Food Allergies

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Education Gaps

Food allergy prevalence has been increasing in recent decades. Clinical presentation varies depending on the pathophysiology involved. Food allergy is the most common cause of anaphylaxis in the pediatric population. Children with food allergies often experience nutritional deficiency due to diet restriction. Understanding the pathogenesis, diagnosis, treatment, and prevention strategies has the goal of improving the quality of life of affected children and their families.

Objectives After completing this article, readers should be able to

1. Recognize different clinical presentations of food allergies.
2. Understand the role of different diagnostic tools for food allergies.
3. Recognize the correct management based on disease pathogenesis.
4. Review the available evidence about the efficacy of different food allergy prevention strategies.

Abstract

Food allergy is 1 of the 4 manifestations of the "atopic march," along with eczema, allergic rhinitis, and asthma. Depending on the pathophysiologic immune mechanisms behind a food allergy, it can be classified as immunoglobulin E–mediated, non–immunoglobulin E–mediated, or mixed. The prevalence of food allergies has risen worldwide during the past few decades, becoming a significant global health concern. Patients experiencing food allergies and their caregivers are heavily burdened personally, socially, emotionally, and financially. The health-care system is also considerably affected. Pediatricians, as primary health-care providers, are often challenged with these patients, becoming the first-line for the recognition and management of food allergies. The purpose of this review is to provide a comprehensive summary of food allergies, including the most up-to-date information, recent guidelines, and recommendations.

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ABBREVIATIONS

CMA	cow milk allergy
EoE	eosinophilic esophagitis
FPIES	food protein–induced enterocolitis syndrome
Ig	immunoglobulin
IL	interleukin
OFC	oral food challenge
sIg	specific immunoglobulin
SPT	skin prick testing

INTRODUCTION

When a child experiences a negative reaction to a food, this reaction is considered to be a food allergy. Clinicians in the primary care setting are frequently challenged with these patients. It becomes essential for the diagnosis and subsequent management of these patients to distinguish a true food allergy from other kinds of adverse food reactions. Food allergy is 1 of the 4 manifestations of the "atopic march," along with eczema, allergic rhinitis, and asthma. Food allergy is defined as "an adverse health effect arising from a specific immune response that reproducibly occurs upon exposure to a given food." (1) Depending on the pathophysiologic immune mechanisms behind a food allergy, it can be classified as either immunoglobulin (Ig) E–mediated, non–IgE-mediated (cell-mediated), or mixed (IgE- and cell-mediated). (2)(3) It is essential to distinguish a true food allergy from other kinds of nonimmunologic adverse food reactions, which do not involve the immune system. Examples of nonimmunologic food reactions are toxic reactions (scombroid poisoning, ciguatera); food intolerances caused by pharmacologic agents such as caffeine, alcohol, and tyramine in aged cheeses; food intolerances caused by flavoring and preservatives such as monosodium glutamate, reactions due to metabolic and gastrointestinal disorders (lactase deficiency and gastroesophageal reflux), reactions due to accidental contaminations such as pesticides, psychologic reactions (food aversions and food phobias), and neurologic responses, such as auriculotemporal syndrome. (4) Any food can trigger an allergic reaction; however, only a handful of foods (peanut, tree nuts, milk, egg, wheat, soy, fish, and shellfish) are known to be responsible for most reactions. (5)(6)(7)(8) Food allergy has become a significant global health concern with rising prevalence. (5)(9)

EPIDEMIOLOGY

The true global incidence and prevalence of food allergy in children are difficult to estimate due to lack of a standard definition. However, there is general consensus that the prevalence of food allergies has continued to rise worldwide during the past few decades. (5)(9) Industrialized countries are more affected, and the United States is not an exception. Children are more affected by food allergies than adults. (10) An increase of up to 1.2% per decade was reported by Keet et al (11) through an analysis of temporal trends in self-reported pediatric food allergy. Recent data suggest that approximately 8% of children have this condition, 2.4% of children experience multiple food allergies, and as many as 3% of children report anaphylactic reactions. (10)

Increasing awareness by both parents and doctors also plays a role, making it difficult to accurately estimate what is attributable to a true increase in clinical disease versus increasing awareness by families and health-care providers. (12) Overestimation of prevalence is common in studies considering self-reported food allergies. Prevalence is reduced when allergies are confirmed by oral food challenge (OFC). (13)

Approximately 90% of food allergies are caused by milk, egg, soy, peanut, tree nuts, wheat, fish, and shellfish. (5)(6)(7)(8) Consequently, most prevalence studies are focused on these foods. Multiple investigators from several countries, including the United States, the United Kingdom, Canada, and China, agree that the prevalence of peanut and tree nut allergies is increasing around the globe. (14)(15)(16) The prevalence of peanut and tree nut allergies is estimated to be 0.4% to 1.3% in children. (17)(18)(19)(20)

Racial/ethnic differences in prevalence have been reported among children with food allergies. Non-Hispanic black children and Hispanic children were found to have very high rates of food allergies in a study published by McGowan et al, (21) who evaluated a high-risk inner-city cohort of 516 black and Hispanic children. Similarly, African American and Hispanic children are more likely to have allergic reactions to common allergens, such as peanut, milk, egg, wheat, soy, corn, fish, and shellfish, as well as higher rates of anaphylaxis and emergency department visits. (22) These differences may be related to several factors that stem from food preferences in racial/ethnic groups and differences in awareness, socioeconomic status, access to health-care, genetic differences, and other aspects that need further investigation. (3)(23)

Research to support the idea of risk factors for food allergy are limited. This topic continues to be controversial. There are several risk factors that are irrefutable and have been proved with solid evidence. Recently, a report from the National Academy of Sciences was published considering the evidence for many risk factors. Current risk factors and the evidence behind them (strong, limited, or nonexistent) are summarized in the Figure. (6)

PATHOGENESIS

In general, food allergies are divided into 3 main categories: IgE-mediated, non–IgE-mediated, and mixed reactions. IgE-mediated reactions include acute urticaria, anaphylaxis, and pollen-food syndrome. Non–IgE-mediated reactions contain food protein–induced allergic proctocolitis of infancy, food protein–induced enterocolitis syndrome (FPIES), pulmonary hemosiderosis (Heiner syndrome), and celiac disease.

