

Recognition and Management of Pediatric Food Allergy in the Emergency Department

Hemant P. Sharma, MD, MHS,*† Darlene K. Mansoor, MD, MS,*† Irene J. Mikhail, MD,*†
Cindy Nguyen, MD,*† and Bruce L. Klein, MD‡

Abstract: Recently, the National Institute of Allergy and Infectious Diseases sought to establish consistency in definitions, diagnostic criteria, and management practices concerning food allergies (FAs). This review aimed to summarize and highlight the relevant findings of these guidelines for the emergency department provider, as pediatric patients often present to the emergency department with FAs or other disorders mimicking FAs.

Key Words: food allergy, anaphylaxis, treatment

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Food allergies (FAs) affect up to 8% of children in the United States, and their prevalence seems to be rising.^{1–3} Not only do FAs pose a significant burden on the health care system and on patients' quality of life, but they also are potentially life threatening.^{4–8} Patient care in the emergency department (ED) constitutes much of the economic impact of FAs. A recent study found that 20% of health-related costs associated with FA were attributed to ED visits, totaling \$45 million annually.⁸ It is estimated that FAs account for up to 50% of reported anaphylaxis cases presenting to the ED.⁹ Paralleling the increase in overall FA prevalence, there has also been an increase in food allergic reactions presenting to the ED.^{1,2} In 2000, it was estimated that there were approximately 30,000 annual visits to the ED resulting from FA.¹⁰ More recent studies, however, indicate that this may be an underestimation. For instance, one study found that from 2001 to 2006, the number of visits to a large academic pediatric ED for food-induced anaphylaxis more than doubled.¹¹

Although no studies have specifically addressed the management of FAs in pediatric EDs, a multicenter study of adult EDs found low concordance of ED management of FAs with established guidelines.¹² In this review, the definition of FA will be discussed, as well as the classification of FAs based on distinct underlying immunologic mechanisms. The clinical presentations most likely to be encountered by the ED provider will then be reviewed. Finally, the essential role of the ED physician in treating and preventing reactions will be examined.

DEFINITION OF AND DIFFERENTIAL DIAGNOSIS

An FA is defined as an adverse health effect that is due to a specific immune response and occurs reproducibly upon exposure to a given food.¹³ It is this underlying immune mechanism that

distinguishes FAs from nonimmunologic adverse food reactions, which are much more common than true FA. For example, the estimated prevalence of true FA is 6% to 8% in young children and 3% to 4% in adults, despite the observation that 20% to 30% of the general population report that they or their children have a "food allergy."^{1,2,14,15} Therefore, non-immune-mediated adverse food reactions are often incorrectly perceived or labeled as FAs. The distinction between immune- and non-immune-mediated adverse food reactions is particularly important in the ED setting, where appropriate diagnosis and management of reactions is critical. Figure 1 depicts the various types of adverse food reactions, both immune and non-immune mediated.¹³ In this section, the various nonimmunologic adverse food reactions that may present in an ED setting are reviewed.

Metabolic disorders represent one category of nonimmunologic adverse food reactions. Examples include lactose intolerance, galactosemia, and alcohol intolerance, all of which involve host-specific defects in metabolizing certain food components. Patients with lactose intolerance, for instance, have a deficiency of the lactase enzyme, which is required to digest the carbohydrate lactose found in milk and dairy products. As a result, they may present with episodic symptoms of abdominal pain, bloating, gas, diarrhea, and nausea after ingestion of milk and dairy products.¹⁶ Although many patients with lactose intolerance report they are "allergic" to milk, this condition is actually a food intolerance, not an FA, because it lacks any underlying immune etiology and therefore does not progress to a life-threatening systemic reaction.

Other nonimmunologic food reactions are caused by responses to pharmacologically active components in foods, such as caffeine and food-borne toxins. Scombroid fish poisoning is an example of a toxic adverse food reaction that can closely mimic an immunoglobulin E (IgE)-mediated food allergic reaction. It is caused by histaminic chemicals found in spoiled dark meat fish, such as tuna, mackerel, and sardines, which result in pseudo-allergic symptoms such as flushing, urticaria, angioedema, nausea, abdominal cramping, and diarrhea upon ingestion.¹⁷ Despite the allergic appearance of these symptoms, the underlying mechanism of scombroid poisoning is nonimmunologic, and therefore, it is not an FA. In the ED, further history should be obtained to differentiate IgE-mediated fish allergy from scombroid poisoning, particularly if the patient reports repeated tolerance of fish previously. For example, if other individuals who ate the same fish developed similar symptoms, the likely diagnosis is scombroid poisoning, not a fish allergy, and the patient need not avoid fish or carry emergency medications. If the diagnosis of fish allergy versus scombroid poisoning remains uncertain, referral to an allergist should be considered for performance of a diagnostic oral food challenge.

Psychological disorders, such as anorexia nervosa, food aversions, and food phobias, may also cause nonimmune adverse food reactions. Finally, nonimmune food reactions may be related to neurologic disorders, such as auriculotemporal syndrome (facial redness or sweating after eating tart foods) and gustatory rhinitis (rhinorrhea after eating, especially hot or

From the *George Washington University School of Medicine, †Division of Allergy and Immunology, Children's National Medical Center, Washington DC; and ‡Johns Hopkins University School of Medicine, Baltimore, MD. Disclosure: The authors declare no conflict of interest.

Reprints: Hemant P. Sharma, MD MHS, Division of Allergy and Immunology, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010 (e-mail: hsharma@cnmc.org).

