Anaphylaxis criteria have been established and reviewed elsewhere, but briefly, they involve cardiac/circulatory symptoms, respiratory symptoms, or any presentation involving 2 organ systems (eg, severe gastrointestinal and skin symptoms).⁴³

The differential diagnosis for food allergy includes metabolic intolerance, toxic effects of foods, food poisoning, metabolic deficiencies, and food aversions.⁵ In cases in which a food allergy is suspected, the food should be eliminated from the diet. Removal of the offending agent should prevent further symptoms from developing. Care must be taken to factor in

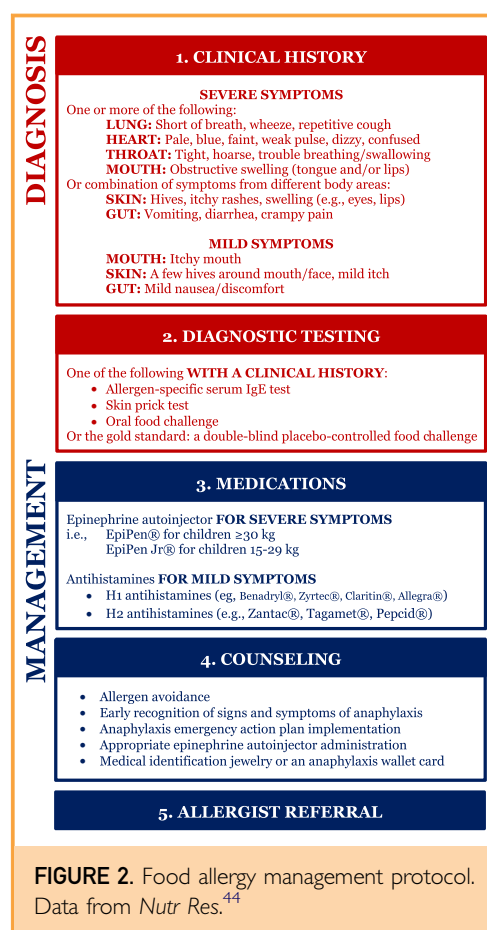


FIGURE 2. Food allergy management protocol.
Data from *Nutr Res*.⁴⁴

the confounding influence of observer bias when undertaking an at-home elimination diet, especially if atopic dermatitis is the presenting symptom. Patients who undergo dietary elimination for suspected food allergy should be referred to an allergist.

Diagnostic Testing and Test Interpretation

Allergy tests are used to confirm suspected cases of food allergy. Testing without suspicion of a symptom-provoking episode is not recommended, and findings are often misleading or inaccurate because of false-positive results.⁴⁵ Three diagnostic tests include the skin prick test, the specific serum IgE test, and the oral food challenge. Atopy patch testing, intradermal food testing, and IgG4 food testing are not recommended for assessment of food allergy.

Skin prick tests are currently conducted by specialists in allergy or immunology. Skin testing directly assesses the presence of mast cell–bound allergen-specific IgE. Skin prick testing involves introduction of allergen extracts into the skin. A positive reaction is defined as a wheal at least 3 mm greater than the negative control. The negative predictive value is more than 95%, while the positive predictive value is less than 50%; therefore, there are many false-positive results. Antihistamines should be discontinued before testing.

Serum IgE tests quantify free specific serum IgE but do not measure IgE bound to mast cells that participate in a reaction. IgE tests are available to primary care physicians and may be of benefit during the initial assessment, as long as testing is limited to what reasonably may have provoked the reaction.⁵ Use of laboratory-offered standard panels of common foods should be discouraged. All positive and negative test results need to be correlated with the patient's clinical history. A positive test result alone does not establish the diagnosis of clinical food allergy. Rather, it provides evidence of sensitization, ie, an immunologic response.⁴⁶ Oftentimes, however, primary care physicians have varying comfort levels in interpreting laboratory tests to diagnose food allergy, and many do not feel adequately prepared by their medical training to care for children with food allergy.³ The cutoff value is the concentration of specific IgE for a particular food allergen that is 90% predictive of a clinical reaction to the food. Increasing levels of specific IgE and wheal response to skin prick testing beyond the cutoff level correlate with an increased likelihood

of having clinical food allergy but not necessarily with reaction severity. For example, established cutoff values for serum-specific IgE testing include: egg (child 3-17 years), 7 kU/L; egg (child ≤ 2 years), 2 kU/L; cow's milk (child 3-17 years), 15 kU/L; cow's milk (child ≤ 2 years), 5 kU/L; peanut (child < 18 years), 14 kU/L; and fish (child < 18 years), 20 kU/L.

