NCC Pediatrics Continuity Clinic Curriculum: **Food Allergies**

Faculty Guide

Goals & Objectives:

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

Pre-Meeting Preparation:

Please read the following enclosures:

- "Food Allergies" *(Pediatrics in Review, 2020)*
- "Updates in Food Allergy Prevention in Children" *(Pediatrics, 2023)*

Conference Agenda:

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

Post-Conference: *Board Review Q&A*

Extra-Credit:

- "Clinical Management of Food Allergy" *(Pediatric Clinics of North America, 2015) alternate review article*
- "The Learning Early About Peanut Allergy Study: The Benefits of Early Peanut Introduction and a New Horizon in Fighting the Food Allergy Epidemic" *(Pediatric Clinics of NA, 2015)*
- "Diagnosis of Food Allergy" *(Pediatric Clinics of North America, 2015)*

Hot Topics Video (7 min)

- "Options for Multiple Food Allergies - Food Avoidance or Pharmacologic Treatment?" *(NEJM, 2024)*
- "Peanut oral immunotherapy in very young children" *(Lancet, 2022)*
- "Diagnosed Allergic Conditions in Children Aged 0–17 Years:United States, 2021" *(NCHS Data Brief, 2023)*

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

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- **EAACI guidelines on the management of IgE-mediated food allergy** *(Allergy, 2025)*
- "Food Allergy and Food Intolerance -- New Developments" (*Global Pediatrics, 2024)*
- "The Learning Early About Peanut Allergy Study: The Benefits of Early Peanut Introduction and a New Horizon in Fighting the Food Allergy Epidemic" *(Pediatric Clinics of NA, 2015)*
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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.

AUTHOR DISCLOSURE Drs Cosme-Blanco, Arroyo-Flores, and Ale have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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.

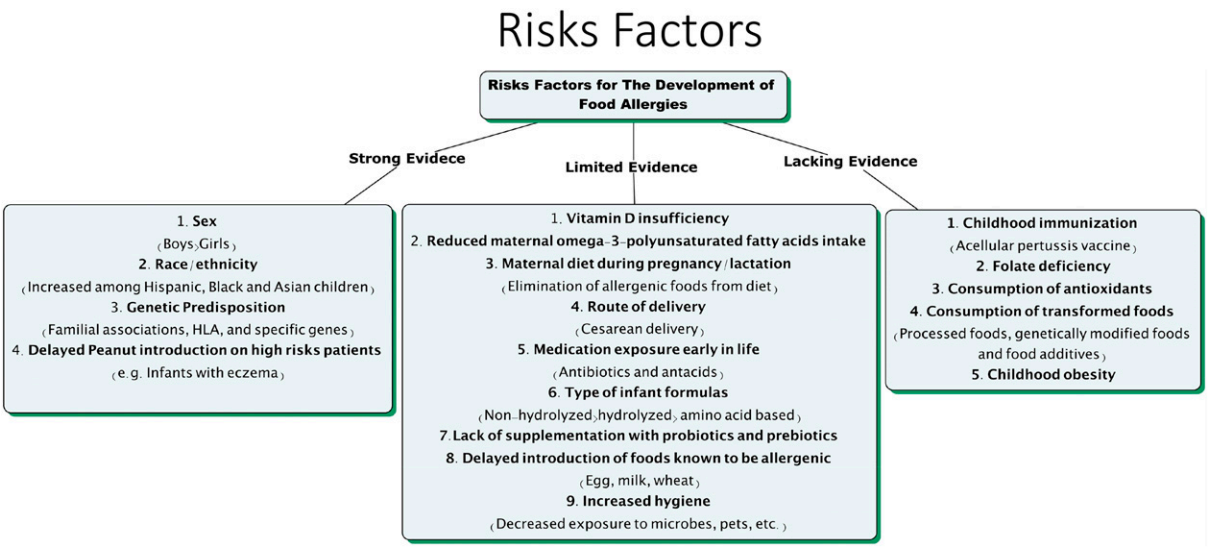

Figure. Risk factors for the development of food allergies based on strength of evidence.

