Clarifying the Hazy Concepts of Food Allergies and Sensitivities

Lauren Loeb, MD,[1] David C. Cangemi, MD,[1] Jacqueline D. Squire, MD,[2] and Brian E. Lacy, PhD, MD[1]

[1]Division of Gastroenterology & Hepatology, Mayo Clinic, Jacksonville, Florida

[2]Department of Allergic Diseases, Mayo Clinic, Jacksonville, Florida

Corresponding author:
Dr Lauren Loeb
Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
Tel: (904) 953-8433
Fax: (904) 953-2000
E-mail: Loeb.lauren@mayo.edu

Abstract: Food allergies, food sensitivities, and adverse reactions to food represent common reasons for gastroenterology and allergy referral. The epidemiology of these disorders is changing; food allergies are more common than previously thought, and there is a heightened sense of awareness about food sensitivities. Symptoms do not always accurately predict the underlying pathophysiology nor distinguish the underlying etiology. This may lead to unnecessary testing, which is often unrewarding and expensive. Myths and misconceptions about food allergies and sensitivities are common and may lead to unwarranted treatment using untested therapies. Importantly, a missed diagnosis of a true food allergy can have serious consequences. This article discusses the differences between food allergies and sensitivities, including their epidemiology, underlying pathophysiology, key symptoms, and diagnostic criteria, as well as their treatment options.

Keywords
Food allergies, food sensitivities, hypersensitivity reactions, gluten, oral food challenge, immunotherapy

Eating should be an enjoyable event. However, many people find that ingesting food causes abdominal discomfort, nausea, bloating, urgent diarrhea, or a variety of other symptoms, raising concerns that a food allergy is the root cause of their abdominal distress. Unfortunately, there are a number of myths and misconceptions about food allergies. For example, many patients and health care providers believe that food allergies are quite uncommon, although recent studies demonstrate that food allergies are more prevalent than in the past.[1] The reason for the change in the epidemiology is unclear, although a variety of theories have been proposed. One theory is that children are now raised in an overly clean environment (the hygiene hypothesis), limiting exposure to antigens early in life, and thus predisposing children to allergies later in life.[2] Other hypotheses include an increased intake of processed foods and the overuse of antibiotics, both of which can alter the gut microbiome, amplifying the likelihood of developing allergies.[3,4] Another misconception is that testing of hair or stool can diagnose a food allergy.[5] This is not only incorrect but also potentially dangerous if a true food allergy remains undiagnosed and untreated. Finally, many patients and providers mistakenly believe that food allergies are the same

Table 1. Common Food Allergies and Their Prevalence

	Children	Adults
Shellfish	0.1%	2%-3%
Peanuts	1%	0.6%-2%
Tree nuts[a]	0.5%	0.6%-1%
Fish	0.1%	0.4%-1%
Cow's milk	2.5%	0.3%-1%
Egg	1.5%	0.2%
Wheat	1%-3%	0.4%
Sesame	0.1%	0.1%
Soy	0.4%	0.4%

Adapted from Sicherer SH et al.[9]
[a]Tree nuts: walnuts, almonds, hazelnuts, pecans, cashews, pistachios.

Table 2. Common Food Sensitivities

Food chemicals[a]	Dietary sources
Glutamates	Tomato, avocado, pickled herring, cheese, stock cubes, yeast extract
Vasoactive amines (eg, histamine)	Wine, beer, ripe and ripened cheeses, cured and processed meat products, tinned fish
Salicylates	Coffee, tea, green apples, banana, lemon, nectarine, plums, grapes, grapefruit, tomato, carrots, cucumber, peas, herbs, spices
Caffeine	Coffee, tea, chocolate, cola drinks, energy drinks

[a]The table lists major offending food chemicals and dietary sources with high levels of these chemicals.

as a food sensitivity or intolerance. This article provides up-to-date information on adverse reactions to foods, with an emphasis on distinguishing food allergies from food sensitivities, highlighting symptoms, appropriate diagnostic testing, and treatment options.