Oral food challenge is a procedure that should only be undertaken by an allergist. The procedure involves incremental feeding of a pre-specified amount of a food (either in an open or blinded procedure) under strict medical supervision. Emergency medication must be on hand in case of an allergic reaction. Oral food challenge has been described in detail elsewhere.⁴⁷

Prescription of Potentially Lifesaving Medications

Food avoidance is the first line of treatment for children with food allergies because there are no recommended preventive medications.⁵ In addition to food avoidance, primary care clinicians should prescribe both antihistamines and an epinephrine autoinjector for all children presenting with a likely food allergy. Parents and caretakers should be directed to use antihistamines for mild symptoms (eg, a few hives, mild nausea/discomfort) and the epinephrine autoinjector for severe symptoms (eg, diffuse hives, shortness of breath, any respiratory symptom, obstructive swelling of the tongue and/or lips that interferes with breathing, or circulatory symptoms). Antihistamines should not be used in place of epinephrine.

For severe reactions, epinephrine will relieve symptoms and can be dosed every 5 to 15 minutes if symptoms are not responding.^{23,24,39} In some cases, a child may require a second dose of epinephrine; thus, patients are advised to carry 2 epinephrine autoinjectors in case of an emergency. Adjunctive treatment for severe reactions includes bronchodilators, H₁ and H₂ antihistamines, corticosteroids, vasopressors, glucagon, and atropine.⁵ In any reaction, corticosteroids have limited benefit because their role is to prevent late-onset activation of immune mediators (such as leukotrienes) that are recruited to the site of reaction, in what is called a *biphasic reaction*. The importance of coadministering both H₁ and H₂ antihistamines is an emerging focus of anaphylaxis education to prevent severe cardiac deficit.⁵⁴

TABLE 2. Eight Common Food Allergy Scenarios in the Primary Care Setting: Appropriate Action and Rationale

Scenario	Appropriate action	Rationale
A parent of a baby <1 y presents with one of the following complaints: • Colic/irritability • Constipation • Watery stool	• Reassurance, evaluation, or treatment of the underlying issue (eg, stool softener, normal variation) • No need to change formula at this time	• The diagnosis of food allergy is unlikely, and the symptoms provide no evidence of an immunologic disorder • Further evaluation is needed to explore these complaints⁵
A mother of a newborn seeks advice about which foods she should avoid while breast-feeding to prevent development of allergy. Alternatively, a pregnant mother inquires about what not to eat during pregnancy to prevent food allergy in her child	• There is currently no evidence supporting avoidance of any particular food during pregnancy or during breast-feeding	• Conflicting data exist • No clear recommendation can be made • No longitudinal prospective study has been published to address these concerns, although 2 English studies are under way • There is emerging evidence that early child exposure may be beneficial in preventing specific food allergies^{5,48,49}
A child presents with atopic dermatitis, and the parent expresses concern about food allergy based on what they have heard or read	• Obtain a detailed history to determine the likelihood that food exposure is provoking a discrete episode of atopic dermatitis and the degree of underlying atopic dermatitis • Treat the eczema using moisturizers and appropriate-potency topical corticosteroids. Ask parent to keep a diary of food eaten before an breakout for a month to help clarify cause and effect	• Food allergy is a potential cause in only 35% of those with moderate to severe atopic dermatitis • The older allergy literature overspecifies a relationship between food-specific IgE and food allergy in this population, and care must be taken to not overtest or interpret the results too literally • Often, avoidance is prescribed and no treatment for the underlying atopic dermatitis is provided • Allergy referral is recommended^{5,50}
A parent raises concern about the increasing prevalence of food allergy and desires either blood testing or allergy referral for their child	• Reassure the parent that allergy testing is not accurate enough to predict what someone may be allergic to and can only help in the evaluation of a suspected allergic reaction that has occurred	• Allergy testing cannot “predict” future risk. Also, IgE testing has a poor positive predictive value. The tests are sensitive and generally detect any allergen-specific IgE to food that is present, but it is often poorly understood that simply having allergen-specific IgE is not indicative of having an allergy (eg, having the antibody does not necessarily indicate disease)^{5,48}
A child presents with what is deemed a “mild” food allergy, with a history of hives associated only with a particular food	• Anaphylaxis management must be provided, an epinephrine autoinjector should be prescribed, and the child should be trained to use it • Referral to an allergy specialist for longitudinal care is recommended	• Any food allergy can be progressively more severe on the next exposure. All children with food allergy should be given epinephrine and be trained to use it. Yearly follow-up is recommended for retesting⁵
A parent seeks food testing for their child based on a “family history” of a food allergy in a close relative	• Obtain a thorough history and establish if your patient has had difficulty with any food or if food is being withheld because of the concern. If so, consultation with an allergist is recommended	• There is minimal evidence that family history poses much risk. The younger sibling of a peanut-allergic child does have a mildly elevated risk of peanut allergy and should be referred to an allergist for further evaluation^{5,35,51}
An egg-allergic child presents for an influenza or MMR vaccination (both contain trace amounts of egg)	• Provide the vaccination in your office and observe as you would any other child per ACIP guidelines	• The risk of MMR provoking a reaction in an egg-allergic child was disproven in 1995. Similarly, the risk for influenza vaccine was disproven in 2011, and the ACIP changed their formal guidelines^{52,53}