A combination of IgE-mediated and non–IgE-mediated reactions may be observed in eosinophilic esophagitis (EoE), eosinophilic gastroenteritis, and atopic dermatitis.

The skin, nasal mucosa, respiratory tract, and gastrointestinal mucosa constitute the barriers between the environment and internal tissues. Malfunction of the barrier, immaturity of the immune system, and dysfunction of T-cell tolerance predispose individuals to the development of food allergies. (24) Conditions such as atopic dermatitis lead to abnormal processing of allergens through the dermal immune system, which leads to allergic reactions. (25)(26)(27)(28)

IgE-mediated reactions are known as type I hypersensitivity. These reactions require previous exposure to the trigger agent. In the initial step, the allergen crosses the body's barrier to be taken up by antigen-presenting cells. The processed allergen is presented to a $CD4^+$ type 2 T helper cell, which, in turn, produces cytokines (interleukin [IL]-4, IL-5, and IL-13). These cytokines will favor the production of IgE specific for this food allergen. These specific Ig (sIg) E molecules bind to mast cell and basophil surface IgE receptors, which then await further exposure to the same food allergen. This process is known as sensitization. Reactions that occur after sensitization are immediate and trigger mast cell/basophil activation, which releases mediators, such as histamine, tryptase, prostaglandins, and leukotrienes. These mediators lead to tissue inflammation and recruitment of inflammatory cells. Eosinophils are one of the cells recruited to the inflamed tissue and help to further propagate inflammation.

In pollen-food syndrome, the affected individual is sensitized to pollen allergens through the respiratory tract. On ingestion of cross-reactive plant foods, such as nuts, vegetables, or fruits, degranulation of mast cells and basophils occurs through the IgE-mediated pathway. (29)(30) The allergens involved in this syndrome are heat- and acid-labile. Reactions are triggered by raw food and tend to occur locally in the oral mucosa. Once the allergen reaches the stomach, it is broken down by the acid, and the allergic reaction does not progress further.

Non–IgE-mediated reactions have a slower onset and are mostly driven by T cells but may involve other cells such as macrophages, eosinophils, or neutrophils.

In food protein–induced allergic proctocolitis of infancy, inflammation is seen in the distal colon and rectum secondary to trigger foods, such as cow milk and soybean. Even ingestion through human milk can lead to symptoms. (31) Eosinophils have been found in tissue biopsies of the colon of infants affected by food protein–induced allergic proctocolitis. Inflammation causes rectal bleeding without affecting the absorption of nutrients because the proximal intestinal mucosa is not damaged. It is not yet clear why inflammation is limited to the distal colon and rectum.

In FPIES, the exact mechanism is unknown. It is thought that intestinal inflammation is mediated by T cells after ingestion of trigger foods. The most commonly associated foods in infants are cow milk and soybean. Tissue biopsy will show flattened villi, tissue edema, and inflammatory infiltration of eosinophils, lymphocytes, and mast cells. Similarly, the mechanism of pulmonary hemosiderosis (Heiner syndrome) is unclear.

Celiac disease is a multifactorial immune disorder triggered by ingestion of the gliadin component of gluten found in wheat, barley, and rye. Ingestion of gluten leads to villous atrophy in the small intestine and malabsorption.

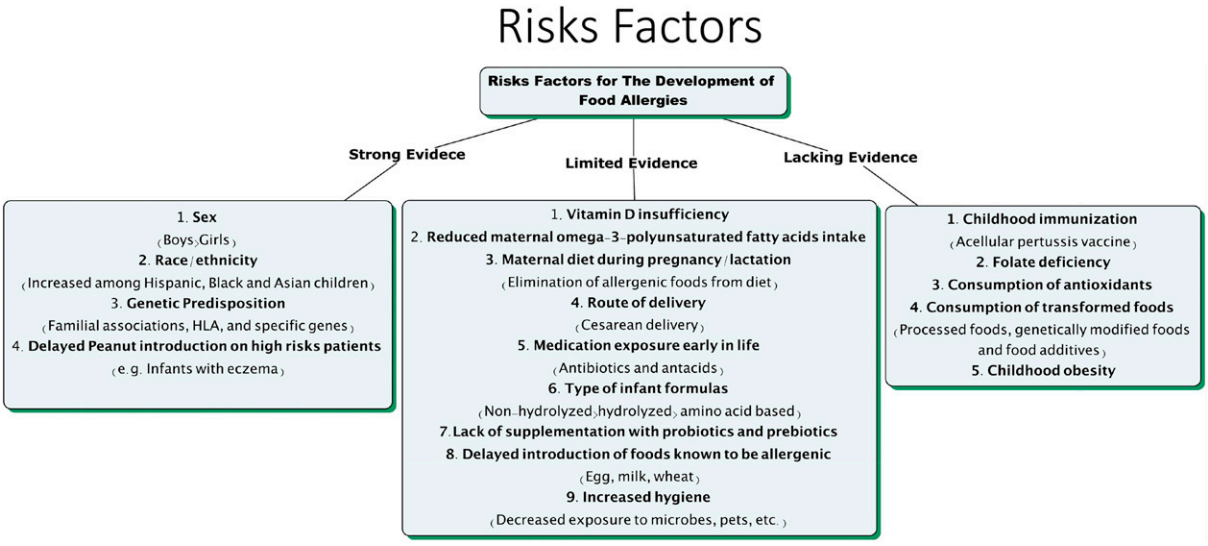

Figure. Risk factors for the development of food allergies based on strength of evidence.