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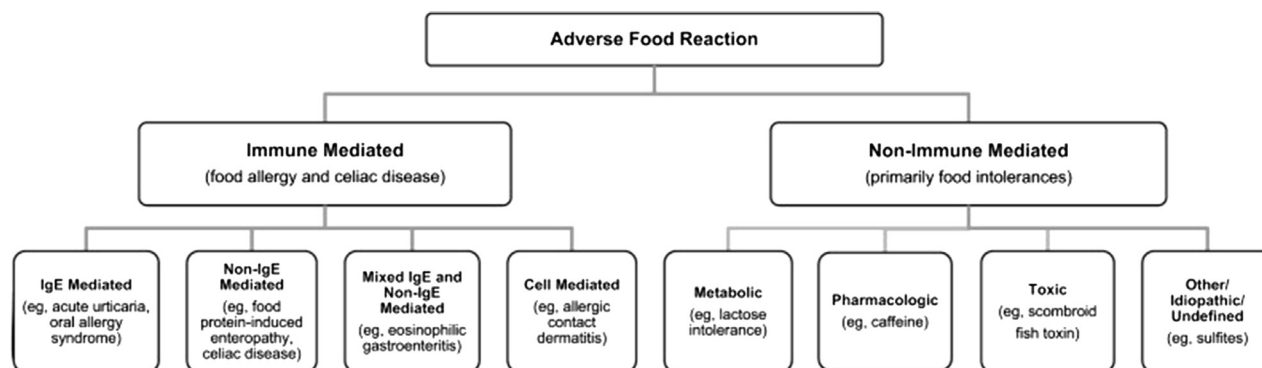


FIGURE 1. Classification of adverse food reactions from Boyce et al.¹³

spicy foods). Table 1 summarizes the differential diagnosis of nonimmunologic adverse food reactions.

CLASSIFICATION OF FAs

Given that FAs are immune mediated, an understanding of their underlying immunologic mechanisms allows reactions to be categorized into 1 of 4 groups as follows: (1) IgE-mediated reactions; (2) mixed IgE-mediated and non-IgE-mediated reactions; (3) non-IgE-mediated reactions; and (4) cell-mediated reactions (Table 2).¹³ In this review, the first 3 of these groups will be discussed because of their relevance to the ED setting. Immunoglobulin E-mediated food allergic reactions will be reviewed in greatest detail because they are the most common FA presentation observed in the ED.

TABLE 1. Differential Diagnosis of Nonimmunologic Adverse Food Reactions

Host-specific metabolic disorders	Carbohydrate malabsorption ■ Lactase deficiency (lactose intolerance) ■ Sucrose-isomaltase deficiency (sucrose intolerance) Galactosemia Alcohol intolerance
Response to pharmacologically active food component	Scombroid poisoning (tuna, mackerel, mahi mahi, sardines, anchovies) Caffeine Tyramine (aged cheeses, pickled fish) Theobromine (tea, chocolate)
Toxin-mediated reactions (food poisoning)	Fish: ciguatera poisoning (grouper, snapper) Shellfish: saxitoxin Fungal toxins: aflatoxins, trichothecenes, ergot
Psychological reactions	Anorexia nervosa Food aversions Food phobias
Neurologic reactions	Auriculotemporal syndrome Gustatory rhinitis

Conditions which are not FAs. From Mansoor DK, Sharma HP. Clinical presentations of food allergy. *Pediatr Clin North Am.* 2011;58:315–326.

IMMUNOGLOBULIN E-MEDIATED FAs

Immunoglobulin E-mediated food allergic reactions present with acute symptoms, usually minutes to hours after ingestion of the culprit food. A diagnosis of IgE-mediated FA should be considered in a patient presenting to the ED if the allergic symptoms occurred shortly after ingesting a food, particularly if symptoms followed ingestion of the given food on more than one occasion.¹³ The rapid time course of these reactions is mediated by surface IgE on tissue mast cells and circulating basophils, which develop during initial sensitization to the food. Upon reexposure to the food antigen, IgE cross-linking results in the rapid release of preformed allergic mediators that cause the immediate signs and symptoms. Newly synthesized mediators may also be released, resulting in a delayed phase of symptoms a few hours later.

There is one recently recognized form of IgE-mediated FA in which this characteristically rapid time course may not be observed. Allergic reactions to meats containing a carbohydrate antigen called *galactose-alpha-1,3-galactose* (alpha-gal) are usually delayed 4 to 6 hours after ingestion.¹⁸ These patients have IgE antibody to alpha-gal, and it is likely that antigen digestion and/or processing is responsible for the delayed onset of their symptoms. This condition is also the only IgE-mediated FA identified to date in which the food antigen is a carbohydrate, and not a protein. The remainder of this review will focus on the more common IgE-mediated reactions to food proteins.

Patients with IgE-mediated FA may present to the ED with a variety of manifestations, including urticaria and angioedema, rhinoconjunctivitis, bronchospasm, gastrointestinal (GI) anaphylaxis, and generalized anaphylaxis. Two additional conditions with IgE-mediated mechanisms which might present to the ED are food-dependent exercise-induced anaphylaxis and oral allergy syndrome.

