

Clinical Manifestations of Food Allergy

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Abstract

Adverse reactions to foods are a diverse group of clinical syndromes resulting from immunologic and non-immunologic responses to food ingestion. Symptoms can range from mild, self-limiting reactions to severe, life-threatening reactions depending on the mechanism. This review primarily focuses on the clinical manifestations of immunologically derived adverse food reactions or food allergies.

The true prevalence of food allergy is unknown. Up to 25% of the general population believes that they may be allergic to some food; however, the actual prevalence of food allergy diagnosed by a provider appears to be 1.5% to 2% of the adult population and approximately 6% to 8% of children. This discrepancy makes it imperative that clinicians are aware of the different food allergy syndromes. With a clear understanding of the clinical manifestations of food allergies, an accurate diagnosis and treatment plan can be formulated. Failing to do so may result in unnecessary dietary restrictions that may adversely affect nutritional status, growth, and quality of life.

Most food allergic reactions are secondary to a limited number of foods, and the most common foods causing allergic reactions in children include milk, egg, peanuts, tree nuts, and fish. In adolescents and adults, allergies to peanuts, tree nuts, fish, and shellfish are most prevalent. Food allergies can result from immunoglobulin E (IgE)-mediated, non-IgE-mediated, or mixed IgE/non-IgE mechanisms. The purpose of this review is to discuss the clinical manifestations of each of these types of food allergy.

CME EDUCATIONAL OBJECTIVES

1. Recognize differences between immunologic and non-immunologic food reactions.
2. Understand that immunologic food reactions can manifest as immunoglobulin E (IgE)-mediated reactions, non-IgE-mediated reactions, or mixed IgE/non-IgE-mediated reactions.
3. Recognize the clinical symptoms involved in adverse food reactions due to IgE-mediated, non-IgE-mediated, and mixed IgE/non-IgE-mediated mechanisms.

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An adverse reaction to food is any clinically abnormal response to an ingested food or food additive. Two broad classifications of food reactions, non-immunologic and immunologic, should be considered during the diagnostic evaluation of any patient with a history of adverse reaction to foods.^{1,2} The distinction between these two categories is critically important due to the diverse range of clinical risks associated with each.

For example, an adverse reaction to milk may be due to a life-threatening immunologic response to milk protein or the result of a non-immune (metabolic) response due to an inability to digest lactose. The natural history, diagnostic evaluation, and treatment options differ significantly between immunologic and non-immunologic food reactions; therefore, it is important for the clinician to be aware of these differences.

NON-IMMUNOLOGIC FOOD REACTIONS

Non-immunologic food reactions are considered food intolerances and can be due to toxic effects, pharmacologic properties of the food, characteristics of the host such as metabolic disorders, and idiosyncratic responses.^{1,3} Adverse reactions due to nonimmunologic responses or food intolerances can mimic symptoms of an immunologic response; the clinician should be aware of the potential overlap in clinical presentations. Failure to recognize this overlap may result in misclassification of adverse food reactions and lead to unnecessary avoidance of major food groups or, more importantly, inappropriate management of a potentially life-threatening immunologic adverse food reaction.

A classic example of a nonimmunologic adverse food reaction is lactose intolerance in which patients with lactase deficiency may tolerate small amounts of dairy with little to no symptoms but may have gastrointestinal symptoms in-

TABLE 1.

Nonimmunologic Adverse Reactions to Foods

Type of Reaction	Example
Metabolic	Lactase deficiency or galactosemia
Chemical	Gustatory rhinitis
Toxic	Scromboid fish poisoning, bacterial food poisoning (eg, <i>Salmonella</i> , <i>Shigella</i>)
Pharmacologic	Caffeine, tyramine
Anatomic	Auriculotemporal (Frey) syndrome or gustatory flushing syndrome due to foods
Irritant	Acidic fruits and vegetables
Other/idiosyncratic	Monosodium glutamate, nitrates, sulfites

cluding bloating, pain, or diarrhea with ingestion of larger amounts. These patients may opt to consume dairy products with a lactase enzyme replacement to minimize symptoms. This approach, however, would be detrimental and potentially life-threatening if symptoms were due to an immunologic response to dairy.

It is also important to note that most adverse reactions to food additives such as artificial colors and preservatives have no defined immunologic mechanisms and are categorized as food intolerances if reproducible reactions occur. A detailed discussion of all nonimmunologic food reactions is beyond the scope of this review; however, nonimmunologic reactions commonly mistaken for immunologic food reactions are listed in Table 1.