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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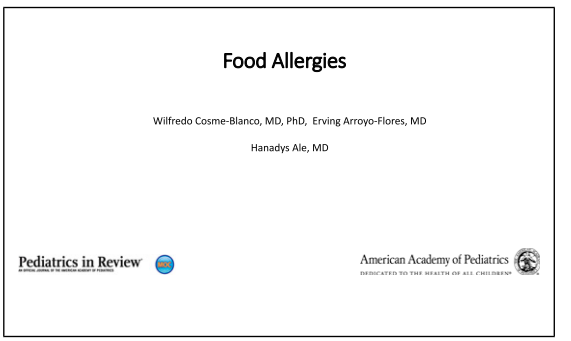

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Updates in Food Allergy Prevention in Children

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Although significant evidence exists that feeding early has a role in the prevention of food allergy, this intervention in isolation may not be sufficient. Recent evidence highlights that early introduction of peanut specifically has had no significant impact on the populational prevalence of peanut allergy. Other factors that may contribute to food allergy prevention include regularity of ingestion once an allergen is introduced and consideration to the form in which the allergen is introduced (such as baked versus cooked egg). There are also many practicalities to early feeding and some discrepant viewpoints on these practicalities, which has led to poor implementation of early feeding strategies. In general, preemptive screening before food introduction is not recommended by most international allergy societies. Although there is little guidance to inform early introduction of allergens other than milk, egg, and peanut, the mechanism of sensitization is thought to be similar and there is no harm to early introduction. In terms of frequency and duration of feeding, there is little evidence to inform any concrete recommendations.

It is now widely accepted that early food introduction has a role in the prevention of food allergy, especially in higher-risk infants. Seven years ago, the Learning Early About Peanut (LEAP) study was a literal "leap" forward as the first randomized controlled trial to demonstrate a significant (81%) relative risk reduction in the development of peanut allergy with early (age 4–11 months) versus delayed (age 5 years) peanut introduction in atopic infants.[1] The LEAP study found a preventive effect in both peanut skin test-negative (13.7% vs 1.9%; $P < .001$) and skin test-positive infants (35.3% vs 10.6%; $P = .004$), which supported early peanut introduction as a means of both primary and secondary prevention. Since the LEAP study, there have been several randomized controlled trials demonstrating a preventive effect with early introduction for several different allergens including cow's milk,[2] egg,[3] and multiple allergens.[4] A systematic review and meta-analysis noted moderate certainty evidence that both early peanut and egg ingestion had a role in food allergy prevention.[5] Multiple international guidelines published over the past several years have uniformly adopted early food introduction as a means of food allergy prevention.[6–12]

Despite the significant evidence that early introduction plays a role in food allergy prevention, increasingly, it has become evident that this is only part of the solution. A recent populational study by Soriano et al in Australia demonstrated that, although peanut introduction in the first year of life has increased more than threefold (21.6%–85.6%) from 2007 to 2018 (before and after early introduction guidelines), there has only been a nonsignificant decrease in peanut allergy in the population over this time (3.1%–2.6%; difference −0.5% [95% confidence interval (CI) −1.4% to 0.4%]; $P = .26$).[13] The authors of this population-level study concluded that "the high prevalence of peanut allergy … despite early peanut introduction, suggests an important contribution of other … factors.

abstract

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An increase in less-researched environmental factors, potentially interacting with genetic susceptibility, could have masked the protective association with earlier peanut introduction."[13] In addition, although there has been near-uniformity in guideline uptake of early food introduction, there remains controversies around its implementation. There are discrepant viewpoints regarding which infants (eg, all infants versus only high-risk ones) should be targeted for early introduction strategies, and whether any infants should be preemptively screened before food introduction.[14–16] Perhaps as a result of these controversies, there has been variable acceptability of early feeding strategies among key stakeholders, including both patients and physicians.[17–19]

The goal of this article is to review what remains less well understood regarding food allergy prevention. Because food allergy is common, often lifelong, and has increased in prevalence over time,[20] a secondary goal is to provide some key strategies to clinicians in navigating this ever-evolving landscape with their patients.

DOES QUANTITY MATTER: THE ROLE OF "REGULAR" ALLERGENIC SOLID FOOD INGESTION AND FOOD ALLERGY PREVENTION

The Soriano et al study has highlighted that, although there is a role for early food introduction, feeding early alone may not be sufficient. In examining the sentinel studies on food allergy prevention, a key component of all study protocols was regularity of allergen ingestion, in addition to early food introduction. As 1 example, in the most effective egg prevention randomized controlled trial to date, the PETIT study, 147 infants with eczema were introduced to heated egg powder at 6 months of age (or avoidance until a year of age), but also were required to eat the heated egg powder at least daily, resulting in such a significant protective effect with early introduction (8% in the early introduction had egg allergy compared with 38% in the placebo group) that the trial was halted prematurely.[3] Similarly, in the LEAP study, infants in the early introduction group ate peanut at least 3 times a week (6 g per week) until 5 years of age.[1] In keeping with this hypothesis, Soriano et al highlighted in their populational study that, although early peanut introduction had increased dramatically in Australia, <30% of infants were eating peanut 2 or more times per week and >20% had only eaten peanut <5 times.[21] It is possible that the lack of change in prevalence of peanut allergy that was demonstrated may be partially explained by lack of regularity of peanut ingestion. However, no early introduction study has shown that a specific allergen quantity was necessary for successful early introduction.