Urticaria and Angioedema

Individuals experiencing IgE-mediated food allergic reactions commonly present with cutaneous symptoms of urticaria, angioedema, flushing, and pruritus. These symptoms develop due to the cross-linking of food-specific IgE on cutaneous mast cells. Mast cell degranulation releases allergic mediators, such as histamine, which causes pruritus, and vasodilatory mediators, which cause local swelling. The specific location of the mast cells determines whether urticaria and/or angioedema develop. In urticaria, mast cells in the superficial dermis are involved, whereas in angioedema, those in the deep dermis and subcutaneous tissues are implicated. On physical examination, urticarial lesions, or hives, appear as erythematous, raised, and well demarcated or coalescent plaques, often with central pallor and blanching upon pressure. They are pruritic. The swelling observed in angioedema

TABLE 2. Food-Induced Allergic Disorders

Immunopathology	Disorder	Clinical Features	Typical Age	Most Common Causal Foods	Prognosis
IgE-mediated	Urticaria/angioedema	Triggered by ingestion or direct contact	Children > adults	Major allergens	Depends on food
	Rhinoconjunctivitis/asthma	Accompanies food-induced allergic reaction but rarely isolated symptom. May be triggered by ingestion of aerosolized food protein.	Infant/child > adult, except for occupational disease	Major allergens (occupational: wheat, egg, seafood)	Depends on food
	Anaphylaxis	Rapidly progressive, multiple-organ system reaction	Any age	Any allergens but more commonly peanut, tree nuts, shellfish, fish, milk, and egg	Depends on food
	Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion followed temporally by exercise	Onset in late childhood/adulthood	Most common: wheat, shellfish, celery	Presumed persistent
	Oral allergy syndrome	Pruritus, mild edema confined to oral cavity. Uncommonly progresses beyond mouth (<10%) or anaphylaxis (1%–2%)	Onset after pollen allergy established (adult > young child)	Raw fruit/vegetables (cooked forms tolerated)	May be persistent; may vary with seasons.
Mixed IgE- and non-IgE-mediated	AD	Associated with food in 30%–40% of children with moderate/severe eczema	Infant > child > adult	Major allergens, particularly egg and milk	Usually resolves
	Eosinophilic GI disorders	Symptoms vary on site(s)/degree of eosinophilic inflammation	Any age	Multiple	Likely persistent
Non-IgE-mediated	Dietary protein-induced proctitis/proctocolitis	Mucus-laden, bloody stools in infants	Infancy	Milk (through breastfeeding)	Usually resolves

Classification based on underlying immunopathology. From Mansoor DK, Sharma HP. Clinical presentations of food allergy. *Pediatr Clin North Am.* 2011;58:315–326.

is due to the leakage of plasma into subcutaneous or mucosal tissues. Angioedema is characteristically asymmetric, involving nongravitationally dependent areas, and is nonpitting.¹⁹ It may affect the face, hands, buttocks, genitals, abdominal organs, or the upper airway. Owing to its broad differential, swelling may pose a diagnostic challenge in the ED. The presence of accompanying hives is often helpful in distinguishing angioedema owing to an underlying mast cell–driven mechanism from other nonallergic forms of angioedema.

Immunoglobulin E–mediated FA should be considered in the differential diagnosis of patients presenting to the ED with acute urticaria, particularly if a recent food exposure preceded the onset of hives. It is estimated that at least 20% of acute urticaria is due to FA.^{20,21} However, if history reveals that urticaria have persisted for greater than 6 weeks, they are then considered chronic, and FA is rarely a cause. Although as many as half of patients with chronic urticaria believe foods are triggering their symptoms, only 2% to 10% actually have food-induced urticaria in placebo-controlled challenges.^{21,22}

The route of food exposure causing urticaria and angioedema is often ingestion but may also be direct contact, which causes acute contact urticaria, in which hives are localized only to the areas of food contact. Although any food may trigger an IgE-mediated FA, some are more commonly implicated. The most common foods to cause acute urticaria and angioedema are cow's milk, egg, peanut, tree nuts, soy, wheat, fish, and shellfish. Contact urticaria may be triggered by these foods, as well as by raw meats and raw fruits and vegetables.^{23,24}

Emergency department providers should be aware that hives and swelling, although common signs of food allergic reactions, are not always present. Up to 20% of cases of

anaphylaxis do not involve any skin symptoms.²⁵ Unfortunately, the lack of skin symptoms may result in delayed recognition and treatment of systemic allergic reactions. This is supported by the observation that 80% of fatal food-induced anaphylaxis is not associated with skin findings.²⁵ Therefore, one should be careful not to exclude the diagnosis of a food-induced reaction, simply owing to the absence of cutaneous symptoms.

Rhinoconjunctivitis

Although rhinoconjunctivitis is frequently part of systemic food allergic reactions, it is uncommonly the only presenting symptom.²⁶ Ocular and nasal symptoms that may be observed during systemic allergic reactions include periocular pruritus, edema, conjunctival erythema, and tearing as well as sneezing, nasal itching, congestion, and rhinorrhea.¹³

Nasal congestion in infants has anecdotally been ascribed to cow's milk ingestion, but there is actually no evidence to support this notion. Only 0.08% to 0.2% of infants were observed to develop nasal symptoms after oral milk challenges performed in 3 studies.^{14,27,28}

Bronchospasm

A study in which children with atopic dermatitis (AD), asthma, and FA underwent double-blind placebo-controlled food challenge (DBPCFC) showed that 15% developed symptoms of acute bronchospasm after food allergen ingestion, with 8% having a 20% or greater decrease in forced expiratory volume in 1 second.^{29–31}

Food allergy is a rare cause of isolated bronchospasm.²⁶ More characteristically, acute lower respiratory symptoms of cough, chest tightness, dyspnea, and wheezing are part of a more generalized

FA reaction. It is important to note that respiratory symptoms, such as laryngeal edema and bronchospasm, are the primary cause of death in food-induced anaphylaxis.³² Furthermore, the risk of death from food-induced anaphylaxis is higher in those with asthma and increases with the severity of asthma.³² For those reasons, episodes of food-induced anaphylaxis involving bronchospasm should be treated aggressively, first with intramuscular (IM) epinephrine and then bronchodilators.

