Classification of adverse food reactions

Amanda L. Cox, M.D and Scott H. Sicherer, M.D.

ABSTRACT

Foods can induce adverse reactions by a variety of mechanisms. An understanding of the characteristic signs and symptoms and the related mechanisms of adverse food reactions allows the clinician to efficiently diagnose and treat patients. Adverse reactions to foods can be classified based on whether there is a nonimmunologic or immunologic basis for symptoms. Food intolerance, or a nonimmunologic reaction, includes a range of responses to foods that result primarily from an individual's intrinsic inability to metabolize a component of the food, e.g., *lactose sugar in dairy products. Other nonimmunologic adverse reactions may be attributed to food toxins or pharmacologic properties pharmacologic properties of foods themselves. Immunologic adverse reactions, in contrast, involve immune responses to food and are termed food allergy. Food allergy may further be categorized based on the underlying immunopathophysiology as immunoglobulin E (IgE) mediated, non–IgE mediated, or cell mediated. Some chronic allergic responses involve a combination of immune mechanisms. This review provides a general classification system for adverse food reactions and describes specific conditions.*

(J Food Allergy 2:3–6, 2020; doi: 10.2500/jfa.2020.2.200022)

Individuals present to medical attention with a panoply of symptoms attributed to food. The clinician must consider whether the symptoms are indeed related to food ingestion or some other cause, and, if related to food ingestion, the culprit food(s) must be identified. This diagnostic process relies heavily on obtaining a careful history and placing that history in the context of the various ways that food can result in adverse reactions.[1] Knowledge of the underlying pathogenesis and general categories of adverse food reactions allows for a more streamlined diagnostic approach and better medical management. The purpose of this review is to provide information with regard to the major types of adverse food reactions that will be expounded in later sections of the Primer. The categories and definitions used here are primarily those described in the U.S. Guidelines for the Diagnosis and Management of Food Allergy.[2] Adverse food reactions can be broadly categorized as those with a nonimmunologic etiology and those with an immunologic basis (termed food allergy). The categories of adverse reactions with examples of specific disorders are shown in Fig. 1.

From the Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, New York

S.H. Sicherer reports royalty payments from UpToDate and from Johns Hopkins University Press; grants to his institution from the National Institute of Allergy and Infectious Diseases, from Food Allergy Research and Education, and from HAL Allergy; and personal fees from the American Academy of Allergy, Asthma and Immunology as Deputy Editor of the Journal of Allergy and Clinical Immunology: In Practice, outside of the submitted work. A.L. Cox has no conflicts of interest to declare pertaining to this article

Funded by Food Allergy Research & Education (FARE)

Address correspondence to Amanda L. Cox, M.D., Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574

E-mail address: amanda.cox@mssm.edu

NONIMMUNE ADVERSE REACTIONS

Nonimmunologic adverse food reactions include intolerances that may be due to an individual's metabolic response to a food or due to intrinsic pharmacologic or toxic effects of foods themselves. Relatively little literature exists for many of these adverse reactions, which suggests that they are rare or have controversial aspects.

Metabolic

Food intolerances are common and include adverse food reactions that generally relate to an inability to metabolize or fully digest a food component. Symptoms are typically isolated to the gastrointestinal tract, although other body systems may also be involved. Food intolerances are not life threatening but can produce significant discomfort, the severity of which is generally related to the amount of food consumed.

Specific digestive enzyme deficiencies or insufficiencies lead to an inability to metabolize or fully digest particular food components and are associated most often with gastrointestinal discomfort symptoms of bloating, flatulence, diarrhea, and abdominal pain or cramping. Lactose intolerance, the most common food intolerance, is characterized by a deficiency of lactase enzyme in the small intestine and results in a relative inability to metabolize lactose in dairy products. As a result of lactose malabsorption, the sugar moves through the gut without being digested. The symptoms of lactose intolerance result from hydrogen gas release due to bacterial