Tissue biopsy has also shown increased intraepithelial lymphocytes, epithelial apoptosis, and crypt hyperplasia. (32)(33)(34) Celiac disease is associated with a genetic predisposition in individuals who have the *HLA-DR3-DQ2* or *HLA-DR4-DQ8* gene. (34) Anti-gliadin, anti-tissue transglutaminase, and anti-endomysial IgA antibodies may be present. (35)(36)(37) Celiac disease is also associated with other autoimmune disorders, such as IgA deficiency.

The pathogenesis of EoE is not completely defined. EoE is characterized by a combination of IgE-mediated and non–IgE-mediated reactions. EoE is an immune-mediated chronic inflammation with eosinophil accumulation limited to the esophagus. It is thought that foods and/or inhaled allergens trigger a type 2 T helper–mediated reaction with the production of IL-5, IL-13, and eotaxin-3. (38) These mediators recruit eosinophils to the esophageal tissue and promote local inflammation. (39)(40) Inflammation may lead to esophageal tissue remodeling with strictures and narrowing of the esophageal caliber. (41)(42) The pathogenesis of eosinophilic gastroenteritis is very similar to that of EoE, resulting in significant infiltration of eosinophils of the gastric and duodenal mucosa. (43)

CLINICAL PRESENTATION

Food allergies can have a variety of clinical presentations. Signs and symptoms of food allergy depend on the involved pathophysiologic immune mechanisms. (2)(3) IgE-mediated reactions are characterized by a rapid onset of symptoms (minutes to <2 hours after ingestion). Affected children might present with only mild symptoms, such as pruritus and urticaria. However, some reactions can be severe or life-threatening, involving more than 1 organ system. This severe allergic reaction is known as anaphylaxis, which is defined as "a serious allergic reaction that is rapid in onset and may cause death." (44)

In contrast, non–IgE-mediated reactions, also known as cell-mediated reactions, have a more delayed onset and present with more subacute and chronic manifestations. Symptoms are typically isolated to the gastrointestinal tract and/or skin. (2)

As stated previously herein, some diseases have a mixed IgE-mediated and non–IgE-mediated mechanism. Therefore, this group is characterized by features seen in both categories. Detailed clinical manifestations and key features of each category are summarized in the Table.

DIAGNOSIS

Unfortunately, at this moment, a single laboratory test that can give a clear positive or negative diagnosis does not exist. The first step in the diagnostic approach to pediatric food allergy is the history and physical examination. Once a food allergy is suspected, certain characteristics during the offending episode should be considered, such as the timing of onset of clinical symptoms after food ingestion, the clinical presentation, and the severity and duration of symptoms, to help discriminate the possible mechanism and the eventual laboratory tool or confirmatory test required to confirm a suspected diagnosis. Furthermore, the significance of the results obtained from different diagnostic tools depends on the history and physical examination.

As discussed previously herein, an IgE-mediated allergic reaction (type I hypersensitivity reaction) is suggested when symptoms appear quickly, usually less than 2 hours after ingestion. Skin and oral signs and symptoms are usually the first and most common features to appear, making this mechanism more likely. To diagnose an IgE-mediated reaction, skin prick testing (SPT) and serum sIgE to suspected foods are usually the first-line laboratory approaches.

SPT is widely used because it is safe, quick, cost-effective, and convenient. In this method, a prick containing a commercial food extract is used to perform a skin scratch. A positive result is obtained when a wheal with surrounding erythema appears within 15 to 20 minutes after the scratch. A wheal diameter 3 mm or larger than the negative control is considered positive. (45) A positive control (histamine) is included with every testing. Many devices are available to perform this procedure. SPT should not be performed in patients with dermatographism or severe atopic dermatitis or in those who are taking antihistamine medications. Intradermal skin testing to assess food allergy is not recommended because it increases the chance of irritation and severe reactions during testing.

In vitro testing by measuring serum sIgE to foods could be an important adjunct evaluation to SPT when the diagnosis is not clear or when the patient does not tolerate SPT or has dermatographism or atopic dermatitis. Serum sIgE levels are not affected by the use of antihistamine medications.