Ingestion is not the only route of exposure by which foods may cause lower respiratory reactions. Bronchospasm may rarely be caused by airborne exposure to food allergens, such as inhalation of vapors generated during the cooking of eggs, fish, and shellfish.³³

Gastrointestinal Anaphylaxis

Food allergy may present to the ED with GI manifestations. In patients with IgE-mediated FA, these symptoms are referred to as GI anaphylaxis or immediate GI hypersensitivity because they present acutely, as opposed to other forms of GI FA in which symptoms are more chronic. Gastrointestinal anaphylaxis is usually accompanied by IgE-mediated symptoms in other organ systems.³⁴ The upper GI symptoms of nausea and vomiting typically occur within minutes of ingestion, whereas lower GI symptoms of abdominal pain, cramping, and diarrhea may occur either immediately or after a delay of up to several hours after ingestion.¹³

Generalized Anaphylaxis

Patients experiencing severe food allergic reactions may present to the ED with generalized anaphylaxis. The specific diagnostic criteria for anaphylaxis are discussed elsewhere in this review.

Among patients treated for anaphylaxis in the ED, FA is the most common cause, accounting for one third to one half of cases.^{9,35,36} The foods most commonly implicated include peanut, tree nuts, shellfish, fish, milk, and egg. Food-induced anaphylaxis is life threatening, and several risk factors seem to increase the risk of a fatal reaction, including adolescent or young adult age, coexistent asthma, and reactions owing to peanut or tree nuts.¹³ Perhaps, the most critical risk factor relevant to the ED setting is that more than 90% of FA fatalities involved delayed or no administration of epinephrine.³⁷

Food-Dependent Exercise-Induced Anaphylaxis

Emergency department providers should be aware of a rare form of anaphylaxis known as food-dependent (or food-associated) exercise-induced anaphylaxis. In this IgE-mediated condition, symptoms manifest only if the patient exercises 2 to 4 hours after ingestion of the food allergen.³⁴ Of note, the patient is able to tolerate the food if ingestion is not followed by exercise. Presumably, exertion alters gut absorption, allergen digestion, or both, resulting in allergen cross-linking of IgE and the development of allergic symptoms.³⁸

Patients usually react to 1 or 2 foods, with wheat, shellfish, celery, fish, fruit, and milk being the most common culprits. Immunoglobulin E antibodies against the causative foods are usually detectable by skin prick testing (SPT) or serum IgE testing. Female sex, late adolescent to early adult age, and coexistent atopic disease seem to be risk factors for this condition.³⁹

Oral Allergy Syndrome

Another form of IgE-mediated FA that may present to the ED is oral allergy syndrome, also referred to as pollen-associated FA syndrome. Patients with oral allergy syndrome experience immediate pruritus, tingling, and/or mild swelling

of the lips, tongue, palate, and throat after eating certain raw fruits and vegetables.⁴⁰ It occurs in up to half of pollen allergic patients. Heat-labile food proteins of plant origin, which are structurally similar and thereby cross-reactive with pollen allergens, are responsible for these symptoms. Patients can usually tolerate cooked or heated forms of the causative fruits and vegetables, owing to the heat-labile nature of the proteins.

Although some patients may be alarmed by the symptoms at first, it is almost always a mild localized reaction limited to the oropharynx, which subsides within minutes of ingestion. Less than 10% of patients experience more systemic symptoms, and only 1% to 2% progress to anaphylaxis.³⁸

MIXED IGE- AND NON-IGE-MEDIATED FAS

In addition to “pure” IgE-mediated presentations of FA, there are mixed IgE- and T cell-mediated immunologic mechanisms that contribute to more chronic medical conditions such as AD and GI FA. Patients with AD and GI FA may have detectable IgE antibody. However, their pathophysiology is more likely related to food-responsive T cells that migrate to the site of involvement.³⁸

Patients with diseases such as AD and eosinophilic gastroenteropathies, including eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EG), are less likely to present to the ED for acute allergic reactions but often have more chronic delayed presentations of FA.

Atopic Dermatitis

Patients may present to the ED with a history of a chronic rash, so it is important to be able to distinguish AD from other skin conditions in children. Atopic dermatitis usually begins in infancy and tends to be chronic. It presents with extreme pruritus and a rash in a typical distribution involving the flexor surfaces, such as the antecubital and popliteal fossae, wrists, ankles, and neck.