IMMUNOLOGIC FOOD REACTIONS

Immunologic responses to foods are considered food allergies or food hypersensitivity reactions and can be further classified as immunoglobulin E (IgE)-mediated, non-IgE-mediated or mixed (IgE/non-IgE mediated) responses (see Table 2). A food allergy arises from a specific immune response that occurs reproducibly on exposure to a given food.¹ Food allergies are most commonly due to IgE-mediated immune responses, but

non-IgE immune responses such as food protein-induced enterocolitis syndrome (FPIES) or mixed IgE/non-IgE reactions such as atopic dermatitis are important clinical syndromes to be recognized by clinicians.

IgE-MEDIATED REACTIONS

Oral tolerance of ingested food allergens results from suppression of the immune system when the gut mucosa comes in contact with dietary proteins. Failure to develop or a breakdown in oral tolerance results in excessive production of food-specific IgE antibodies. These food-specific antibodies bind high-affinity IgE receptors on mast cells and basophils and low-affinity IgE receptors on macrophages, monocytes, lymphocytes, eosinophils, and platelets.⁴ Upon re-exposure to the offending food, the food allergen binds to the food-specific antibodies on mast cells and/or basophils, and mediators such as histamine, prostaglandins, and leukotrienes are released. These mediators then promote vasodilatation, smooth muscle contraction, and mucus secretion resulting in the symptoms of immediate hypersensitivity. The activated mast cells also release various cytokines important in inflammatory cell recruitment responsible for late-phase allergic responses.

TABLE 2.

Immunologic Food Reactions

IgE-Mediated	Non-IgE-Mediated	Mixed (IgE and non-IgE-Mediated)
Generalized		
Anaphylaxis		
Cutaneous		
Urticaria	Contact dermatitis	Atopic dermatitis
Angioedema	Dermatitis herpetiformis	
Morbiliform rash		
Flushing		
Gastrointestinal		
Oral allergy syndrome	Food protein-induced enterocolitis	Eosinophilic esophagitis
Immediate gastrointestinal hypersensitivity	Food protein-induced enteropathy	Eosinophilic gastroenteritis
	Food protein-induced proctitis	
	Celiac disease	
Respiratory		
Acute rhinoconjunctivitis	Food-induced pulmonary hemosiderosis	Asthma
Laryngospasm	Heiner's syndrome	
Bronchospasm		

IgE = immunoglobulin E.

Generalized Anaphylaxis

Anaphylaxis is an acute, life-threatening systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral basophils.^{5,6} Foods are the most commonly reported trigger of anaphylaxis among children and adolescents.^{6,7} Onset of symptoms during food-induced anaphylaxis is abrupt and most often occurs within minutes of ingestion. Any organ system or groups of systems can be involved in an anaphylactic reaction. Severe or life-threatening generalized anaphylactic reactions involve the respiratory and cardiovascular systems and can result in death if treatment is delayed.

Fatal and near-fatal IgE-mediated reactions to foods have been described.⁸⁻¹⁰ The most common food allergens reported to cause fatal or near-fatal reactions are peanuts and tree nuts. Fatality risk factors include a history of asthma, history of previous serious reaction, and delayed administration of epinephrine. Patients with fatal or near-fatal reactions had known allergies to the causal food and had unintentionally ingested the food allergen. This highlights the importance of education regarding allergen avoidance and strict-label reading practices to avoid future allergic reactions. Patients should also be taught appropriate treatment strategies to employ during a reaction.

SIDEBAR.

Oral Allergy Syndrome (Pollen-Associated Food Allergy)

- Pollen
 - Ragweed
 - Birch
 - Mugwort
 - Grass
 - Latex
- Fruit/Vegetable
 - Melon (cantaloupe, honeydew, etc), banana
 - Apple, cherry, apricot, carrot, potato, kiwi, hazelnut, celery, pear, peanut, soybean
 - Celery, fennel, carrot, parsley
 - Kiwi, tomato, watermelon, potato
 - Banana, avocado, chestnut, kiwi, fig, apple, cherry

Cutaneous

The skin is the most common target organ in IgE-mediated food reactions; cutaneous symptoms occur in more than 80% of allergic reactions to foods.^{1,11} The ingestion of food allergens can lead either to immediate cutaneous symptoms, such as urticaria or angioedema, or exacerbate chronic conditions such as atopic dermatitis. Flushing, pruritis, and morbiliform rash are other acute cutaneous manifestations that commonly occur during allergic reactions to foods. Food allergy is typically not a cause of chronic urticaria.