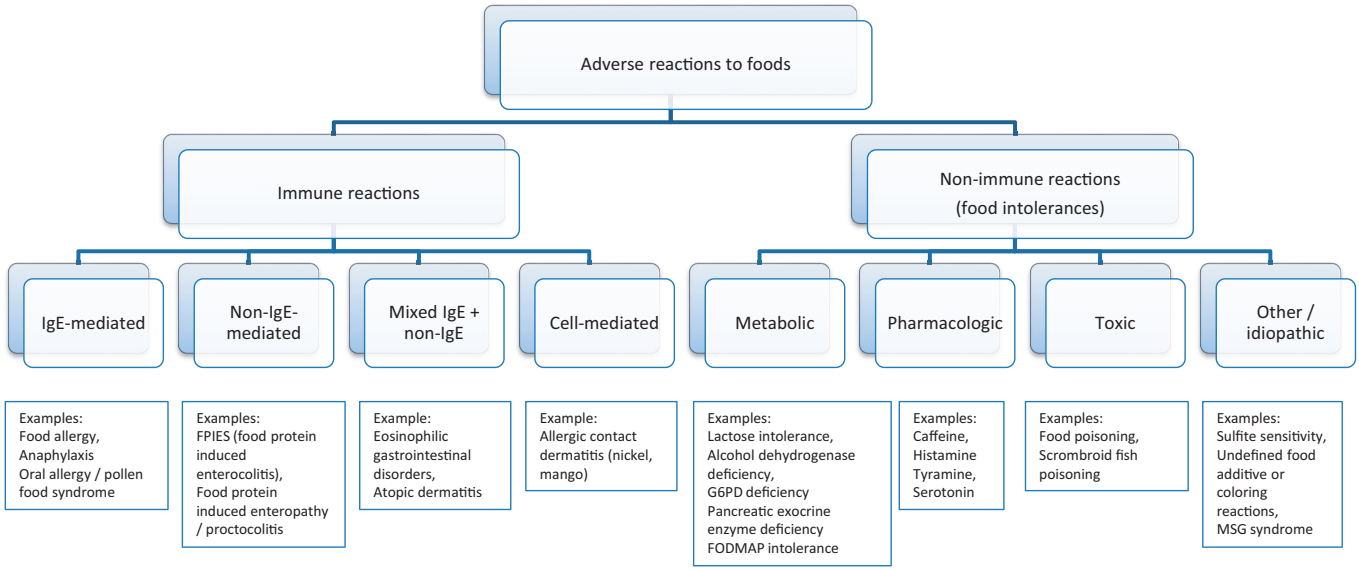

Figure 1. *Classification of adverse reactions to foods. Reactions are considered nonimmunologic or immunologic, with subtypes as pictured for each of these categories. Examples of each are provided.*

fermentation of lactose, and liquid drawn into the gut by the presence of sugars which leads to loose stools.[3]

Approximately 70% of the world's population has lactose intolerance to varying degrees. It usually develops gradually from childhood into adulthood as the enzyme is lost and is considered a normal variant of human metabolism rather than a disease. The prevalence varies by race and/or ethnicity, with very high rates (~90%) seen in Asians and lower rates reported for whites (5–20%). The onset of lactose intolerance also varies by race. Japanese and Chinese individuals who are lactose intolerant lose most of the enzyme in early childhood, whereas northern Europeans reach their lowest levels in their 20s.[4]

A transient form of lactose intolerance can result from a viral gastrointestinal infection that temporarily damages the lining of the gut, causing a short-term reduction in lactase enzyme. Lactose intolerance is generally a clinical diagnosis made based on an individual's reported symptoms related to ingestion of dairy. The symptoms may vary according to the amount of dairy product ingested and the lactose content of the dairy product. Intolerance of very-low–to–moderate doses of lactose is suggestive of irritable bowel syndrome (IBS).[5] Available diagnostic tests for lactose intolerance, including breath hydrogen testing or small bowel biopsy lactase enzyme assay, are reserved for cases in which the diagnosis is in question. Measures to treat lactose intolerance include avoidance of dairy, use of lactose-free substitute foods, or supplementation with replacement enzymes.