For food allergy diagnosis, the wheal size and higher levels of sIgE to a specific food correlate with an increased chance of clinical allergy but do not correlate with reaction severity. (3)(46)(47)(48) Serum sIgE level cutoff values have been established to predict allergic reactions at different ages to certain foods. (3) SPT and sIgE have better sensitivity than specificity, 70% to 100% and 40% to 70%, respectively. (49) SPT using fresh foods has been demonstrated to be superior to SPT using commercial extracts. (50) As a result of the moderate specificity of these diagnostic approaches, screening panels for food

TABLE. **Clinical Manifestations of Food Allergies Based on the Pathophysiology Mechanism**

DISORDER	CLINICAL PRESENTATION	PATHOPHYSIOLOGIC FEATURES	TYPICAL AGE AT PRESENTATION	COMMON CULPRIT FOOD	NATURAL COURSE	TARGET ORGANS	ADDITIONAL INFORMATION
IgE-mediated reactions							
Acute urticaria and angioedema	Hives (welts or wheals) that are intensely pruritic, sometimes accompanied by angioedema (swelling deeper in the skin).	IgE antibodies to food proteins.	Children>adults	Major food allergens (peanut, tree nuts, fish, shellfish, egg, cow milk, wheat, and soy)	Food-specific.	Skin	Food commonly causes acute urticaria (20%) but rarely chronic urticaria.
Pollen-food syndrome	Symptoms confined to the oropharynx (pruritus and mild swelling of the lips, tongue, palate, and throat) that subside within minutes after ingestion. Rarely progresses to systemic reactions.	Labile food proteins (eg, profilins) found in certain fruits and vegetables are homologous and cross-react with allergenic pollen proteins, to which the patient has been sensitized through the respiratory route.	Adults>children	Raw fruits and vegetables	Persistent. Varies with seasons.	GI tract	Birch-allergic patients can develop symptoms with apple, peach, pear, cherry, and carrot. Ragweed-allergic patients can develop symptoms with melons and banana. Mugwort-allergic patients can develop symptoms with celery, carrot, and mustard. Cooked forms of fruits are typically well-tolerated.
Anaphylaxis	Serious multisystemic allergic reaction that is rapidly progressive and can be potentially life-threatening.	IgE antibodies to food proteins resulting in massive release of chemical mediators (eg, histamine and tryptase) from mast cells and circulating basophils.	Any age	Any, but mostly peanut, tree nuts, fish, shellfish, egg, and cow milk	Food-specific.	Multiple organ systems (skin, respiratory, cardiovascular, GI tract, neurologic)	May follow a biphasic course, with recurrence of symptoms hours after the initial onset. Skin symptoms may be absent.
Non–IgE-mediated reactions (cell-mediated)							
Food protein–induced enterocolitis syndrome	Profuse, repetitive vomiting and diarrhea, leading to dehydration and lethargy after approximately 2 h of trigger food ingestion in the acute setting. If long-term exposure, weight loss and failure to thrive.	Exact underlying mechanism is not clearly understood. Possibly, intestinal inflammation may be mediated by increased TNF-α and decreased expression of TGF-β receptors in the intestinal mucosa.	Infants	Cow milk and soy protein are most common; in addition, rice, oat, and meat	Resolves in most patients by age 3 y.	GI tract	Negative IgE test to the trigger food in most cases. Specific laboratory findings include acidosis, methemoglobinemia, and increased neutrophil levels.

Continued

TABLE. (Continued)

DISORDER	CLINICAL PRESENTATION	PATHOPHYSIOLOGIC FEATURES	TYPICAL AGE AT PRESENTATION	COMMON CULPRIT FOOD	NATURAL COURSE	TARGET ORGANS	ADDITIONAL INFORMATION
Food protein–induced proctitis and proctocolitis	Passage of blood-tinged stools and mucus in an otherwise healthy infant 2–8 wk of age without an anal fissure.	Inflammation of the distal colon mediated by eosinophils.	Young infants (as early as the first week after birth)	Cow milk in the mother's diet; can also occur in formula-fed infants	Rapid resolution with complete elimination of the offending protein.	GI tract (rectum and colon)	Reactions to other foods are also possible (egg, soy, and corn).
Pulmonary hemosiderosis (Heiner syndrome)	Recurrent pneumonia with pulmonary infiltrates, hemosiderosis, iron deficiency anemia, and failure to thrive.	Pathogenesis unclear. Precipitins to cow milk can be found in serum. Lymphocytes show abnormal proliferative responses to milk proteins. Peripheral eosinophilia is seen. Deposits of immunoglobulins and C3 may be found on lung biopsy.	Infants	Cow milk	Resolution after elimination of causative food.	Respiratory (lungs)	Rare syndrome in infants. Pork and egg also being reported as culprits in Heiner syndrome.
Celiac disease (gluten-sensitive enteropathy)	Chronic diarrhea, anorexia, abdominal distention and pain, failure to thrive, or weight loss. In older children and adults, GI manifestations are similar but usually milder.	Immune-mediated process resulting in mucosal inflammation, crypt hyperplasia, and villous atrophy of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically predisposed individuals (*HLA-DR3-DQ2* and/or *HLA-DR4-DQ8*).	Any	Gluten protein found in wheat, rye, and barley	Symptoms resolve after gluten is eliminated from the diet.	GI tract (small intestine)	Lane-Hamilton syndrome is the coexistence of celiac disease and idiopathic pulmonary hemosiderosis.
Mixed IgE- and cell-mediated reactions							
Atopic dermatitis	Worsening erythema and pruritus of eczematous lesions that may occur within minutes to a few hours if the reaction is IgE-mediated, but may take hours to days if the reaction is non–IgE-mediated. Persistent lesions if the food is eaten long term.	Skin barrier abnormalities, defects in innate immunity response, Th2-skewed adaptive immune response, and altered skin resident microbial flora are involved in the pathogenesis.	Children>adults	Any	Symptoms improve by late childhood, but the disease may persist into adulthood in a variable proportion of patients. The elimination of suspected	Skin	A family history of atopy (eczema, asthma, or allergic rhinitis) and the loss-of-function mutations in the filaggrin (*FLG*) gene, involved in the skin barrier function, are major risk factors for atopic dermatitis.