Continued on next page

TABLE 2. Continued

Scenario	Appropriate action	Rationale
A child presents to your office after being treated with epinephrine in the emergency department for acute development of cough, hives, and vomiting within 2-3 h after exposure to a tree nut (or any food)	- Obtain a complete history, keeping in mind the high probability that this was indeed provoked by the food - Prescribe an epinephrine autoinjector and provide training on how to use it - Refer to an allergist and instruct that the child avoid that particular food item until further evaluation can be conducted	This presentation would be suggestive of a food allergy in a patient of any age. In children with such a specific history, testing would likely be confirmatory and can be done at any age. This child should be immediately referred to an allergy specialist, told to temporarily avoid that particular food, and be prescribed an epinephrine autoinjector⁵

ACIP = Advisory Committee on Immunization Practices; MMR = measles-mumps-rubella.

Previous research has shown that patients wait an average of 4 months after a referral for their first allergist consultation.⁵⁵ In the interim, the child has the potential to experience an additional adverse food allergy–related event. Hence, even if primary care clinicians are uncertain of the food allergy diagnosis, they should always prescribe potentially lifesaving epinephrine and antihistamines and counsel caretakers and children on appropriate food allergy management.

Counseling and Education for Patients and Caregivers

Providing comprehensive counseling to families of children with food allergy remains integral to keeping the child with food allergies safe. Comprehensive counseling includes (1) food avoidance and appropriate nutritional monitoring, (2) label reading, (3) recognition of the signs and symptoms of anaphylaxis, (4) how and when to use the epinephrine autoinjector, (5) appropriate long-term follow-up to assess longitudinal prognosis, development of potential tolerance, and development of other allergic conditions, and (6) provision of documentation for school (eg, food allergy emergency action plan, individualized education plan [IEP]/Section 504 plans).⁵

Primary care clinicians should always train affected families in recognition of symptoms and appropriate epinephrine administration. They also can and should create an emergency action plan for the child and train his or her family in appropriate emergency food allergy action plan implementation (Figure 3). Please refer to the following website, www.foodallergy.org, for an updated version of the food allergy action

plan. Depending on the specific food or number of foods removed from the diet, nutritional counseling is often not only helpful to preserve the family's QoL but may also be medically necessary to prevent malnutrition.⁵⁶⁻⁵⁸

The child's food allergy will need to be managed at home, at school, and within his or her community. It remains integral to the safety of the child that all institutions (eg, school) and people who come into contact with the child (eg, coaches, schoolmates) are aware of the child's food allergy. To assist in managing the child's diet, children with food allergy, their families, and other persons entrusted with care of the child should receive education on reading labels, sources of exposure to the allergen, and use of self-injectable epinephrine. This is of particular importance for child care providers but also others such as grandparents who may supervise an allergic child. In addition, families are often advised to provide their child with medical identification jewelry in the case of an emergency outside of the child's home.