Deficiency of alcohol dehydrogenase leads to an inability to metabolize alcohol. Symptoms may include flushing and vomiting, and the problem is common in people of Asian descent. Symptoms of gastrointestinal intolerance can also develop in those who are unable to absorb certain sugars, such as "FODMAPs" which are short-chain fermentable carbohydrates, including fermentable oligosaccharides (found, for example, in wheat, garlic, and onion), disaccharides (*e.g.*, as lactose), monosaccharides (*e.g.*, fructose in various fruits, honey, and corn syrup), and polyols (*e.g.*, xylitol, mannitol, maltitol, and sorbitol, which are found in fruits and sweeteners). FODMAP intolerance often occurs in individuals who also have IBS.[6] Not all IBS is associated with FODMAP intolerance however, and, despite patient-perceived food-specific symptoms, the underlying pathophysiology of IBS does not have a clearly defined relationship to food.[7]

Certain enzyme deficiencies have more serious ramifications beyond mere gastrointestinal discomfort. Glucose-6-phosphate dehydrogenase deficiency, a genetic disorder, can present with acute hemolysis upon intake of certain foods or medications that precipitate oxidative injury to red blood cells. Cystic fibrosis, which is associated with pancreatic exocrine enzyme insufficiency, can result in an inability to digest fat and protein as well as malabsorption of fat-soluble vitamins A, D, E, and K. Physiologic manifestations of cystic fibrosis–related pancreatic insufficiency may include steatorrhea, failure to thrive, and secondary effects of vitamin deficiencies, such as coagulation defects and bone mineralization defects.[8]

Pharmacologic

Individuals can also experience nonimmunologic symptoms due to intrinsic pharmacologic effects of ingredients in food such as to caffeine, histamine,

tryptamine, tyramine, serotonin, and phenylethylamine. Individual sensitivity to these components also likely plays a role. The monosodium glutamine symptom complex characterized by headache, myalgia, diaphoresis, flushing, and chest heaviness, may be due to sensitivity to the amino acid neurotransmitter glutamate. Sulfiting agents used as preservatives in foods can provoke wheezing in a subset of individuals with severe asthma.[9] Individuals with migraine disorder may experience headaches or symptom attacks triggered by specific foods, including chocolate, caffeine, aspartame, monosodium glutamine, nitrites, and nitrates.[10]

Toxic

Nonimmunologic reactions can also occur due to direct toxic effects of foods. Bacterial food poisoning is a primary example and can produce gastrointestinal and neurologic manifestations. Scombroid poisoning is a unique form of food poisoning that results in symptoms that mimic allergic reactions. In scombroid poisoning, bacterial overgrowth due to spoilage of certain dark-meat fish such as tuna and mahi-mahi, results in an accumulation of histamine-like chemicals. Upon ingestion, excess histamine causes acute skin and gastrointestinal symptoms, including flushing, rash, headache, and diarrhea.

Other, Idiopathic, Unproven

For some individuals, ingestion of foods with high levels of natural histamine content, such as fermented foods, aged cheeses, processed meats, and wine, can cause symptoms that mimic IgE-mediated immunologic food reactions.[11] Intolerances to certain flavorings, food coloring, and additives are commonly reported; however, true allergies to these are rare and not well characterized.