Continued

TABLE. (Continued)

DISORDER	CLINICAL PRESENTATION	PATHOPHYSIOLOGIC FEATURES	TYPICAL AGE AT PRESENTATION	COMMON CULPRIT FOOD	NATURAL COURSE	TARGET ORGANS	ADDITIONAL INFORMATION
					food allergens frequently improves symptoms within weeks. Food triggers should be considered only in moderate-severe cases refractory to good skin care.		
Eosinophilic esophagitis	Feeding disorders and failure to thrive seen mostly in infants and young children, whereas older children typically present with dysphagia, food impaction vomiting, and abdominal pain.	Eosinophil-predominant inflammation supported by IL-5, IL-13, and eotaxin-3.	Any	Multiple (cow milk, egg, soy, corn, wheat, and beef are common culprits)	Persistent, but elimination of food allergens or elemental diets result in clinical and histologic improvements in most patients.	GI tract (esophagus)	Strong association with atopic conditions (food allergies, environmental allergies, asthma, and atopic dermatitis).
Eosinophilic gastroenteritis	Mimics pyloric stenosis in infants and irritable bowel syndrome in adolescents and adults. Symptoms vary depending on the layer and portion of the GI tract that is involved.	Eosinophil-predominant inflammation supported by IL-5, IL-13, and eotaxin-3.	Any	Multiple	Persistent, but elimination of food allergens or elemental diets result in clinical and histologic improvement in up to half of patients.	GI tract (predilection for the distal antrum and proximal small bowel, but entire GI tract may be involved)	Strong association with atopic conditions (food allergies, environmental allergies, asthma, and atopic dermatitis) in approximately half of patients.

GI=gastrointestinal, Ig=immunoglobulin, IL=interleukin, TGF-β=transforming growth factor β, Th2=type 2 T helper, TNF-α=tumor necrosis factor α.

allergies are not recommended due to the high chance of false-positives. In contrast, a negative test result can rule out an IgE-mediated reaction with greater than 90% accuracy. (51) It is important to emphasize that a positive result only means sensitization and not clinical allergy. Correlation with the history and physical examination findings is required.

OFC has been used to establish a precise diagnosis when the history and laboratory tests performed are inconclusive, to determine the role of a specific food in chronic diseases, and to elucidate whether a specific allergy has been outgrown. OFC can be used for IgE-mediated and non–IgE-mediated food allergies. OFC consists of giving gradual increasing doses of the tested food while monitoring for possible reactions. This procedure is usually performed under direct medical supervision. Depending on the history of severity and likelihood of reaction, OFC could be performed in an outpatient or inpatient setting. The gold standard diagnostic tool for food allergy is the double-blind, placebo-controlled OFC. (47) To assess the role of specific food in the exacerbation of chronic diseases such as atopic dermatitis or EoE, an elimination diet is preferred over OFC because an elimination diet could be diagnostic and therapeutic. (3)

Atopy patch testing is sometimes used for diagnosing diseases where a mixed mechanism plays a role in atopy pathogenesis. Atopy patch testing increases the sensitivity and specificity when combined with other diagnostic tools. (52)(53)(54) However, the main concern regarding atopy patch testing is that there is no standardized protocol. At least for IgE-mediated reactions, evidence shows no significant benefit of routinely using the atopy patch over SPT or serum sIgE. (55)

Large screening panels are often offered by different companies promising an accurate food allergy diagnosis. However, there is lack of scientific validity about the usefulness of ordering food sIgG or sIgG4 as diagnostic tools for food allergy. (56) The presence of sIgG or sIgG4 to food is a normal immune response after any food exposure. Similarly, there are no controlled trials supporting the use of hair analysis, provocation/neutralization, kinesiology, electrodermal testing, or lymphocyte activation for food allergy diagnosis. (1)(57)(58)(59)

MANAGEMENT

The management of a food allergy is planned once the mechanism of the reaction is established. Anaphylaxis is a severe IgE-mediated reaction that could be life-threatening. Therefore, its quick recognition is critical to prevent serious complications. Intramuscular epinephrine is the first-line treatment for anaphylaxis. An increase in mortality has been associated when the use of this medication is delayed. (60) An epinephrine autoinjector kit must be prescribed to patients with a history of an anaphylactic reaction to food. In addition, appropriate training in its use should be given to the patient and family. It is also important to educate the patient about the possibility of a biphasic anaphylactic reaction, ie, a recurrence of symptoms usually within 8 hours of resolution of the initial episode and without new exposure to the offending antigen. (61) This second phase of symptoms can be milder, similar, or more severe than the initial episode, and definitely potentially fatal. (61) Biphasic anaphylactic reaction can occur in 10% to 30% of the cases. (62)

There are 3 commercially available autoinjector dosage forms: 0.1 mg (patients weighing <15 kg), 0.15 mg (patients weighing 15–30 kg), and 0.3 mg (patients weighing >30 kg). Antihistamines, glucocorticoids, and β-agonists are considered adjuvants for anaphylaxis treatment. (47)(63) The use of antihistamines is not recommended as a first-line treatment for severe allergic reactions or anaphylaxis. (60)(64) To treat an acute IgE-mediated reaction, antihistamine medications may be beneficial to control only mild symptoms, such as rash or pruritus. (64)

Patients with FPIES can present with severe dehydration and lethargy after repetitive vomiting or explosive diarrhea secondary to a specific food exposure. Therefore, prompt intravenous fluid resuscitation may be needed.