Respiratory

Upper respiratory symptoms such as sneezing, rhinorrhea, nasal congestion and pruritis are common during allergic reactions to foods. Nasal symptoms typically occur in conjunction with other organ system involvement, and isolated nasal symptoms are considered rare.¹²

Lower respiratory symptoms are potentially life-threatening manifestations of IgE-mediated reactions to foods that require prompt medical intervention.^{4,13}

Symptoms can include dyspnea, wheezing, coughing, and laryngospasm. Although lower respiratory symptoms can occur in any person experiencing food anaphylaxis, patients with concomitant lung disease such as asthma are at increased risk of severe symptoms.⁵ Lower respiratory symptoms due to food allergy are temporally related to food ingestion and are typically accompanied by other organ system involvement. It is not likely that chronic lower respiratory symptoms or poorly controlled asthma would be the sole manifestations of food allergy.^{14,15}

Ocular

Ocular symptoms typically occur concurrently with respiratory manifestations of IgE-mediated reactions to foods.^{4,13} Symptoms may include periocular and/or conjunctival erythema, pruritus, and tearing.

Gastrointestinal

Oral allergy syndrome (OAS), also referred to as pollen-associated food allergy syndrome, is considered a form of local IgE-mediated allergy that is confined almost exclusively to the oropharynx and rarely involves other target organs.^{16,17} OAS affects patients who are allergic to pollens (eg, ragweed, birch) and results from oral contact or ingestion of foods that cross-react with homologous pollen antigens (see Sidebar).

OAS most commonly is associated with the ingestion of fresh fruits and vegetables rather than processed or cooked foods. Symptoms include pruritus and/or tingling of the lips, tongue, roof of the mouth, and throat, with or without swelling. The symptoms generally resolve without progression to systemic involvement (See Table 3).

Immediate gastrointestinal (GI) hypersensitivity is a form of IgE-mediated food allergy that may accompany allergic manifestations in other target organs.^{12,13} Symptoms generally include

TABLE 3.

Gastrointestinal Food Allergic Disorders

Disorder	Key Features
IgE-mediated	
Oral allergy	Oral pruritus, mild angioedema of oral cavity
Gastrointestinal immediate hypersensitivity	Acute nausea, vomiting, pain, diarrhea
Mixed IgE and non-IgE-mediated	
Eosinophilic esophagitis	Dysphagia, post-prandial nausea and vomiting, epigastric pain
Eosinophilic gastroenteritis	Vomiting, abdominal pain, diarrhea, malabsorption, and failure to thrive
Non-IgE-mediated	
Food protein-induced enterocolitis	Vomiting, diarrhea, poor growth, lethargy, dehydration
Food protein-induced enteropathy	Malabsorption, emesis, poor growth, diarrhea
Food protein-induced proctocolitis	Bloody diarrhea, mucous in stools, normal growth
Celiac disease	Malabsorption, failure to thrive, diarrhea

IgE = immunoglobulin E.

nausea, abdominal pain, abdominal cramping, vomiting, and/or diarrhea. Upper GI symptoms may occur within minutes and lower GI symptoms may occur either immediately or with a delay of up to several hours^{18,19} (see Table 3).

MIXED IgE-MEDIATED AND NON-IgE-MEDIATED REACTIONS

Cutaneous

Atopic dermatitis (AD) is a chronic skin disorder that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, chronically relapsing course, and association with asthma and allergic rhinitis.²⁰ Food allergy has been strongly correlated with the development and persistence of AD, especially during infancy and early childhood. In children younger than 5 years, 35% to 40% are allergic to at least 1 food.^{20,21} AD patients with food allergy typically fail to respond to conventional medical therapy or may have frequent exacerbations of underlying skin disease if causal foods are not

strictly avoided. Dietary elimination of relevant food allergens may result in clearing or significant improvement of the skin.

Gastrointestinal

Allergic eosinophilic gastroenteropathies are a group of disorders characterized by eosinophilic infiltration of at least 1 layer of the gastrointestinal tract, absence of vasculitis, and often peripheral eosinophilia^{22,23} (see Table 3). These disorders are defined by the site(s) of involvement and include eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE). Symptoms for each of these syndromes are related to the specific anatomical site of involvement.

EoE is characterized by clinical symptoms of esophageal dysfunction and histological evidence of eosinophil-predominant inflammation.²⁴ Patients often have evidence of other atopic disease and may have specific IgE to causative food allergens; however, positive IgE testing to foods is not required

for diagnosis. Symptoms may include feeding difficulties, nausea, vomiting, abdominal pain, dysphagia, and regurgitation. In severe cases, esophageal strictures and obstruction may occur.

On endoscopy, EoE patients can have esophageal furrowing, exudates, and “trachealization” but the esophagus may be visually normal, highlighting the importance of biopsy in making the diagnosis.^{24,25} Esophageal biopsy with at least 15 eosinophils per high-power field (hpf, 400x magnification) despite treatment with a high-dose proton pump inhibitor is suggestive of an EoE diagnosis.