FOOD ALLERGY

The term "food allergy" refers to adverse immunologic responses to food. The immunopathophysiology of food-allergic responses can be subdivided into IgE-mediated, non–IgE-mediated, mixed IgE- and non–IgE-mediated, and cell-mediated reactions all of which have characteristic symptom patterns and manifestations.[2]

IgE Mediated

In IgE-mediated food allergy, an individual first becomes "sensitized" to a particular food component, typically a protein, through the gut, skin, or respiratory tract, and produces allergen specific IgE that binds to IgE receptors on mast cells and basophils. On re-exposure, allergen binds and cross-links surface-bound IgE, leading to cell degranulation and release of chemical mediators that produce the physiologic symptoms of an acute allergic reaction (see "Pathophysiology of IgE-mediated food allergy"[12]). IgE-mediated food reactions are generally rapid in onset, occurring within minutes to hours of ingestion or exposure to a culprit food. In addition to the more common manifestations of IgE-mediated food allergy, additional food-triggered IgE-mediated syndromes can occur, including oral allergy syndrome, also known as pollen-associated food allergy syndrome, food-dependent exercise-induced anaphylaxis, delayed reactions to mammalian meat caused by sensitization to galactose-alpha-1,3-galactose, a carbohydrate, and others described in the "Clinical manifestations of IgE-mediated food allergy"[13] section in this Primer.

Mixed IgE and non–IgE Mediated

Eosinophilic gastrointestinal diseases and atopic dermatitis (AD) represent food allergic conditions that are manifestations of mixed IgE and non-IgE (cell mediated) mechanisms. Eosinophilic gastrointestinal diseases include eosinophilic esophagitis (EOE) and eosinophilic gastritis (EG)/eosinophilic gastroenteritis (EGE), and comprise features of both IgE- and non–IgE-mediated immune responses to foods (see "Food allergy and eosinophilic gastrointestinal disorders"[14]).

Although the exact immune mechanisms are uncertain, the inflammation in EOE and EG/EGE is characterized by eosinophilic infiltration of esophageal and gastric mucosa, respectively, and can present with reflux-like symptoms, abdominal pain, dysphagia, and food impactions. Clinical presentation differs, depending on age. EOE and EG/EGE are thought to be both IgE mediated and cell mediated, and a role for foods in the pathogenesis of EOE has been confirmed by clinical and histologic improvement that are observed with elimination and elemental diets for many patients with EOE, despite lack of a clear role for elimination diets for EG/EGE. Although distinct from standard IgE-mediated food allergy, IgE-sensitization and IgE-mediated food allergy are frequently seen in patients with EOE, and total IgE is often elevated in patients with EG/EGE.[15]

AD is a complex inflammatory condition of the skin that results from an impaired skin barrier, defective innate immune responses, and T helper 2 (T_H2) skewed adaptive immune responses. Exposure to food and environmental allergens can exacerbate acute eczematous flares.[16] Nonetheless, although there is a high prevalence of allergic disease among individuals with AD and IgE sensitization is common among children with AD, the direct role of food allergy in AD is controversial, and food-exacerbated AD may be present in only a subset of patients with AD (see "Food allergy and atopic dermatitis"[17]).

Non-IgE Mediated

Immunologic adverse reactions to foods for which there is no apparent role for IgE include food protein–induced enterocolitis syndrome, protein-induced enteropathy/proctocolitis, and celiac disease (see "Food protein–induced enterocolitis syndrome"[18] and "Food protein-

induced enteropathy and proctocolitis"[19]). Although allergic proctocolitis symptoms are isolated to the gastrointestinal tract, the other disorders have symptoms and signs beyond the gastrointestinal tract, as described further in those sections of the Primer. The hallmark symptoms of food protein–induced enterocolitis syndrome are gastrointestinal, although there are systemic manifestations as well. Celiac disease is not typically considered a food allergy and is a systemic disease with a number of distinct symptoms and clinical implications (*e.g.*, anemia, cancer risk), which are not elaborated on here.