Strict avoidance of the specific food is recommended as the main treatment for IgE-mediated and non–IgE-mediated food allergies, once a food allergy has been established. The task of eliminating 1 or more products from a diet could be complicated. Age, nutritional status, culture, and religious beliefs must be taken into consideration. For example, for infants allergic to cow milk, an extensive hydrolyzed or amino acid–based formula is recommended. (65)(66) Soy formula can also be used in cases of IgE-mediated cow milk allergy (CMA). In breastfed children, maternal avoidance has been suggested due to the possibility of allergen presence in human milk. (67)(68)(69) The decision to remove specific foods could result in growth restriction, nutritional deficits, and negative effects on the quality of life. (70)(71)(72)(73) Therefore, it is imperative to take a good clinical history and choose the best diagnostic tools. Education of the patient and caregivers is critical to prevent further allergic episodes. Adequate orientation about cross-reactivity, food labeling, and allergen-free substitutes is of utmost importance; hence, a nutrition expert should be

involved in educating the patient and caregivers. Information about prevention and treatment during accidental exposure should be given to the patient, caregivers, friends, and school or summer camp staff as part of the team of food allergy management. (47)

NEW THERAPIES

Multiple studies are underway to identify effective treatments for food allergies. Future therapies aim to eliminate food hypersensitivity reactions. Some strategies have been effective in making patients able to ingest higher quantities of food allergens without having severe reactions and even without reactions in some cases. (74)(75)(76)(77) The importance of this finding is to help develop a safety net for accidental exposures. Proposed strategies include oral immunotherapy, sublingual immunotherapy, percutaneous patch, and adjunctive use of monoclonal antibody drugs. It is not clear whether these techniques lead to temporal desensitization or true tolerance. During temporal desensitization, the patient must continue to frequently ingest a defined minimum quantity of the food to be able to prevent reactions. However, as found in drug allergies, if the patient does not take the established dose in a defined time frame, the allergic reaction will not be prevented. Currently, oral immunotherapy seems to be the most effective therapy to induce desensitization. Oral immunotherapy consists of exposing the patient to a gradually increasing quantity of the ingested food. (74)(75)(76)(77)(78) Although good results have been reported, oral immunotherapy is associated with an increased risk of adverse effects. Adverse reactions during oral immunotherapy seem to be more common during infection, menstrual cycle, exercise, seasonal allergy, and nonsteroidal anti-inflammatory drug use. (79)(80) In comparison, sublingual and epicutaneous immunotherapies show a higher safety profile but less effective results. Epicutaneous immunotherapy consists of applying a small quantity of the food on the skin covered by a patch. The patches are changed every 24 to 48 hours. (81)(82) Current clinical trials have evaluated their efficacy within 1 year of treatment. (81)(83) Efficacy with longer periods of treatment is unknown. Young children have shown a higher response to treatment. (81) Taking into account the mild adverse effects and ease of application, it seems that young children might benefit from this treatment in the future.

Omalizumab, a monoclonal anti-IgE antibody, has been used successfully to desensitize patients with food allergies. (84) The adjunctive use of omalizumab permits faster desensitization and higher final ingested dose compared with placebo. (85) Unfortunately, omalizumab does not seem to increase the likelihood of sustained tolerance. (86)

Apart from the adjunctive use of monoclonal antibodies, it has been proposed that monoclonal antibodies could directly inhibit allergic reactions. Gain-of-function mutations in the α subunit of the IL-4 and IL-13 receptors have been associated with an increased risk of food allergies. (87)(88) The monoclonal antibody dupilumab may be effective in decreasing or blocking food allergy reactions due to its activity of inhibiting IL-4 and IL-13 receptors. In a recent case report, a 30-year-old woman with a history of anaphylaxis to corn was able to tolerate this food after treatment with dupilumab. (89) Clinical trials (NCT03679676, NCT03793608, NCT03682770) are underway to determine the role and effectiveness of dupilumab for the treatment of food allergies. The use of biological medications, although possibly effective, will be limited due to their current high costs.

PROGNOSIS AND NATURAL COURSE

It is essential for those managing patients with food allergies to understand the prognosis and natural course of this disease. There are key factors that need to be considered because these factors play an important role in the natural history of food allergies; these key factors include clinical characteristics (symptom severity on ingestion, threshold dose required to elicit a reaction, age at time of diagnosis, and presence of comorbid conditions) and allergic sensitization (wheal size on an SPT or food sIgE levels). For patients who experience severe symptoms with a minimal trigger dose, the likelihood of allergy persistence is higher. (90) Similarly, younger age at the time of diagnosis along with other atopic comorbid conditions correlate with a more persistent phenotype. (90) A larger wheal size on an SPT and/or a higher level of sIgE have been correlated with food allergy persistence. (91) Certain IgE-mediated food allergies are more likely to resolve during childhood (cow milk, egg, wheat, and soy), whereas other food allergies, such as peanut and tree nuts, usually persist into adulthood. (92)(93)(94)(95)(96)(97)(98)

IgE-mediated and non–IgE-mediated conditions also vary on their time course and likely resolution. CMA usually presents early in childhood and has a very favorable prognosis. For IgE-mediated CMA, the median age at resolution is 10 years; resolution is defined as passing an OFC, or an sIgE of less than 3 kUA/L along with no symptomatic ingestions for at least 1 year. (99) Patients who tolerate cow milk protein baked into foods have a higher likelihood

of CMA resolution. (100) Non–IgE-mediated CMA has been found to be outgrown even sooner. For example, milk protein–induced proctocolitis usually disappears by 1 year of age, when milk can be reintroduced into the diet without strict medical supervision. (101) FPIES triggered by cow milk is also usually outgrown early in life, by age 2 to 3 years, but a systematic food challenge is necessary in an appropriate medical setting once the patient has not had any recent reactions because a systematic food challenge is considered a high-risk procedure. (102)