Perhaps the best illustration of the potential importance of regularity of ingestion as a means of food allergy prevention stems from the cow's milk allergy prevention literature. There have been several observational and randomized controlled trials that have consistently demonstrated that delayed ingestion and/or irregularity of ingestion increase the risk of cow's milk allergy. In a 2010 prospective study of 13 019 general population infants, delayed (after 14 days) and/or irregular (<1 per day) cow's milk ingestion significantly increased the risk of cow's milk allergy compared with introduction in the first 14 days of life with regular daily exposure thereafter (odds ratio [OR] 19.3; 95% CI 6.0–62.1).[22] In a case control study of 51 patients with confirmed cow's milk allergy compared with matched controls, as well as unmatched patients with egg allergy, there was a significantly increased risk of cow's milk allergy among infants with delayed (>1 month after birth) and/or irregular (<1 per day) cow's milk exposure (adjusted OR 23.74; 95% CI 5.39–104.52 compared with control, adjusted OR 10.16; 95% CI 2.48–41.64 compared with egg allergy group).[23] In a prospective study of 1992 general population (eg, "standard risk") infants who were recruited on the basis of parental feeding preference to either exclusive breastfeeding or at least 1 meal of cow's milk formula per day (with or without breastfeeding) for the first 2 months of life, there was a significantly reduced prevalence of cow's milk allergy at a year of age among those infants who were regularly exposed to cow's milk formula (relative risk 29.98, $P < .001$).[24] In a recent randomized controlled trial of early cow's milk exposure, subgroup analysis of infants who ingested cow's milk formula in the first 3 days of life found a significantly higher incidence of cow's milk allergy among any infant in whom cow's milk formula was discontinued (<1 month, 1–2 months, 3–5 months) compared with continuous ongoing ingestion until 6 months of age ($P < .001$ for all groups).[25]

There is also emerging, although limited, evidence that the preventive effect of regular ingestion may persist into later childhood, in particular among at-risk children. In a follow-up study of 146 siblings of peanut allergic children (aged 3.4–7.5 years) who had tolerated peanut a median of 2.9 years earlier, the risk of peanut allergy was 0% (95% CI 0–6) among those patients eating peanut at least once monthly, 3% (95% CI 0.5–15) in patients eating peanut less than monthly, and 18% (95% CI 5–48) for children who had not eaten peanut at all.[26]

The Canadian Society of Allergy and Clinical Immunology (CSACI) is the first allergy society internationally that has recently released a statement reiterating the importance of regular ingestion of common allergens, recommending that both early introduction and regular ingestion of age-appropriate amounts of allergens multiple times per month (with a goal of at least once weekly) are likely to be useful in food allergy prevention.[27] The CSACI further recommends that, once introduced, single or occasional exposures to an allergen could be detrimental and, if an allergen is not a common component of the diet

(and hence regular ingestion not feasible), avoidance may be preferable to intermittent ingestion.

FORM FOLLOWS FUNCTION: IS PREVENTION BECAUSE OF THE FORM OF THE ALLERGEN ITSELF?

For some common allergens such as egg, the degree of allergenicity can vary with the method of preparation (Fig 1). Egg and milk are heat-labile allergens, where the proteins creating the allergen are mainly the result of 3-dimensional protein folding and can be denatured with increasing temperature (eg, conformational epitopes), whereas with peanut, tree nut, and seed, the allergenic proteins are the result of contiguous linear areas (eg, linear epitopes) and are not heat-labile. There is some evidence that the form in which egg is introduced (eg, baked versus cooked versus raw) may influence its tolerability and effectiveness at food allergy prevention, given that a higher cooking temperature can denature the primarily conformational epitopes, and reduce the allergenicity.[11] There are 5 randomized controlled trials on early egg introduction as a means of egg allergy prevention which had very discrepant results with respect to safety and effectiveness, and it has been hypothesized that this is related to the form in which egg is introduced in these studies.[11] The most effective study, the previously described PETIT study, used gently heated egg (eg, poached) as its study protocol, a form subjected to a mild degree of heat denaturing. In contrast, the other 4 randomized controlled trials used raw pasteurized powdered egg and demonstrated either no significant protective effect with early egg introduction[28–31] and/or significant safety concerns.[30,31] Pragmatically, it is unlikely that raw egg from a culinary standpoint would be introduced outside a study protocol, and the choice of a raw egg was because of ease of use in a study protocol (crystallized form), but this trend in the literature suggests that the form of allergen itself may influence the effectiveness of early introduction.