Heiner syndrome is an extremely rare disorder attributed to non-IgE antibody and cellular responses to cow's milk, and results primarily in pulmonary hemorrhage and infiltrates, anemia, and failure to thrive in affected infants.[2] Allergic contact dermatitis is a form of eczema that results from cell-mediated reactions to chemical haptens. Foods, *e.g.*, mango, can trigger allergic contact dermatitis from topical exposure and may result in pruritus, erythema, papules, and edema.[20] Some chemicals in foods or metals in foods (nickel) have been identified as a cause of a systemic form of contact dermatitis.[21]

CONCLUSION

A general understanding of the non–immune-mediated and immune-mediated classification of adverse reactions to foods as well as recognition of subcategories of each provide a basic framework for assessment of an individual's diverse array of symptoms attributed to food. A deeper understanding of the etiology for these presentations facilitates the appropriate use of allergy testing and accurate diagnoses, suitable management and therapy, as well as informed patient education. The general classification presented here is subject to change as additional research improves the understanding of the pathophysiology of various adverse food reactions and their subtypes.

CLINICAL PEARLS

- Adverse food reactions to foods can be categorized as nonimmunologic (intolerance, not life threatening) or immunologic (food allergy, possibly life threatening).
- A careful history will aid the clinician in identifying whether the etiology of an adverse food reaction is nonimmunologic or allergic.
- Immunologic and nonimmunologic adverse reactions to food are associated with characteristic symptoms and chronicity, and differ with regard to severity and impacts on overall health; in contrast to nonimmunologic reactions, true IgE-mediated food-allergic reactions can be rapid in onset and life threatening.
- The recognition of typical signs and symptoms of various adverse food reactions guides the clinician in appropriate diagnosis, application of testing, management, and patient education.

REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. Allergy Clin Immunol. 2018; 141:41–58.
2. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010; 126(Suppl):S1–S58.
3. Zhao J, Fox M, Cong Y, et al. Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2010; 31:892–900.
4. Storhaug CL, Fosse SK, Fadnes LT. Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017; 2:738–746.
5. Zhu Y, Zheng X, Cong Y, et al. Bloating and distention in irritable bowel syndrome: the role of gas production and visceral sensation after lactose ingestion in a population with lactase deficiency. Am J Gastroenterol. 2013; 108:1516–1525.
6. Hayes PA, Fraher MH, Quigley EMM. Irritable bowel syndrome: the role of food in pathogenesis and management. Gastroenterol Hepatol (N Y). 2014; 10:164-174.
7. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome–etiology, prevalence and consequences. Eur J Clin Nutr. 2006; 60:667-672.
8. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. J Cystic Fibros. 2017; 16(Suppl):S70–S78.
9. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. J Allergy Clin Immunol. 1981; 68:26-32.
10. Martin VT, Behbehani MM. Toward a rational understanding of migraine trigger factors. Med Clin North Am. 2001; 85:911-941.
11. Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr. 2007; 85:1185–1196.
12. Shreffler W. Pathophysiology of IgE-mediated food allergy. J Food Allergy. 2020; 2:7–10.
13. Varshney P, Pongracic JA. Clinical manifestations of IgE-mediated food allergy. J Food Allergy. 2020; 2:22–25.
14. Brown-Whitehorn T, Spergel JM. Food allergy and eosinophilic gastrointestinal disorders. J Food Allergy. 2020; 2:39–43.
15. Yun MY, Cho YU, Park IS, et al. Eosinophilic gastroenteritis presenting as small bowel obstruction: a case report and review of the literature. World J Gastroenterol. 2007; 13:1758-1760.
16. Werfel T, Breuer K. Role of food allergy in atopic dermatitis. Curr Opin Allergy Clin Immunol. 2004; 4:379-385.
17. Banzon T, Leung DYM, Schneider LC. Food allergy and atopic dermatitis. J Food Allergy. 2020; 2:35–38.
18. Anvari S, Davis CM. Food protein–induced enterocolitis syndrome. J Food Allergy. 2020; 2:48–54.
19. Tam J. Food protein-induced enteropathy and proctocolitis. J Food Allergy. 2020; 2:55–58.
20. Hershko K, Weinberg I, Ingber A. Exploring the mango-poison ivy connection: the riddle of discriminative plant dermatitis. Contact Dermatitis. 2005; 52:3-5.
21. Veien NK. Systemic contact dermatitis. Int J Dermatol. 2011; 50:1445–1456. □