Egg allergy is usually outgrown during childhood by the median age of 6 years, reported in different studies. (93)(103) In egg allergy, similar to CMA, the tolerance of baked egg products correlates with a higher rate of allergy resolution. (104) Furthermore, the introduction of baked eggs in the diet may speed the process. (104) In contrast, a predictor of poor prognosis is an elevated egg sIgE level. Patients with greater than 50 kUA/L are less likely to develop tolerance. (105)

Soy and wheat allergies also have a good prognosis. Approximately 45% of soy-allergic patients develop tolerance by 6 years of age. (91) For patients with a wheat allergy, the numbers are very similar: approximately 50% of wheat-allergic patients outgrow their allergy by 7 years of age. Continued resolution into adolescence has been noted for both soy and wheat. (91) Non–IgE-mediated wheat allergy, in the case of celiac disease, has a different natural course. Lifelong persistence is common and requires eliminating gluten from the diet indefinitely for patients to be symptom free. (106)

The prognosis for peanut and tree nut allergies is less favorable than that for other food allergies discussed previously herein. Only 20% to 25% of patients with a peanut allergy and 9% of patients with tree nut allergies are capable of outgrowing them. (97)(98)(107)(108) Resolution of peanut allergy does not translate into tolerance of tree nuts or seeds. Tree nut allergy may persist or later develop in patients who have outgrown their peanut allergy. (109)

PREVENTION

As discussed previously herein, food allergy prevalence has been increasing in recent years, affecting the quality of life of patients and their families and contributing to a significant economic burden. (110)(111) Moreover, there are no cures for food allergies. Therefore, a large effort has been placed on designing prevention interventions at different stages of life, even antenatally. In this section we discuss the current evidence of different primary and secondary prevention interventions for food allergies. The goal of primary prevention is to avoid initial sensitization. Secondary prevention is focused on avoiding allergy development once the patient is sensitized.

The American Academy of Pediatrics (AAP) endorsement of the recommendation for early introduction of highly allergenic foods went against what the AAP previously recommended. It was observed that children from the United Kingdom had a higher prevalence of peanut allergy compared with their counterparts in Israel, where peanut is introduced at early ages. (112) The Learning Early About Peanut Allergy (LEAP) study demonstrated that the early introduction of peanut in high-risk patients is an effective primary and secondary prevention intervention. The study showed a decrease in peanut allergy development by 60 months of age, despite previous status of sensitization. (113) Similar results were obtained in the Enquiring About Tolerance (EAT) study, where exclusively breastfed general population infants had early introduction of peanut by 3 months of age. (114) Current guidelines recommend early introduction of peanut at 4 to 6 months of age in children with severe eczema and/or egg allergy after being evaluated by sIgE or SPT to peanut. (115)

Available data about the early introduction of egg as a preventive measure of allergy are conflicting, as the population, dosage, and form of introduction are not consistent among studies. (114)(116)(117)(118)(119) Only 2 randomized controlled trials, of 6 available, showed a statistically significant decrease in their primary outcome. The Beating Egg Allergy Trial (BEAT) showed a reduction in sensitization, and the prevention of egg allergy was seen in the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study. (116)(117)

There are limited data assessing the role of the early introduction of cow milk as a primary or secondary prevention intervention. The EAT study showed no difference in the development of a milk allergy between exclusive breastfed infants where cow milk was introduced in their diet at 3 vs 6 months of age. (114) A prospective Israeli birth cohort showed that the introduction of cow milk protein within the first 14 days of the infant's life protected against the development of IgE-mediated allergy to this food. (120) A more recent retrospective case-control study demonstrated that infants with delayed cow milk introduction had a higher odds ratio of developing allergy to this food compared with the group that introduced cow milk in the first month of life. (121)

It is important to consider that the early introduction of highly allergenic foods did not alter the duration of breastfeeding. (122) Because tolerance and sensitization to foods start early in life, different antenatal interventions have been

studied to provide primary prevention. Current guidelines do not recommend the use of probiotics, prebiotics, vitamin supplementation, or any specific restriction during pregnancy due to a lack of evidence that its use results in the prevention of food allergies. (57)

Similar to antenatal intervention, there is no evidence demonstrating effectiveness in food allergy prevention with the use of hydrolyzed formula, prebiotic or probiotic, avoidance diet during lactation, special skin care, or vitamin supplementation during infancy. Consequently, antenatal intervention is not recommended by current guidelines. (57) The role of breastfeeding in food allergy primary prevention has been contradictory. A recent meta-analysis found no protective effect of breastfeeding on the development of food allergy. (123)

WHEN TO REFER TO AN ALLERGIST

Pediatricians and primary health-care providers need to have a clear understanding of when a referral to a specialist is appropriate. Referral to an allergist should occur as soon as a food allergy is suspected. Finding the specific food causing the allergy could be a challenging process, and close monitoring is necessary. Incorrect diagnosis or management may be detrimental to the health of the affected child in many ways. It might cause nutritional deficiencies that can potentially result in growth impairment. (70)(71)(72) Furthermore, some allergic reactions to food are life-threatening, and expert education of the patient and caregivers is essential. The allergist will be able to give a more definitive diagnosis using specialized diagnostic tools and can establish specific management strategies, including multidisciplinary care.