There may be a further protective effect based on the way egg is heated (cooked versus baked), although evidence is limited to 1 study. A 2010 population-based cross-sectional study of 2589 infants demonstrated that, among infants with diagnosed egg allergy, in addition to a protective effect with early introduction, first exposure to cooked egg (egg cooked on a stove) reduced the risk of egg allergy compared with first exposure to egg in baked goods (egg baked into goods in the oven) (OR 0.2; 95% CI 0.06–0.71).[32] Joint guidance on prevention through the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI), and the CSACI recommends that egg be introduced in cooked forms only, avoiding any raw, pasteurized egg-containing products where possible.[11] The British Society of Allergy and Clinical Immunology specifies that, when egg is introduced at ~6 months of age, it should be introduced in a cooked form (scrambled egg, omelet, soft- or hard-boiled egg).[7] Further studies on this topic are needed, and it is not known to what degree this applies to the literature regarding other allergens such as cow's milk.

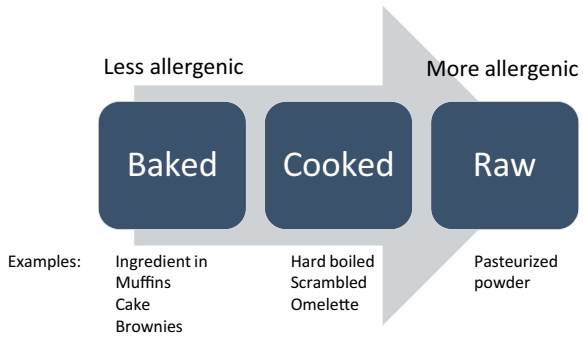

FIGURE 1
Various preparations of egg and impact on allergenicity.

TO SCREEN OR NOT TO SCREEN FOR PEANUT ALLERGY, THAT IS THE QUESTION

Largely as a result of a priori decisions made in the LEAP study, the National Institute for Allergy and Infectious Diseases (NIAID) released an addendum guideline in 2017 for the prevention of peanut allergy in the United States, which recommended that infants with LEAP risk criteria (egg allergy and/or severe eczema) be strongly considered for preemptive testing before peanut introduction.[10] The American Academy of Pediatrics (AAP) supports this recommendation, although notes that "it is hoped that the screening process for the infants at highest risk will not be a deterrent or generate 'screening creep' for infants not in the high-risk category. Furthermore, these guidelines may be difficult to follow in communities where there is no access to the medical care needed for their implementation."[9]

Although targeted screening was supported by the NIAID in 2017, these recommendations are not in keeping with other international guidelines published since the LEAP study such as the Australasian Society of Clinical Immunology and Allergy, the British Society of Allergy and Clinical Immunology, the AAAAI, the ACAAI, or the CSACI. None of these societies recommend routine preemptive screening in infancy before allergenic solid food introduction (Fig 2).[7,11,33] The CSACI has strongly advocated against screening, noting that screening testing in infants is not recommended, irrespective of level of risk.[12] Health economic modeling has shown that screening is most likely to overestimate the rate of allergy, leading to cost accumulation because of false-positive testing being considered as a surrogate for allergy.[34]

There are several limitations to screening on a population level before peanut introduction (Table 1). Firstly,