Definitions

Immune-mediated Adverse Food Reactions

A food allergy is an immune-mediated adverse reaction to food. Food allergies most commonly present with skin involvement but can also affect the cardiovascular system and respiratory and gastrointestinal tracts.[6] Food allergies can be immunoglobulin E (IgE)-mediated (oral allergy syndrome, systemic anaphylaxis), non–IgE-mediated (protein-induced enterocolitis/enteropathy, eosinophilic proctitis, celiac disease), or mixed IgE- and non–IgE-mediated (eosinophilic esophagitis/gastritis/gastroenteritis).[7] Classic symptoms of food allergies include urticaria, angioedema, lip and palate pruritus, bronchospasm, laryngospasm, rhinorrhea, dysphagia, abdominal pain, emesis, diarrhea, or hypotension.[8] Symptoms occur reproducibly on exposure to the food and are absent during avoidance. The most common food allergens include shellfish, peanuts, tree nuts, fish, cow's milk, egg, wheat, sesame, and soy (Table 1).[9]

Nonimmune-mediated Adverse Food Reactions

Food sensitivities are nonimmune-mediated adverse reactions to food. Broadly speaking, food sensitivities can be stratified into host-independent and host-dependent based on differences in pathophysiology.[10] Host-independent food sensitivities may be caused by pharmacologic chemicals, such as glutamates, histamines, salicylates, and caffeine that are typically added to preserve or improve the appearance of certain foods (Table 2).[11] Host-dependent food sensitivities include enzyme or transport deficiencies, nonceliac gluten sensitivity, and nonspecific reactions such as functional and psychological disorders.[12] In contrast to food allergies, the severity of food sensitivities tends to be directly related to the amount of food ingested.[13] Although food sensitivities can involve multiple organ systems, the most commonly affected organ system is the gastrointestinal tract, resulting in symptoms of abdominal pain, bloating, distention, flatulence, and diarrhea.[7] The most common dietary sources that cause food sensitivity include wheat/gluten, dairy, fruits and vegetables, fats, spices, and caffeine.[11]

Other adverse food reactions that are nonimmune-mediated (but often classified separately as their own categories) are metabolic errors and toxic reactions. Metabolic errors include phenylketonuria, tyrosinemia, homocystinuria, galactosemia, and organic acidemia. Metabolic errors can present as a wide spectrum of symptoms, including neurologic dysfunction, psychiatric disorders, cardiovascular disease, constipation, cirrhosis, renal disease, and neutropenia.[14-18] Toxic reactions can result from bacterial toxins such as *Staphylococcus aureus,* aflatoxin, scombroid, ciguatera, and saxitoxin. Exposure to these toxins can result in headaches, nausea, vomiting, abdominal pain, diarrhea, hepatocellular carcinoma, paralytic respiratory failure, ataxia, and paresthesia.[19-21]

Epidemiology

As many as 6.5% to 13% of US adults self-report at least 1 food allergy.[22-24] It is important to recognize that