Referral to an Allergist

Children presenting with a clinical history of likely food allergy should be referred to an allergist for diagnostic testing.⁵ In some circumstances, it is necessary to perform an oral food challenge to verify the history. Although the current criterion standard for diagnosing true food allergy is a double-blind, placebo-controlled oral food challenge, there is an emerging trend toward use of open challenges.⁵⁹ In addition, the allergist will formulate an emergency anaphylaxis action plan, reinforce how and when to use epinephrine, provide anticipatory

guidance pertaining to avoidance strategies (eg, label reading), and help to facilitate a dialogue with schools or child care centers, if necessary. Primary care physicians should be encouraged to comanage the condition with the allergist and should be aware of the special needs of the food-allergic individual. This may include social support given the effects that food allergy can have on QoL.⁶⁰

EMERGING FOOD ALLERGY TREATMENTS

Avoidance Diets

Avoidance diets are a mainstay of the management of food allergy, although there are no controlled studies evaluating their efficacy.⁴ Initiating an elimination diet is an important step that bears an important responsibility. Avoiding an “obvious” trigger is straightforward, although care must be taken to not solely rely on sensitization as the only determination of allergy if the history does not strongly support allergy. Handling of potentially cross-reactive foods is more difficult (eg, peanut, tree nut).^{5,46} There is limited data on the known actual risk with most cross-reactivity, as opposed to the theoretical risk described by experts, although the clinical experience with cross-reactivity has been conservative, favoring avoidance. Overreliance on serum-specific IgE testing indicating “allergy” contributes to this practice. In a recent study, Fleischer et al⁶¹ very eloquently demonstrated how unnecessary many of the widespread dietary elimination diets are. They showed that nearly 89% of avoidance diets in 125 children with atopic dermatitis and food allergy (diagnosed by serum specific IgE) were unnecessary. Nutritional deficits have been reported from widespread dietary avoidance.⁶² Nutritional consultation is highly recommended for children in whom widespread avoidance is necessary. It is known that as the number of food avoidances increases, QoL diminishes, which promotes poor adaptation and anxiety in the family.^{57,63} Strategies to prevent unnecessary avoidance include use of challenge to confirm food allergy (when indicated), avoiding changing from cow’s milk formula to other formulas for colicky children without true signs of IgE/non-IgE-mediated allergy, and discontinuation of the practice of screening children without a history of an exposure with a reaction.

The standard approach for management of food allergies has been complete avoidance of

the allergen and clinical management of symptoms on accidental exposure. However, although successful avoidance can prevent the occurrence of allergic reactions, it is difficult to ensure avoidance at all times because of the ubiquitous presence of food in our society. Not only is allergen avoidance difficult to execute, it is also associated with increased anxiety and impaired QoL.^{57,60} Thus, recently there has been a particular focus on the search for treatment or a cure. Several potential therapeutic modalities are being investigated. These include OIT and sublingual immunotherapy (SLIT) in addition to Chinese herbal medicine.

Immunotherapy

Oral immunotherapy takes advantage of the body’s natural tendency to tolerate items presented to the immune system through oral exposure. Through repeated oral exposure to incremental amounts of a particular food allergen, immunotherapy is theorized to induce a change in the immune system by promoting regulatory T cells. This process is modulated by the transcription factor FoxP3 and mediated by the cytokines interleukin 10 and transforming growth factor β . This change is accompanied by up-regulation of allergen-specific IgG4 and decrease of IgE. The overall intended effect of the process is tolerance; however, OIT may also result in desensitization.⁶⁴ Adverse effects of OIT vary widely, ranging from mild oropharyngeal or skin reactions to anaphylaxis.

The basis of any immunotherapy is similar to that for standard subcutaneous immunotherapy (SCIT), colloquially known as “allergy shots.” In SCIT, individuals are gradually immunized via injection to their identified allergens, starting with a very dilute concentration and increasing it until a maintenance peak dose is reached that will alter the body’s response to the allergen. The body is exposed to incremental increases in the potency and quantity of the allergen until a tolerance is reached, reflected by the aforementioned cytokine changes. SLIT is an alternative form of OIT that is also being investigated as a food allergy therapy.^{65,66} SLIT is also administered orally as both drops or tablets, which are either swallowed or held under the tongue and spit out. The allergen is taken up by mucosal antigen-presenting cells (eg, Langerhans cells, myeloid dendritic cells) in a mechanism distinct from SCIT and OIT.⁶⁶

Food Allergy Action Plan

Emergency Care Plan

Place
Student's
Picture
Here

Name: _____ D.O.B.: ____/____/____

Allergy to: _____

Weight: _____ lbs. Asthma: ☐ Yes (higher risk for a severe reaction) ☐ No

Extremely reactive to the following foods: _____

THEREFORE:

- ☐ If checked, give epinephrine immediately for ANY symptoms if the allergen was *likely* eaten.
☐ If checked, give epinephrine immediately if the allergen was *definitely* eaten, even if no symptoms are noted.