Defects in the skin barrier in patients with AD may increase the risk of transcutaneous sensitization and the development of FA.^{41–43} Approximately 30% to 40% of children younger than 5 years with moderate-to-severe AD may also have IgE-mediated food hypersensitivity.^{44–46}

The converse, whether food hypersensitivity is a contributing cause in AD, is controversial.⁴⁷ However, AD and FA seem to be highly associated, as recognized by the recent National Institute of Allergy and Infectious Diseases (NIAID) guidelines.¹³ The improvement in symptoms after the elimination of the suspected food(s) and the exacerbation of AD with repeat exposure to the food(s) has been demonstrated in several studies. In 1 study, 113 patients with severe AD underwent DBPCFC.⁴⁸ Sixty-three of the children (56%) were noted to have positive food challenges, and most children (84%) had skin symptoms. When placed on elimination diets based on the food challenge results, these children exhibited significant improvement in skin symptoms. The foods most commonly associated with eczema were egg, milk, and peanut.

Double-blind placebo-controlled food challenges were positive in 40% of cases among 600 children with AD in another study.⁴⁵ Again, a high percentage of patients (75%) had positive challenges resulting in skin manifestations, suggesting specific foods as triggers. These manifestations consisted of macular, morbilliform, and/or pruritic rashes in the flexural areas characteristically affected in AD.

Therefore, for patients presenting to the ED with severe AD exacerbations, it would certainly be reasonable to consider referral to an allergist/immunologist for evaluation of potential FA.

Eosinophilic GI Disorders

Eosinophilic esophagitis and EG are also due to mixed IgE- and T cell-mediated immunologic mechanisms. Eosinophilic esophagitis involves inflammation of the esophagus as evidenced by the presence of greater than 15 eosinophils per high-powered field on esophageal biopsy.⁴⁹ Symptoms are commonly experienced after eating, but it may be difficult for patients to identify the culprit food because reactions are often delayed. Patients present with a wide range of chronic GI symptoms based on age. Typically, young children (median age, 2 years) present with failure to thrive and feeding difficulties, older children with vomiting (median age, 8.1 years) and abdominal pain (median age, 12.0 years), and teenagers with dysphagia (median age, 13.4 years) and sometimes food impaction (median age, 16.8 years).⁵⁰ Patients with food impactions may present to the ED.

A significant number of patients with EoE also have other allergic diseases, such as allergic rhinitis (57%) and IgE-mediated FA (46%).⁵⁰ Food allergens and possibly aeroallergens may contribute to EoE. In 1 study, the foods most likely to be implicated were cow's milk, egg, soy, corn, wheat, and beef.⁵¹ Elimination diets of the suspected food(s) or complete elimination of food and use of an elemental formula have been shown to result in clinical and histologic improvement in most children with EoE.⁵¹ Nondietary treatments include topical swallowed or systemic steroids and esophageal dilation of strictures. Owing to their adverse effects, systemic steroids are usually reserved for severe EoE-associated symptoms, such as inability to swallow or intractable vomiting, both of which may be observed in the ED.

If eosinophils are found in more distal portions of the GI tract, patients are diagnosed as having EG. These patients may present clinically at any age. The symptoms depend on the segment of the GI tract involved. Any segment of the GI tract from the esophagus to the colon, including the bile ducts, may be affected.^{52,53} Symptoms include abdominal pain, nausea, diarrhea, and weight loss secondary to malabsorption. Infants may develop outlet obstruction, with projectile vomiting after feeding. In adolescents, symptoms may be similar to irritable bowel syndrome.⁵³ Like EoE, a majority of patients (50%) will also have other allergic diseases.^{54,55}

NON-IGE-MEDIATED FAs

Non-IgE-mediated FAs are primarily mediated by T cells and result in delayed reactions. These disorders are often chronic and include food protein-induced allergic proctocolitis, food protein-induced enterocolitis syndrome (FPIES), celiac disease, and food-induced pulmonary hemosiderosis (Heiner syndrome).

Food Protein-Induced Allergic Proctocolitis

Allergic proctocolitis is characterized by T cell-mediated eosinophilic inflammation of the rectum and colon. It often presents in breastfed infants between the ages of 2 and 8 weeks.^{56–59} It is seen less commonly in infants who are fed cow's milk- or soy-based formulas. The affected infants are healthy appearing but may present with mucus and blood in their stools. Some infants may be fussy or have increased bowel movements, but they usually do not have diarrhea. Symptom improvement occurs when the offending food is removed from the mother's diet, usually within 48 hours of food removal. Allergic proctocolitis usually resolves after avoiding the allergen for 6 months to 2 years. There have been case reports of similar presentations in older children.⁶⁰

Food Protein-Induced Enterocolitis Syndrome

Patients with FPIES, which is a more severe form of T cell-mediated GI FA, often present to the ED appearing quite

ill, sometimes in shock. This disorder is underrecognized and frequently misdiagnosed in the ED setting.^{61–63} Infants younger than 9 months are most affected by FPIES, with a peak incidence between 1 week and 3 months of age. Food protein-induced enterocolitis syndrome rarely occurs in breastfed infants and is more common in infants fed cow's milk- or soy-based formulas, with cow's milk and soy being the usual inciting foods. Less common culprit foods include grains (rice, oat, barley), vegetables (sweet potato, squash, string bean, pea), and poultry (chicken, turkey).^{61,62}