EGE is characterized by eosinophilic infiltration of the stomach, small intestine, or both, with variable involvement of the large intestine.^{26,27} Symptoms can include vomiting, abdominal pain, diarrhea, malabsorption, eosinophilic ascites, and failure to thrive. Because eosinophils are normally found in the stomach and intestine, endoscopic findings are more difficult to interpret compared with EoE; therefore, clinicians should consider utilizing the Klein classification of mucosal, serosal, or muscularis to describe the location of the eosinophilic infiltrate in EGE.²⁷

NON-IgE-MEDIATED FOOD HYPERSENSITIVITY

Cutaneous

Food-induced contact dermatitis has been reported in individuals without IgE antibodies to the causal food.²⁸ This reaction typically occurs in food handlers and can be confirmed by patch testing. Implicated foods include fish, shellfish, meats, and eggs.²⁹

Dermatitis herpetiformis (DH) is a manifestation of celiac disease (gluten-sensitive enteropathy) that affects the skin. DH is a chronic blistering skin rash characterized by chronic, pruritic papulovesicular lesions distributed over the extensor surfaces and buttocks.³⁰ Elimination of gluten from the diet typically

results in resolution of skin and gut lesions.

Gastrointestinal

Food protein-induced enterocolitis syndrome (FPIES) is a disorder that commonly presents in early infancy but has also been described in adults.³¹⁻³³ Acute symptoms are usually isolated to the gastrointestinal tract and consist of profuse, recurrent vomiting and/or di-

Food protein-induced proctocolitis generally presents in the first few months of life.

arrhea after ingestion of the offending food. Severe symptoms may occur and can lead to volume depletion, dehydration, and/or hypotension (see Table 3). Although cow's milk and/or soy protein in infant formulas or maternal breast milk are most often responsible for this syndrome, FPIES due to solid food has been described.³⁴

Analysis of peripheral blood typically reveals leukocytosis with a left shift, causing many patients to be incorrectly diagnosed with infection. Objective findings on stool examination consist of gross or occult blood, polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals, and positive reducing substances (indicating malabsorbed sugars). Jejunal biopsies classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells.^{23,35} Symptoms are not mediated by IgE and patients with FPIES do not typically respond to antihistamines and epinephrine. Symptoms should be treated with aggressive fluid replacement and prompt elimination of the offending food.

Food protein-induced enteropathy is characterized by diarrhea, vomiting,

malabsorption, and poor weight gain. It is clinically distinguishable from FPIES because stools are typically non-bloody, vomiting is less prominent, and re-exposure does not elicit acute symptoms after a period of avoidance. Other clinical features include abdominal pain and distention, hypoproteinemia, and edema. Histologic examination reveals patchy villous atrophy and mononuclear cell infiltrates and few eosinophils.

Food protein-induced proctocolitis generally presents in the first few months of life. The disease is typically discovered because of blood (gross or occult) and mucous in the stool. Symptoms are often secondary to cow's milk or soy protein;³⁶ infants with this disorder often do not appear ill. Other distinguishing features include normal growth and absence of vomiting. Gastrointestinal lesions are usually confined to the rectum but can involve the entire large bowel and consist of eosinophilic infiltrates (5-20/hpf), or eosinophilic abscesses in the epithelium and lumina propria.

Celiac disease (or gluten-sensitive enteropathy) is an extensive enteropathy leading to malabsorption. Total villous atrophy and an extensive cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley.^{37,38} Patients present with diarrhea or frank steatorrhea, abdominal distention and flatulence, failure to thrive, and occasionally nausea and vomiting. Oral ulcers and other extra-intestinal symptoms secondary to malabsorption also occur. Endoscopic findings and clinical symptoms resolve with strict elimination of gluten from the diet. Patients must remain on a gluten-free diet for their entire life.

Respiratory

Food-induced pulmonary hemosiderosis (Heiner's syndrome) is characterized by recurrent pulmonary infiltrates, hemosiderosis, gastrointestinal blood

loss, iron-deficiency anemia, and failure to thrive³⁹ due to cow's milk. Peripheral eosinophilia and multiple cow's milk precipitins are diagnostic clues. Symptoms resolve with strict dietary elimination of milk.

CONCLUSION

Manifestations of food allergy involve a diverse group of clinical syndromes. Symptoms can result from both immunologic and nonimmunologic responses to food ingestion and can be mild or severe in nature depending on the underlying mechanism. It is important for the clinician to recognize the specific implications of each food allergy syndrome because the diagnosis, management, and natural history vary significantly based on the underlying disorder. ■

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