Any SEVERE SYMPTOMS after suspected or known ingestion:

One or more of the following:

LUNG: Short of breath, wheeze, repetitive cough
 HEART: Pale, blue, faint, weak pulse, dizzy, confused
 THROAT: Tight, hoarse, trouble breathing/swallowing
 MOUTH: Obstructive swelling (tongue and/or lips)
 SKIN: Many hives over body

Or combination of symptoms from different body areas:

SKIN: Hives, itchy rashes, swelling (e.g., eyes, lips)
 GUT: Vomiting, diarrhea, crampy pain



1. INJECT EPINEPHRINE IMMEDIATELY

2. Call 911
3. Begin monitoring (see box below)
4. Give additional medications:*
 -Antihistamine
 -Inhaler (bronchodilator) if asthma

*Antihistamines & inhalers/bronchodilators are not to be depended upon to treat a severe reaction (anaphylaxis). USE EPINEPHRINE.

MILD SYMPTOMS ONLY:

MOUTH: Itchy mouth
 SKIN: A few hives around mouth/face, mild itch
 GUT: Mild nausea/discomfort



1. GIVE ANTIHISTAMINE

2. Stay with student; alert healthcare professionals and parent
3. If symptoms progress (see above), USE EPINEPHRINE
4. Begin monitoring (see box below)

Medications/Doses

Epinephrine (brand and dose): _____

Antihistamine (brand and dose): _____

Other (e.g., inhaler-bronchodilator if asthmatic): _____

Monitoring

Stay with student; alert healthcare professionals and parent. Tell rescue squad epinephrine was given; request an ambulance with epinephrine. Note time when epinephrine was administered. A second dose of epinephrine can be given 5 minutes or more after the first if symptoms persist or recur. For a severe reaction, consider keeping student lying on back with legs raised. Treat student even if parents cannot be reached. See back/attached for auto-injection technique.

Parent/Guardian Signature _____

Date _____

Physician/Healthcare Provider Signature _____

Date _____

TURN FORM OVER Form provided courtesy of Food Allergy Research & Education (FARE) (www.foodallergy.org) 4/2013

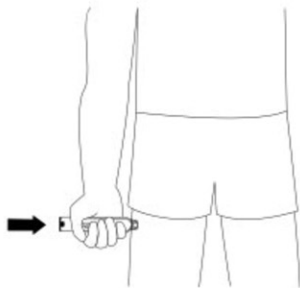
FIGURE 3. Food allergy emergency action plan form. From <http://www.foodallergy.org/treating-an-allergic-reaction>,⁶⁷ with permission.

EpiPen® (epinephrine) Auto-Injector Directions

- First, remove the EpiPen® (epinephrine) Auto-Injector from the plastic carrying case
- Pull off the blue safety release cap



- Hold orange tip near outer thigh (always apply to thigh)



- Swing and firmly push orange tip against outer thigh. Hold on thigh for approximately 10 seconds.

Remove EpiPen® (epinephrine) Auto-Injector and massage the area for 10 more seconds.

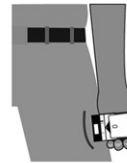
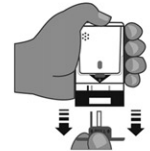


EpiPen®, EpiPen 2-Pak®, and EpiPen Jr 2-Pak® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned subsidiary, Mylan Specialty L.P.

Auvi-Q™ (epinephrine injection, USP) Directions

Remove the outer case of Auvi-Q. This will automatically activate the voice instructions.

Pull off RED safety guard.



Place black end against outer thigh, then press firmly and hold for 5 seconds.

Auvi-Q™
epinephrine injection, USP
0.15 mg/0.3 mg auto-injectors

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Adrenaclick® 0.3 mg and Adrenaclick® 0.15 mg Directions

Remove GREY caps labeled "1" and "2."



Place RED rounded tip against outer thigh, press down hard until needle penetrates. Hold for 10 seconds, then remove.

A food allergy response kit should contain at least two doses of epinephrine, other medications as noted by the student's physician, and a copy of this Food Allergy Action Plan.