Evidence/Summary

- Based on strong evidence, recent epidemiologic evidence suggests that food allergy prevalence continues to increase worldwide.
- Determining the food allergy mechanism is essential to establish the diagnostic tool and management to be used. Therefore, based on consensus, a thorough patient history and physical examination are the most important approaches during food allergy evaluation.
- Based on strong evidence, intramuscular epinephrine is the first-line treatment for anaphylaxis and severe immunoglobulin (Ig) E–mediated allergic reactions.
- Based on strong evidence, certain IgE-mediated food allergies are more likely to resolve during childhood (cow milk, hen egg, wheat, and soy), and others, such as peanut and tree nuts, usually persist into adulthood.
- Based on strong evidence and consensus guidelines, to provide peanut allergy prevention, early introduction of peanut at 4 to 6 months of age is recommended in children with severe eczema and/or egg allergy after being evaluated by specific IgE or skin prick testing to peanut.
- Based on consensus, an allergist referral is necessary to establish a definitive diagnosis and management of food allergy.

SUGGESTIONS FOR QUALITY IMPROVEMENT (QI) PROJECTS

- Development and implementation of formal training for patients with food allergies and their parents on the recognition and anaphylaxis and the proper use and handling of epinephrine autoinjectors.
- Implementation of anticipatory guidance in the supervision visit regarding early introduction of peanut and other highly allergenic foods.

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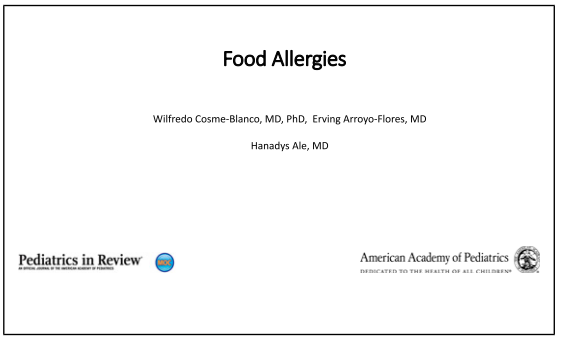
***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/41/8/403.supplemental.**



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1. A 4-year-old girl is brought to the clinic for a health supervision visit. Before being seen, and while in the waiting room, she develops shortness of breath and urticaria over her face, neck, and hands. Quickly, the clinician uses the office epinephrine autoinjector kit and transfers the child to the emergency department for further care. The clinician obtains more information from the parents and learns that the patient was sitting next to a child who was eating trail mix with peanuts and the children were sharing their snacks. Which of the following pathophysiologic mechanisms is most likely to be responsible for the allergic reaction in this patient?
    A. *HLA-DR3-DQ2* gene predisposition.
    B. Immunoglobulin (Ig) A deficiency reaction.
    C. IgE-mediated hypersensitivity reaction.
    D. Type 2 T helper–mediated reaction.
    E. Tolerance reaction.
2. A 10-year-old boy, followed in your practice, was recently diagnosed as having celiac disease. The mother reports that she was advised by the grandmother that she should slowly introduce rye into his diet to promote tolerance of grains. In providing counseling for this mother about the rye food challenge, which of the following is the most appropriate response to provide?
    A. He must be referred for a skin prick test before such a diet change.
    B. He should first start a vitamin supplementation program with probiotics before attempting food challenge.
    C. He should plan to avoid these grains throughout his life.
    D. He would benefit from an oral food challenge in an inpatient setting.
    E. HLA testing should be ordered first to assess his risk of ongoing reaction to grains.
3. A 6-year-old boy whose mother would like guidance on allergy testing is seen in the clinic for follow-up. The patient has already had skin prick testing for food allergies. No allergies were identified. His mother would like further testing due to concerns that he complains of chronic abdominal pain. She has read about hair testing for allergies among other tests and asks whether any of those tests should be performed. Which of the following is the most appropriate response regarding hair testing?
    A. At least 3 inches of hair should be submitted to have an adequate sample.
    B. Can be performed only at research laboratories and is not available clinically.
    C. Repeated skin prick testing should be performed before ordering hair analysis.
    D. The patient must be on an elimination diet and document this over a minimum of 3 months before performing hair analysis.
    E. There are no controlled trials supporting the use of hair analysis.
4. An 18-month-old girl is seen in the clinic for follow-up. She is known to have eczema and has been hospitalized several times for wheezing. She also was recently diagnosed as having peanut allergy. Her family history is significant for asthma and eczema in her mother and 2 siblings. Her 8-year-old brother was allergic to eggs and soy as a toddler but has outgrown these allergies. The mother inquires about the likelihood of the patient outgrowing her allergies. Which of the following is the most accurate response at this time regarding the prognosis of allergies in this patient?
    A. Her risk of persistent food allergies is high.
    B. Prognosis can be confirmed only after performing an oral food challenge with peanuts at home soon.
    C. She is not likely to have other food allergies.
    D. She will likely develop egg and soy allergy.
    E. Younger age at onset is predictive of food tolerance over time.

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5. An 8-year-old boy is seen in the clinic for a health supervision visit. His mother is 30 weeks pregnant. She recalls being counseled that she should avoid introducing peanuts in her son's diet until he was several years old. She asks if she should do the same when her baby is born. She is planning to breastfeed. Several of the boy's cousins have peanut allergies. Which of the following is the most appropriate recommendation?

   A. Introduce eggs to the infant's diet as a protective measure.
   B. Introduce peanuts to the infant's diet by 4–6 months of age.
   C. Introduce peanuts to the infant's diet when she stops breastfeeding.
   D. No good studies available on when to introduce peanuts into the diet of infants.
   E. The mother should avoid nuts in her diet while breastfeeding.