Professional Organization	Last Updated (Year)	Summary of Recommendations
National Institute for Allergy and Infectious Diseases	2017	For infants 4–6 months of age withexisting egg allergy and/or severe eczema, strongly consider skin prick and/or serum IgE testing before introduction.
Australasian Society of Clinical Immunology and Allergy	2017	Introduce without testing for all infants between 4 and 12 months of age, including those with severe eczema and/or existing food allergy.
American Academy of Pediatrics	2019	For infants 4–6 months of age with existing egg allergy and/or severe eczema, skin prick test by an allergist is preferred or serum IgE testing, followed by referral to allergist if positive.
British Society for Allergy and Clinical Immunology	2019	Systematically screening all infants with severe eczema is not currently available in most areas and may not be effective. Introduce without testing for all infants, including those with severe eczema and/or existing food allergy.
American Academy of Allergy, Asthma and Immunology American College of Allergy, Asthma and Immunology Canadian Society for Allergy and Clinical Immunology	2021	No routine screening. When deemed appropriate, medical providers should discuss the role of IgE testing before introduction of foods as a method to determine whether the food will be introduced at home or under supervision in the office setting.
Canadian Society of Allergy and Clinical Immunology	2021	Preemptive screening is not recommended.

FIGURE 2
Differences in screening recommendations from various professional organizations.

although all allergy testing, whether skin prick testing or peanut-specific immunoglobulin E (IgE) testing, is safe, sensitive, and widely available, it is poorly specific and will result in overdiagnosis of peanut allergy.[16] The specificity of skin prick testing and peanut-specific IgE testing is <50%, and most infants with positive allergy tests can tolerate the food of concern when such IgE is identified, meaning the presence of the antibody is not pathognomonic for disease.[35–37] For example, a retrospective chart review of 125 children, of whom 96% had eczema, noted that 80% to 100% of foods which were avoided because of positive allergy testing could be reintroduced into the diet after an oral food challenge.[38] Secondly, preemptive screening on a populational level is not feasible, or actually necessary to promote safe early introduction. HealthNuts, an Australian prospective population-based cohort study, demonstrated that screening all infants with early onset eczema and/or egg allergy would require screening 16% of the population, and would still miss 23% of cases of peanut allergy.[39] In addition, in this study, 29% of infants would require follow-up because of positive testing. The resource limitations associated with a screening approach, resulting in delays in infant ingestion of peanut pending allergy assessment, could inadvertently negate the benefits of early peanut ingestion supported by the LEAP study, with infants missing the window of opportunity for allergy prevention with early ingestion of peanut. Thirdly, although the AAP cautioned against a potential screening creep, the reality of the increased nondiscriminant testing has emerged as a major concern. In 1 recent real-life study, only 48% of patients screened for peanut sensitization fit the NIAID criteria.[40] Another post-NIAID report demonstrated a significant increase in the number of nonhigh-risk infants that were inappropriately screened, receiving testing for a median number of 10 foods.[41] Finally, peanut screening has been shown to be poorly cost-effective, and the Soriano et al study has clearly demonstrated that there can be uptake of early peanut ingestion on a population level in the absence of screening.[13,42]

It is also important to highlight that feeding infants common allergens such as peanut (in an age-appropriate way) is safe, and the process to do so should not be overmedicalized. There has never been a fatality on first ingestion of a food in infancy, even in infants at high risk for food allergy.[43,44] In the LEAP study, for example, of those infants randomized to the early introduction group,

TABLE 1 Pitfalls of Population-Level Screening Before Introduction of Allergenic Foods

Caregiver	Clinician	Systemic Issues
Undue anxiety regarding safety of introduction without testing	Improper interpretation of results	Delay in introduction while waiting for testing or referral
Request for testing before introduction	Inaccurate diagnosis	Not cost-effective
Distrust in changing and contradictory guidelines	Time constraints to discuss during clinical encounters	Disparities in timely access to specialists

only 2.2% had a positive oral food challenge (observed ingestion) at baseline; none required epinephrine and symptoms were predominantly cutaneous.[1] Australian data at a population level have noted that <5% of early peanut introduction has resulted in a severe reaction.[39]

There is always a role for shared decision-making, especially in the context of a family who is not comfortable feeding an allergen such as peanut in the absence of screening testing.[11] However, the ultimate goal in such high-risk infants is early peanut ingestion, and such early introduction is the only identified measure that reduces the risk of peanut allergy. The associated negative impact peanut allergy has on long-term quality of life can be devastating for some families. Fundamentally, LEAP demonstrated the significant protective effect of early peanut introduction in a screened population, but not that screening was preventive or necessary for safe implementation. Furthermore, screening, because of access to care issues, may result in prolonged delays pending timely assessment, which also may paradoxically increase the burden associated with peanut allergy.

WHAT ARE THE PRACTICALITIES OF EARLY FEEDING?