A kit must accompany the student if he/she is off school grounds (i.e., field trip).

Contacts

Call 911 (Rescue squad: () -) Doctor: _____
Parent/Guardian: _____

Phone: () - _____
Phone: () - _____

Other Emergency Contacts

Name/Relationship: _____
Name/Relationship: _____

Phone: () - _____
Phone: () - _____

Form provided courtesy of the Food Allergy Research & Education (FARE) (www.foodallergy.org) 4/2013

FIGURE 3. Continued.

The use of SLIT is associated with a very low incidence of anaphylactic or life-threatening reactions. Adverse effects are generally limited to mild oropharyngeal, pruritic cutaneous, or gastrointestinal symptoms.^{68,69}

Both OIT and SLIT are being studied for the treatment of egg, milk, and peanut allergy in the United States, including National Institutes of Health–sponsored studies at 5 university centers. Preliminary open and placebo-controlled studies in the United States have demonstrated that most patients can be successfully desensitized with limited adverse events. Desensitization requires continuous reexposure to the allergen and is distinct from tolerance, which implies the ability to have interrupted exposure.^{37,38,70-75} More specifically, a recent study by Burks et al⁷⁶ showed that after 24 months of egg OIT, only 28% of patients achieved sustained unresponsiveness to egg after discontinuing their treatment for 8 weeks.

The exact mechanism of action of immunotherapy remains unclear. Patients in OIT trials have suffered anaphylaxis, both during in-office and home dosing phases, and participants have withdrawn from studies because of severe reactions or the inability to progress through the protocol. The most common adverse effects with SLIT have been mild and include oral pruritus, cutaneous pruritus, and diarrhea/abdominal pain.⁷⁷

Long-term outcomes for both therapies, including development of tolerance or adverse effects such as EoE, are unknown. A non-US OIT trial investigating peanut allergies demonstrated limited proof that tolerance could last for 2 weeks after interruption of daily dosing.⁷⁸ A recent US OIT trial investigating egg allergies showed tolerance in a subset of participants that lasted up to 4 to 6 weeks after treatment interruption.⁷⁶ Neither OIT nor SLIT is Food and Drug Administration approved for use in the United States. These therapies are currently in highly experimental phase 1/2a trials, and their efficacy in young patients or patients with severe reactivity has not been investigated. However, there is some evidence of off-label, non—research-based prescribing of these therapies among allergists and otolaryngologists in practice.⁷⁹

Chinese Herbal Medicine

Chinese herbal medicine is another potential therapy for food allergies. Several Chinese herbs

are reported to have anti-inflammatory and anti-allergenic properties. Two specific formulations, labeled *food allergy herbal formula (FAHF) 1* and *2*, are 11- and 9-herb formulations, created by researchers at Mount Sinai School of Medicine.⁸⁰ Murine and early-phase human trials have demonstrated that these formulations can suppress the T helper cell type 2 (allergenic) response through diminished basophil activation and interleukin 5 levels.⁸¹ In the mouse model in particular, *FAHF-2* blocked both the progression of existing food allergy and the development of new food allergy to peanut, fish, and egg.⁸⁰ Most importantly, *FAHF-2* demonstrated no harmful effects for patients and is currently undergoing phase 3 study.^{81,82}

CONCLUSION

Food allergy is a serious and growing health concern in the United States. Primary care clinicians are often the first resource for affected families and play a critical role in the diagnosis of food allergy in children. Recognition and proper management of food allergy in the primary care setting is critical and may prove lifesaving. Accordingly, familiarity with NIAID guidelines for the diagnosis and management of food allergy is essential. The primary care physician can and must play an integral role in supporting the family and advise families on avoidance strategies, safe eating habits, emergency medications, and emergency action plans. At present, strict avoidance is the best management strategy, although therapies such as OIT, SLIT, and Chinese herbal medicine provide hope that one day a viable treatment or cure will become a reality.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

Abbreviations and Acronyms: EoE = eosinophilic esophagitis; FAHF = food allergy herbal formula; NIAID = National Institute of Allergy and Infectious Diseases; OIT = oral immunotherapy; QoL = quality of life; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Potential Competing Interests: Dr Gupta is on the speakers bureau for Mylan Inc. Matthew Greenhawt is a speaker and advisory board member for Nutricia. He also had a prior relationship for the past 12 months as speaker and advisory board member for Thermo Fisher.

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