Children with FPIES who regularly ingest the allergenic food present with chronic severe GI symptoms, including vomiting, diarrhea, poor growth, anemia, and hypoproteinemia.^{64–66} However, in many instances, a child may present to the ED with more acute symptoms of FPIES, typically occurring after an allergen is reintroduced into the diet after a period of restriction or on early exposure to the allergen. In this scenario, children can have profuse and repetitive vomiting, approximately 1 to 3 hours, and occasionally diarrhea, 5 to 8 hours after ingestion of the causative food.⁶³ Affected children often appear quite ill. The repeated vomiting, third spacing of fluid, and systemic inflammatory response may progress to dehydration and, in 15% to 20% of cases, even shock.⁶³ Owing to the severity of their presentation, absence of skin or respiratory symptoms, and delay from food ingestion to onset, children with FPIES may often be misdiagnosed. For example, they may undergo unnecessary, often painful, tests and prolonged hospitalization for misdiagnoses of sepsis, surgical abdomen, metabolic disorder, or anaphylaxis.⁶³ A history of ingestion of a new or previously avoided food a few hours before the onset of vomiting should raise suspicion for FPIES. The diagnosis of FPIES is made clinically and, when unclear, by supervised oral food challenge. Diagnostic endoscopy is not indicated, except to exclude other GI illnesses, especially in the chronic form. Appropriate first-line treatment of FPIES involves avoidance of the culprit food and, in the ED, aggressive intravenous fluid hydration if there are signs of dehydration.^{62,67} For severe episodes, treatment with intravenous corticosteroids may additionally be considered.⁶²

Although it may take weeks for the T cell-mediated inflammation to resolve, removal of the allergen leads to symptom resolution. Food protein-induced enterocolitis syndrome commonly is outgrown. Most children will become tolerant of the culprit food by 3 years of age. At that time, a hospital-based food challenge may be performed to confirm resolution and tolerance.^{62,63}

Celiac Disease

Celiac disease is a chronic condition that is mediated by non-IgE-mediated immune mechanisms. It is due to a T cell-mediated inflammatory response to gluten in grains such as wheat, rye, and barley. Symptoms of malabsorption may include chronic diarrhea, steatorrhea, failure to thrive, short stature, and/or other signs of nutrient or vitamin deficiency.⁶⁸ When gluten-containing foods are removed from the diet, the histologic changes (villous atrophy) of the small intestine and the symptoms resolve within a few weeks to months.

Heiner Syndrome

Heiner syndrome, also known as food-induced pulmonary hemosiderosis, is believed to be related to milk protein ingestion. It is rare and seen mostly in infants 4 to 29 months of age. These children may present to the ED with chronic or recurrent lower respiratory symptoms and signs, such as fever, cough, hemoptysis, wheezing, and dyspnea.⁶⁹ Complications may include recurrent pneumonia with infiltrates, pulmonary

hemosiderosis, iron deficiency anemia, and failure to thrive. In contrast to the IgE antibodies seen in acute FA, Heiner syndrome is associated with increased milk-specific IgG antibodies. This is the only situation where an elevated IgG is diagnostic of FA.⁷⁰ Milk protein elimination leads to resolution of symptoms.

DIAGNOSIS OF FAs

Importance of the Medical History and Physical Examination

The presentation and appropriate diagnosis of FA can be complex. As discussed in the NIAID guidelines,¹³ although the history alone is not sufficient to make a diagnosis of FA, it provides the basis for testing and diagnosis.¹³ During the history, it is important to consider a broad differential diagnosis, to identify possible trigger foods, and to determine if the pathophysiology of the reaction is IgE mediated.^{71,72} It is essential that the events surrounding an allergic reaction be recorded in as much detail as possible. In this regard, the ED provider has a unique opportunity because he or she is often the first medical caregiver a patient sees after having an allergic reaction and because the details and circumstances of the reaction often become obscured as time elapses.

Important areas of the history include the following.

Reaction

- A detailed description of the symptoms experienced by the patient, such as cutaneous manifestations, airway obstruction, GI symptoms, and syncope or presyncope. Each symptom should be explored in detail. For instance, the history of a rash should include its initial presentation, progression, type (urticaria, flushing, pruritus, etc), and resolution.
- The time course of the reaction.
- The timing of food ingestion in relation to the beginning of the reaction.
- Any interventions taken before presenting to the ED.

Suspected Food

- A detailed description of the food(s) ingested before the reaction. If an obvious trigger is not evident, it is important to ask the patient or caregiver to save the food labels and/or to review the ingredients of everything ingested.
- The amount of food ingested before the reaction.
- The form in which the food was ingested (eg, raw or cooked).
- Whether the ingested food had been tolerated previously.

Surrounding Circumstances

- Did other people who ingested the same food experience similar symptoms? Knowing this is important to rule out food poisoning, such as scombroid, which can often mimic FA.⁷³
- The circumstances surrounding the reaction, with special attention to the presence of exercise, alcohol, or medication use.⁷⁴

Additional Questions When a Non-IgE-Mediated Reaction is Suspected

- The course of the symptoms (worsening, improving, etc).
- Their frequency.
- Whether these symptoms recur consistently upon reexposure to suspected foods.
- The presence of similar symptoms in other circumstances.

- Any interventions tried—including self-directed elimination of certain foods to alleviate symptoms—and the responses to these interventions.