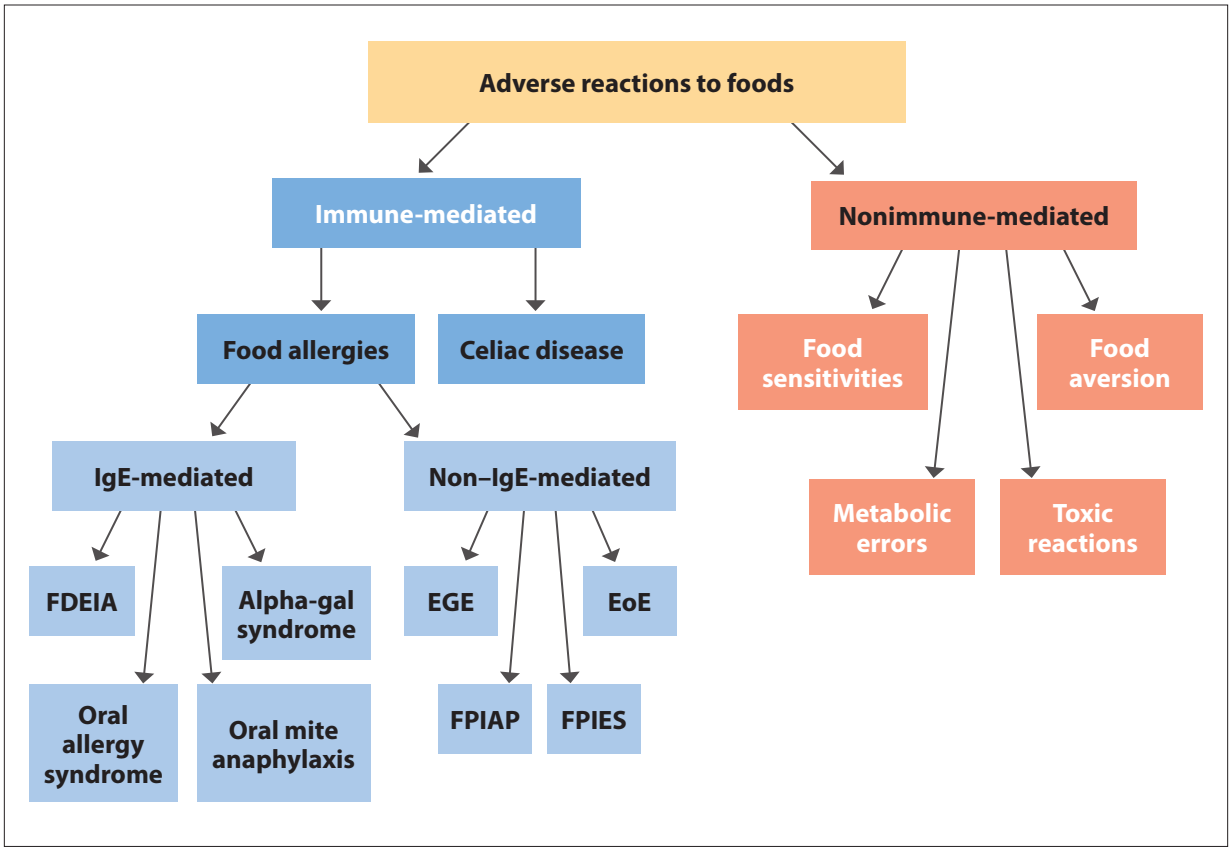

Figure. Adverse reactions to foods can be grouped into 5 broad categories, highlighted in white text.

EGE, eosinophilic gastroenteritis; EoE, eosinophilic esophagitis; FDEIA, food-dependent exercise-induced anaphylaxis; FPIAP, food protein-induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; IgE, immunoglobulin E.

epidemiologic research studies of food allergies are limited by different definitions of food allergies as well as variations in methodologies and the population studied. For example, some studies rely on a survey of self-reported food allergies, while other studies confirm the diagnosis with a medically supervised oral food challenge, the gold standard for diagnosis.[25] Additionally, some investigations are limited to children whose food allergies may resolve with age.[26] Interestingly, food allergies to cow's milk, soy, and wheat more commonly resolve with age, whereas those to peanuts, tree nuts, fish, and shellfish do not.[27]

Several national surveys in countries across the world have reported an increase in the prevalence of childhood food allergies between 1997 and 2011.[28-31] In the United States, the prevalence increased from 3.4% in 1997 to 5.1% in 2011.[32] Again, these data may be confounded by the reliance on self-reporting, which may reflect increases in recognition or awareness rather than a true increase in food allergies.[33] Similar to other atopic conditions, food allergies seem to be more prevalent in populations other than the White, non-Hispanic population.[34] A cross-sectional survey of 40,443 adults in the United States found food allergy rates to be significantly higher among those classified as other than White, non-Hispanic, even after adjusting for income, education level, and physician-diagnosed atopic conditions.[35]

In summary, multiple individual studies and systematic reviews confirm a significant prevalence of food allergies worldwide. Further double-blind, placebo-controlled oral food challenges are needed to establish confidence in food allergy prevalence, especially with regard to racial and ethnic differences.

Pathophysiology

Understanding adverse reactions to foods is essential in order to make the correct diagnosis and initiate proper treatment. Pathophysiologically, reactions to foods can be grouped into 5 broad categories: immune-mediated reactions, food sensitivities, toxic reactions, metabolic errors, and food aversion (Figure).