Although the LEAP study and subsequent guidelines have helped forward the narrative that early introduction of allergenic solids is safe and effective at preventing certain food allergies, how to optimally advise and implement this is still uncertain in many areas. These areas include which allergens to focus on as a priority for early introduction, how often to advise allergenic solid foods are fed, how much quantity of allergen to feed, and how long feeding is required for a full preventive effect.

The bulk of the evidence for benefit of early allergenic solid introduction exists for peanut,[1,5] egg,[5,29–32] and cow's milk.[22–24,45] There are no randomized controlled trials focused exclusively on tree nut, soy, grains, seeds, legumes, finfish, or shellfish (although 2 randomized controlled trials have examined multifood ingestion early in life with discrepant results).[4,46] Some of the lack of data for other allergens may be a pragmatic limitation; given that some investigators consider the effects of early introduction to likely generalize across allergens, further trials with groups randomized to avoidance or delayed introduction may no longer be ethical. There is no evidence of harm from early feeding of other common allergens (in an age-appropriate way), and the mechanism of sensitization is thought to be similar for all common allergens.[12] There is also some observational evidence that dietary diversity early in life may help in the prevention of food allergy.[11,47,48] Guidance on the prevention of food allergy endorsed by the AAAAI, ACAAI, and CSACI recommends specifically egg and peanut introduction at ~6 but not before 4 months of life, but notes no evidence of harm with introduction of other allergens in this time interval and recommends no "deliberate delay" for the introduction of other potentially allergenic complementary foods.[11] The AAP focuses specifically on early peanut introduction because the most conclusive data were available for peanut, but notes no evidence that delaying introduction of other common allergens prevents atopic disease.[9]

In terms of frequency and duration of feeding, there is little evidence to inform any concrete recommendations other than that regularity of ingestion appears to play some role, but it may not be the sole factor. A per-protocol secondary analysis of the Inquiring About Tolerance study, a randomized controlled trial of early (3 months) versus standard (6 months) introduction of 6 common allergens, suggested that a dose of ~2 g of peanut protein and egg white protein per week (~1 boiled egg and 1.5 tsp of peanut butter) was sufficient for maintenance of tolerance, although further studies are required.[3,46] However, a recently published, multicenter, cluster-randomized trial of early (3 months) versus standard introduction of milk, egg, wheat, and peanut found a significant protective effect with early introduction, with no specific dosing requirements in the study (pragmatic design).[4] AAAAI, ACAAI, and CSACI guidance notes "insufficient evidence to support a precise dose and frequency necessary to support tolerance," recommending feeding amounts and types of allergens that the child enjoys in an age-appropriate way with some regular frequency. Similarly, the duration of ingestion required to maintain tolerance is unknown, although a follow-up to the LEAP study, the LEAP-On study, demonstrated that ongoing regular ingestion until 5 years of age was protective against development of peanut allergy in children who then underwent a full year of subsequent avoidance.[49] Although further studies are required, this study does suggest that regular ingestion through toddlerhood can help augment long-term protection, at least for peanut, though it remains unclear if such augmentation is truly necessary.

HOW DO WE OVERCOME BARRIERS?

To effectively implement widespread early introduction of allergenic foods to all infants on a population level, it will require buy-in from caregivers, primary care pediatricians, professional and advocacy organizations, and allergists/immunologists. Caregivers can lose confidence when guidelines change, and particularly when new recommendations contradict previous advice.[50] For almost 20 years before these new recommendations, parents were specifically told to avoid giving their infants any of the "top 8" allergenic foods.[51] This was on the basis of expert opinion at the time and not evidence or studies demonstrating protection through avoidance. However, to now implement a paradigm shift that contradicts previous advice, clinicians and guidelines need to address why the advice has changed, why we can trust this new approach, and why

TABLE 2 Examples to Overcome Barriers to Implementation of Food Allergy Prevention Discussions in the Primary Care Office		
Time in the Office	**Discussion Points**	**Parental Concerns**
Incorporate into well-child visits at every age.	Proactively address in a positive manner; don't wait for families to ask.	Do not rub the food on your child's skin before letting them eat it.
Use preformed smartphrases in the electronic medical record.	Introducing peanut and other allergenic foods in age-appropriate forms is safe for infants.	Food allergy reactions occur within 1–2 h of ingestion and typically cause hives, swelling, or vomiting. If this does not occur, that is reassuring and can keep in their diet.
Have ancillary staff provide written handouts.	The benefit of preventing food allergy outweighs the risk for severe allergic reaction.	Address common childhood conditions unrelated to food allergy that may wax and wane as new foods are introduced (ie, gastroesophageal reflux, constipation or loose stools, and eczema).
	Testing before introduction can cause a delay in ingestion and false-positive results.	Offer to be available for follow-up questions or concerns.
		You do not need to have epinephrine prescribed or available before introducing foods to infants (unless they have existing food allergy).