Physical examination can also aid in the diagnosis of FA.¹³ It should include a detailed examination of the integumentary and respiratory systems, with attention to the presence of hives, angioedema, or wheezing. However, the absence of these findings does not preclude a diagnosis of FA because these symptoms are often transient.¹³

Immunoglobulin E-Mediated Skin Testing and Serum IgE Testing

Although a definitive diagnosis of FA will not be made in the ED, it is important for the ED provider to understand the appropriate role of diagnostic tests. Once a history that is suggestive of an immediate hypersensitivity FA is obtained, the next step in diagnosis is SPT and/or specific serum IgE testing. SPT is best performed by trained personnel working with an allergist/immunologist.⁷²

Skin prick testing provides a measure of sensitization, and the results can be obtained within 30 minutes. Skin prick testing has a higher than 90% negative predictive value.^{75–78} Consequently, a negative result in the presence of a vague history essentially rules out the diagnosis of an IgE-mediated FA. However, when a negative result is obtained in the setting of a more suggestive history, an oral food challenge is needed to confirm or refute the diagnosis.¹³ The positive predictive value, on the other hand, is much lower, and a positive test result does not definitively diagnose an FA.^{75–78} However, a convincing history and a positive skin test result can be considered highly supportive of FA.

Specific serum IgE testing (previously called radioallergen sorbent testing) is another method to test for immediate hypersensitivity FAs. Higher levels of specific IgE to a specific trigger correlate with a higher likelihood of having an allergic reaction. However, levels do not correlate with the severity of a reaction. Similar to SPT, false positive results are common, but there is a high negative predictive value.^{79–86}

The criterion standard for diagnosing an FA is a DBPCFC. However, in some situations, a single blind or open food challenge may be considered diagnostic.¹³

Mixed IgE-Mediated and Non-IgE-Mediated FA Testing

For patients suspected of having mixed IgE-mediated and non-IgE-mediated disease, such as AD and eosinophilic GI disorders (EoE and EG), testing can be used in conjunction with the history.⁷² The diagnosis of AD is a clinical diagnosis, whereas the diagnosis of EoE and EG is clinical and histological. Testing to identify potential IgE-mediated FAs in AD includes SPT and serum-specific IgE. For EoE, trigger foods may be identified through SPT, serum-specific IgE, and atopy patch testing (application of foods to the skin for 48 hours to assess delayed type hypersensitivity).^{13,87}

The diagnosis of non-IgE-mediated FA is based on signs and symptoms occurring reproducibly on exposure to the culprit food and resolution of the signs and symptoms once the food is taken away. Reintroduction of the culprit food and provocation of symptoms confirms the diagnosis. There is no role for IgE testing either by SPT or serum IgE in these patients.

Value of Laboratory Testing in the Acute Setting: Role of Tryptase and Histamine in Evaluation of Food-Induced Anaphylaxis

Laboratory testing is of limited value in the acute setting of an anaphylactic reaction, when attention should be focused on treating the patient. In some settings, when the diagnosis of anaphylaxis is in question, it may be worthwhile to obtain a serum tryptase level. The tryptase level is most accurate within 1 to 2 hours of the reaction.⁸⁸ Because patients are often seen in the ED more than 2 hours after the reaction, the tryptase may be falsely negative. However, a tryptase that is elevated in the acute setting is highly suggestive of an IgE-mediated allergic reaction. The use of plasma histamine may be unrealistic in the ED for many reasons. Histamine usually returns to baseline within 40 minutes. Furthermore, the test is labile, and samples require special handling before processing.¹³ Finally, it is important to note that plasma histamine and tryptase levels are often not elevated in food-induced anaphylaxis.⁸⁸

PREVENTION OF ACUTE ALLERGIC REACTIONS

Currently, there is no cure for FAs. An important focus of the management for FAs is avoidance and prevention. Avoidance of a confirmed relevant food allergen is the basis of all long-term risk reduction measures in patients with anaphylaxis. Clear and concise information about how to avoid triggers is essential in preventing future anaphylactic episodes. For patients with FAs, this will include education about reading food labels properly, avoiding foods that may cross-react with the confirmed food allergen, and substitution of foods to ensure proper nutrition. If the content of a particular food is not known, the food should be avoided. For some allergens, lifelong avoidance may be necessary. This may potentially disrupt activities and lead to anxiety, thus decreasing the quality of life for patients and their families.⁴

MANAGEMENT OF ACUTE ALLERGIC REACTIONS

Accidental or intentional exposure to allergenic foods in patients with FAs will occur. Therefore, it is important to recognize the symptoms and signs of acute allergic reactions and to treat them promptly. The history is the most important tool in determining whether a patient has had anaphylaxis, as well as the cause of the episode. Because their symptoms and signs can overlap, anaphylaxis may be confused with another disease (eg, hereditary angioedema).

Definition of Anaphylaxis

Anaphylaxis is defined as an immediate, systemic hypersensitivity reaction caused by an IgE-mediated immunologic release of allergic mediators. It can present as 1 of 3 clinical scenarios.⁸⁹

1. Acute onset of a reaction with involvement of the skin, mucosal tissue, or both and at least one of the following: (a) respiratory compromise, or (b) reduced blood pressure or symptoms or signs of end-organ dysfunction;
2. Two or more of the following, which occur rapidly after exposure to a likely allergen for that patient: skin or mucosal tissue involvement, respiratory compromise, reduced blood pressure or associated symptoms, and/or persistent GI symptoms;
3. Reduced blood pressure after exposure to a known allergen.

Treatment of Food-Induced Anaphylaxis

Anaphylaxis sometimes occurs despite appropriate avoidance measures. When this happens, it is impossible to predict whether the patient will die within minutes, whether they will recover spontaneously, or whether and how they will respond to treatment. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life threatening.⁸⁹

Intramuscular epinephrine is the first choice for treatment of acute anaphylaxis. In general, treatment in order of importance is as follows: epinephrine; positioning the patient supine with elevation of the lower extremities; and administration of oxygen, intravenous fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents, such as glucagon.

Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected. There is no absolute contraindication to administration of epinephrine in a child. For IM administration, the concentration of epinephrine is 1:1000. The dose for a child is 0.01 mg/kg. The adult dose is 0.2 to 0.5 mg.⁸⁹

In addition to epinephrine, additional medications may be considered. H₁-receptor antagonist antihistamines (eg, diphenhydramine, 1–2 mg/kg [up to 25–50 mg per dose] parenterally) are second line to epinephrine and should not be given instead of epinephrine for treatment of anaphylaxis.⁹⁰ Ranitidine (1 mg/kg in children [50 mg in adults] parenterally), a H₂-receptor antagonist, should also be considered. In the management of anaphylaxis, the combination of diphenhydramine and ranitidine is superior to diphenhydramine alone.⁹⁰ However, the onset of action of these agents is significantly slower than epinephrine, and they should never be used alone in the treatment of anaphylaxis.

Inhaled β -agonists (eg, albuterol metered dose inhaler with appropriate spacer [2–6 puffs] or nebulized [2.5–5 mg in 3-mL saline], repeated as necessary) should be considered for bronchospasm resistant to adequate doses of epinephrine.⁹⁰

Treatment of Biphasic or Protracted Food-Induced Anaphylaxis

Late phase or biphasic reactions, which occur 1 to 78 hours (most within 10 hours) after the initial phase of symptoms, can develop in up to 20% of fatal and near-fatal food reactions.^{35,91,92} Patients are often given systemic corticosteroids at the time of the initial reaction to help prevent a late-phase reaction, although results from studies regarding this practice are conflicting.⁹³ Patients and families should be advised that a late reaction might occur, usually 4 to 24 hours after the initial reaction.

Most episodes of anaphylaxis resolve after the initial epinephrine dose, but 10% to 20% of children may require a second dose. Patients should have access to 2 epinephrine auto-injectors at all times. Scenarios that may require more than 1 auto-injector include the possibility of a misfiring, failure to respond to the first dose, remote location from a health care facility, or caregiver comfort level.

Treatment of Refractory Anaphylaxis

Some patients may not respond to epinephrine. Lack of efficacy may be due to delay in epinephrine injection, suboptimal route or site of injection, use of a lower dose than recommended for the patient's weight, or extremely rapid progression of anaphylaxis. Some medications, such as β -blocking agents, may make patients less responsive to epinephrine during anaphylaxis.⁹¹

On rare occasions, severe refractory anaphylaxis may persist for several hours despite aggressive treatment. Epinephrine can be given intramuscularly every 5 minutes for several doses,

if necessary, to control severe symptoms and increase blood pressure. When severe anaphylaxis is not responding to oxygen, intravenous fluids, and other measures, including repeated doses of IM epinephrine, the use of intravenous epinephrine, vasopressors, and/or glucagon may need to be considered. Because of the risk of potentially lethal arrhythmias, intravenous epinephrine should only be used in profoundly hypotensive patients who have failed to respond to intravenous volume replacement and several IM doses of epinephrine. Prolonged resuscitation is encouraged, if necessary, because a successful outcome is more likely in anaphylaxis.

Observation Period

Observation periods must be individualized because there are no reliable predictors of protracted or biphasic anaphylaxis based on initial presentation.⁹⁴ Most patients should be closely monitored for at least 4 to 6 hours after the initial episode of anaphylaxis, and autoinjectable epinephrine should be available at all times.¹³

Discharge Plan After Treatment of Food-Induced Anaphylaxis

Patients who have a diagnosis of an IgE-mediated FA and anaphylaxis should carry 2 epinephrine auto-injectors at all times. Education on when and how to use this medication properly is essential.⁹⁵ Before leaving the ED, patients should be provided with a prescription for 2 epinephrine auto-injectors. Epinephrine auto-injectors are available in 2 fixed doses—0.15 and 0.3 mg. For infants and children weighing less than 25 kg, the appropriate dose is 0.15 mg per injection. For children weighing more than 25 kg and for adults, 0.3 mg per injection is the appropriate dose. Intramuscular injection into the anterolateral thigh is the preferred method and site of epinephrine administration.⁸⁹

An anaphylaxis emergency action plan is an important component of follow-up care. The action plan should include a description of symptoms and signs of anaphylaxis, indications for epinephrine use, and important emergency telephone numbers.^{96–98} Examples of written action plans can be downloaded from the American Academy of Allergy, Asthma, and Immunology (www.aaaai.org) or Food Allergy and Anaphylaxis network (www.foodallergy.org) Web sites. Foreign-language versions are also available.

Diagnosis and long-term management can be complex. Particularly for patients with FA evaluated in the ED, referral to an allergy/immunology specialist should be strongly considered for additional testing, education, and therapy.⁹⁸

CONCLUSIONS

Food allergies are a growing public health problem that often presents to the ED. We have described the different types of FAs that may present to the ED, as categorized by their underlying immunopathology. Some mixed and non-IgE-mediated FAs that may be encountered in the ED include AD, EoE, and EG, and FPIES. The most urgent role for the ED provider is to recognize and appropriately manage IgE-mediated FA reactions. Epinephrine is first-line treatment for any patient presenting with anaphylaxis, but other medications can be used as adjuncts. Because there is no cure for FA, it is essential to provide patients presenting to the ED with IgE-mediated FA appropriate anticipatory guidance including food avoidance, epinephrine auto-injector prescriptions, and allergy/immunology follow-up.

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