Immune-mediated Adverse Food Reactions

Food allergies are immune-mediated adverse reactions to food consisting of a loss of tolerance to a harmless substance. Food allergies are more common in atopic individuals, including those with asthma, eczema, allergic rhinitis, latex allergies, and medication allergies.[36] Most food allergies are IgE-mediated (type 1 hypersensitivity reactions). Symptoms of a food allergy occur reproducibly on exposure to the inciting food, and symptoms are absent during food avoidance. In a healthy individual without food allergies, type 1 regulatory T cells normally promote tolerance to allergens and help prevent food allergies from developing.[37] However, in atopic individuals and in genetically predisposed individuals, food allergens, which are typically small water-soluble proteins, trigger an inappropriate type 2 T-helper cell response. This causes mast cells, basophils, eosinophils, and IgE-secreting B cells to become sensitized. When an individual is reexposed to the same food allergen, the previously sensitized mast cells and basophils rapidly respond by degranulating and releasing a host of inflammatory mediators, including histamine, leukotrienes, cytokines, and prostaglandins. One well-studied IgE-mediated food allergy is allergy to peanuts,[38] which is present in approximately 0.6% to 2% of adults (Table 1). Less common IgE-mediated food allergies worth mentioning include red meat allergy (alpha-gal syndrome), food-dependent exercise-induced anaphylaxis, oral mite anaphylaxis (pancake syndrome), and oral allergy syndrome, which affects approximately 5% of the population.[39,40] The latter is a localized, not systemic, IgE-mediated response. Oral allergy syndrome develops as a result of cross-reactivity of pollen IgE with, most often, fruits and vegetables. Common examples include birch pollen with rosacea fruit (cherries, apples, peaches, pears) and ragweed with bananas, melons, and kiwis. Celiac disease, the subject of multiple reviews,[41,42] is a type IV hypersensitivity reaction involving a specific T-cell response to gliadin and glutenin found in wheat gluten.[43]

However, some food allergies are non–IgE-mediated, including cellular-mediated disorders of food protein-induced enterocolitis syndrome and food protein-induced allergic proctocolitis (FPIAP).[44,45] These food allergies are typically diagnosed in infancy; the most frequent triggers are cow's milk or soy milk, although several solid foods have been commonly implicated, including rice, oats, and egg.[46] Other non–IgE-mediated food allergies include eosinophilic esophagitis and eosinophilic gastroenteritis, both of which are identified in adults. Recent reviews have been published on these topics.[47] FPIAP, also known as cow's milk protein allergy, is a non–IgE-mediated food allergy associated with developing bloody stools, typically identified in infants and babies.[25,45,48] The exact mechanism for FPIAP is not known.

Food Sensitivities

Nonimmune-mediated food reactions constitute the vast majority of adverse reactions to food. These are generally categorized as a food intolerance or sensitivity. Three common food sensitivities, lactose found in dairy products, sucrose or table sugar, and fructose found in vegetables, arise when there are reduced levels or absence of a key enzyme (eg, lactase or sucrase-isomaltase) or limited ability of cotransporters to absorb sugar (ie, for fructose, GLUT5 and GLUT2).[11,49] Food sensitivities may develop as a result of a reaction to chemicals found within a food, as shown in Table 2. For example, dietary sources containing high levels of glutamate, such as tomatoes, avocado, pickled herring, and some cheeses, can elicit gastrointestinal symptoms in some patients, whereas beer, wine, chocolate, and ripened cheeses, which contain high levels of vasoactive amines, may cause gastrointestinal symptoms in other patients. A simple classification scheme for food sensitivities does not exist given the complexity of food with thousands of chemicals present in varying amounts.

Toxic Reactions

Toxic reactions to foods occur for a variety of reasons. Some of these reactions, such as scombroid, can mimic an allergic reaction. Scombroid develops after ingestion of large quantities of histamine, found in poorly stored dark meat fish (eg, tuna, mackerel, skipjack).[50] Ciguatera, the most common seafood poisoning worldwide, results from ingestion of the toxin ciguatoxin in contaminated fish (eg, barracuda, snapper) from coral reefs in tropical areas.[51] Aflatoxins, produced by a variety of molds, especially *Aspergillus,* may contaminate a variety of foodstuffs, including corn, wheat, millet, rice, and peanuts. Acute poisoning is exceptionally rare but may cause fever, nausea, vomiting, abdominal pain, and hepatitis. Limited doses are not harmful to humans but prolonged exposure to high doses may lead to stunted growth, hepatotoxicity, and liver cancer.[52] *Staphylococcus aureus* produces an endotoxin that can cause severe vomiting and explosive diarrhea after ingestion of contaminated foods, including dairy, poultry, meat, and meat products.[53]

Metabolic Errors

Metabolic errors that may cause adverse reactions to food include phenylketonuria, tyrosinemia, homocystinuria, galactosemia, and organic acidemia. These are uncommon metabolic disorders generally identified in infancy.