it's important to consider. This requires humility, proactive discussion, and time to address parental concerns (Tables 2 and 3). A survey of 2000 soon-to-be or current parents of infants was conducted 1 year after the NIAID addendum guidelines were published, and only 31% of respondents were willing to introduce peanut before 6 months of age.[17] Although current parental attitudes toward early introduction have not been formally studied in recent years, this still warrants time and explanation to families during individual patient encounters. As addressed earlier, the current inconsistency in screening recommendations across various guidelines is only perpetuating the confusion regarding food allergy prevention.

Consistent positive messaging surrounding the safety and benefits of introducing allergenic foods during early infancy is important. This requires clinicians to understand the evidence, commit to proactively discussing during patient encounters, and incorporate this within existing time constraints on patient care. Some practical advice includes not rubbing food on the skin before feeding, reviewing time to onset of food reactions (1–2 hours), discussing other common childhood conditions that wax and wane with food introduction (such as constipation), and offering to be available for follow-up questions (Table 2). Little data exist on how well this is being done by clinicians, but surveys suggest ongoing hesitancy and need for further education.[19] Incorporation into the electronic medical record is 1 method to help standardize and increase the consistency of these conversations. Australia adopted widespread public health messaging surrounding food allergy prevention and has demonstrated increased acceptance and introduction of peanut over the past few years.[21]

Soon after the NIAID addendum guidelines were published in 2017, various companies started producing commercial products containing multiple allergenic foods in palatable forms for infants, such as powders, puffs, cereals, and cookies.[52] These commercial products are marketed directly to consumers and also pediatricians in an effort to have them recommend to families. Aside from the cost associated with these products, there is significant inter- and intraproduct variability in regard to the amount of protein included for each allergen.[53,54] In addition, none of these products have evidence demonstrating that they can prevent food allergy development through their use. With these marketed across the world, caregivers may be led to believe that these commercial products are necessary to prevent food allergy, or that they are safer than giving actual food to their infants. This adds a layer of confusion and mixed messaging that parents have to navigate as they try to understand and incorporate food allergens into their infant's diet.

It may seem like an insurmountable task, but these challenges can hopefully be overcome through dedicated and consistent effort across multiple levels.

TABLE 3 Take-Home Points
Take-Home Points
Introduce all allergenic foods in age-appropriate forms once your infant has shown interest and has tolerated other solids such as purees and cereals.
Once they've tried a new food, it is most important to keep it in their diet consistently, ideally several times each wk.
Infants with higher risk for developing food allergy likely benefit the most from early introduction, but it can help all children.

CONCLUSIONS

Although early introduction has been demonstrated to be a highly effective intervention in the prevention of food allergy, it may not be enough. There may be a role for ongoing regularity of ingestion in the prevention of food allergy, and in fact, regularity of ingestion may play as significant a role as timing of introduction. For some allergens such as egg, the form in which the allergen is introduced may play a role. There is still much to learn about the practicalities of early feeding, although guidance largely applies to peanut, and potentially egg and cow's milk at this time. There are significant harms to a preemptive screening approach for any common allergen, and in general, testing before food introduction is not recommended.

ABBREVIATIONS

AAAAI: American Academy of Allergy, Asthma, and Immunology
AAP: American Academy of Pediatrics
ACAAI: American College of Allergy, Asthma, and Immunology
CI: confidence interval
CSACI: Canadian Society of Allergy and Clinical Immunology
IgE: immunoglobulin E
LEAP: Learning Early About Peanut Study
NIAID: National Institutes of Allergy and Infectious Diseases
OR: odds ratio

honoraria – American Academy of Pediatrics, American College of Allergy, Asthma and Immunology; member – Joint Task Force on Practice Parameters for Allergy/Immunology; and Board of Regents for the American College of Allergy, Asthma, and Immunology. Dr Greenhawt has received past research support to his institution from DBV Technologies and the Agency for Healthcare Research and Quality; receives current research support from Novartis and Silota; is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, and Prota; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Task Force on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, RMEI Medical Education, MedLearningGroup, and multiple state/local allergy societies.

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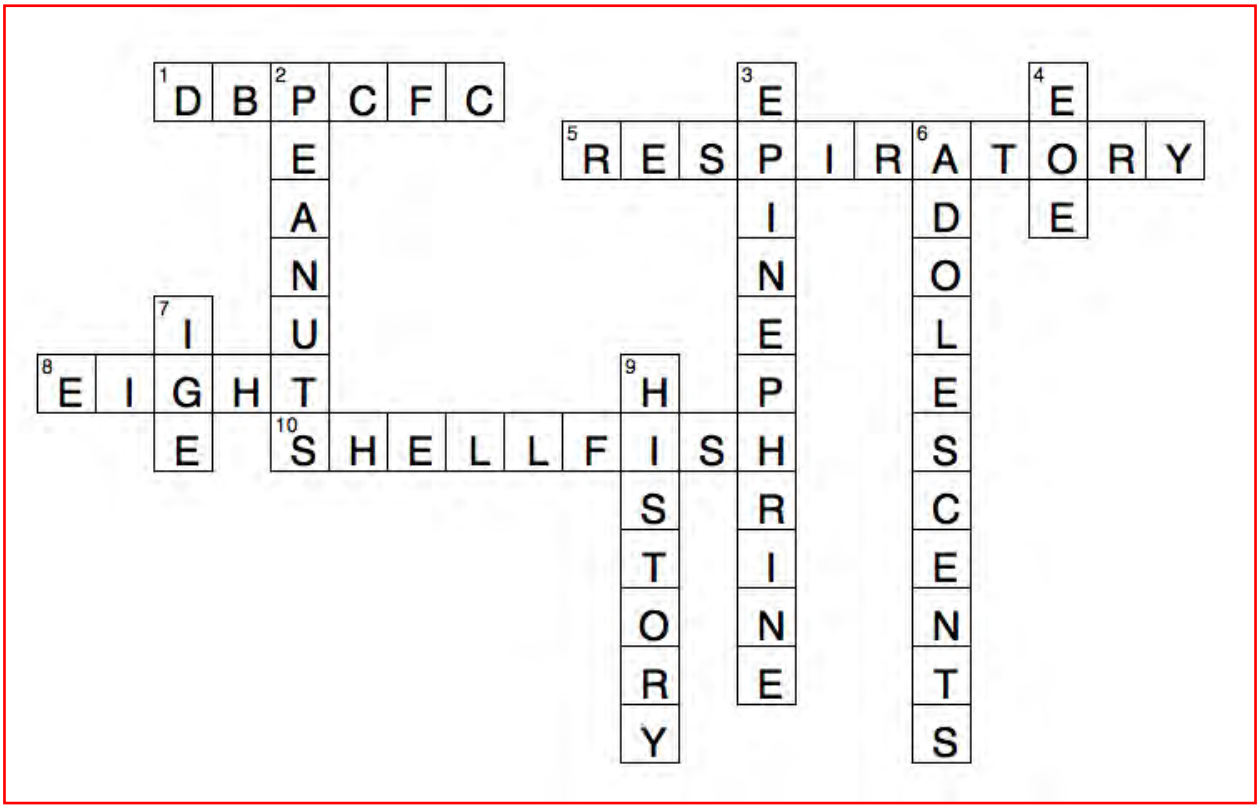
Food Allergies Quiz



ACROSS:

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

DOWN:

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

Food Allergies Cases

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

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

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

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

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

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

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

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

- **Side effects** from epinephrine include tachycardia, flushing, anxiety, nausea, or vomiting. These symptoms can overlap with those of anaphylaxis. It is also important to understand the potential psychological and economic burden of EpiPen need. Don't prescribe it lightly! Reevaluate at every visit whether it is needed, and if so, review how to use it and the importance of having access to it at all times!

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

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

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

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

Case 2:

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

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

- Complementary foods including potential allergens **should not be restricted**. In fact, the newest recommendations include introduction of peanut (and by extrapolation other highly allergenic foods including milk, egg, tree nuts and fish) no later than 4-6 months for children at highest risk of developing food allergies. Once introduced it is important to continue to provide the food, ideally several times weekly.

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

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

Case 3:

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

What additional questions will you ask?

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

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

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

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

Oral Allergy Syndrome (Allergy and Asthma Network)

Food Allergies Board Review

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

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

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

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

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

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

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

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

Of the following, the BEST response regarding anaphylaxis is that

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

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

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

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

E. subcutaneous injection of epinephrine is preferable to intramuscular injection

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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