Food Aversion

The exact cause of food aversion, meaning a strong dislike to a particular food, is unknown. In some patients, this may represent a prior episode of nausea and vomiting inextricably linked with a specific food or a change in sensory

Table 3. Commonly Used Tests for Food Allergy

Diagnostic	Not evidence-based or diagnostic
Oral food challenge	Atopy patch
Serum-specific IgE	Broad food panel
Skin prick	Cytotoxic assays
	Electrodermal skin conductivity
	Facial thermography
	Hair/nail/gastric juice analyses
	Iris pigment evaluation
	Kinesiology
	Serum IgG antibodies

Ig, immunoglobulin.

processing; food aversion is more common in patients with autism spectrum disorder.[54] In other patients, this may arise concurrent with hormonal changes (ie, pregnant women with morning sickness). Patients with gastroparesis and functional dyspepsia may consciously or subconsciously restrict their diet because of symptoms of pain, discomfort, bloating, or nausea and vomiting that develop after eating certain foods. Similarly, many patients with irritable bowel syndrome dramatically restrict their diet owing to the development of gastrointestinal symptoms (eg, pain, bloating, urgent diarrhea) after eating certain foods. Food aversions are neither a toxic event nor an immune-mediated event. Treatment typically involves coordinated care with a dietitian and behavioral therapist.

Diagnosis

The diagnosis of a food allergy is based on a careful history and physical examination (PE); testing is supportive.[55] The classic presentation indicative of a food allergy includes immediate onset of symptoms (typically within 5-60 minutes) after ingestion; itching of the palate and lips; swelling of the lips, tongue, or mouth; rhinorrhea or periorbital edema; urticaria; laryngospasm or bronchospasm; gastrointestinal symptoms of dysphagia, nausea, vomiting, diarrhea, and abdominal pain; and life-threatening symptoms of hypotension and cardiovascular collapse.[56] If these symptoms are reported, it is incumbent on the clinician to ascertain important details about the event that may indicate a true food allergy. What was the relationship between the suspected food ingestion and the onset of symptoms? When did symptoms occur after food ingestion? What other foods/ingredients were present in the meal? What was the volume of the suspect food that was ingested? Were other potential cofactors present (eg, alcohol, anti-inflammatory agents, exercise, a concurrent illness)? Are other allergic diseases or comorbid conditions present (eg, allergic rhinitis, asthma, eczema)? Did the patient require an emergency room or urgent care visit for symptom evaluation? What tests were performed and what treatments were provided?

A PE should be performed to establish a baseline and to determine if there are conditions present that could either make the patient susceptible to food allergies (ie, asthma, allergic rhinitis) or could mimic a food allergy (eg, chronic urticaria, eczema, hereditary angioedema).[57,58] If both the history and PE are consistent with a food allergy, then the patient should be referred to an allergist for testing to confirm the diagnosis. Recommended testing and commonly seen unvalidated testing are provided in Table 3. The suspect food should be excluded from the diet until cleared to resume by the allergist.[3] It is critical to highlight that in a patient suspected of having an IgE-mediated food allergy, an oral food challenge should only take place in a setting equipped to deal with a possible anaphylactic reaction.[59] A skin prick test is used to support the presence of an IgE-mediated allergy. Skin prick tests are reasonably sensitive for patients with IgE-mediated allergies.[56,60] They should not be performed in patients on antihistamines (which should be stopped at least 5 days in advance) and should not be performed in patients with dermatographism or severe eczema. A positive test is generation of a wheal, at least 3 mm in diameter, within 15 to 30 minutes.[61] The negative predictive value for this test is high—approximately 90%.[62] Serum-specific IgE tests can be useful in patients with a strong history of a food allergy. It is important to note that skin prick and IgE testing are not considered screening tests and should only be performed in those with a history suggestive of IgE-mediated food allergy. Therefore, broad food panel testing is not recommended. Also, atopy patch testing is not standardized and not recommended.

Food sensitivities are diagnosed by taking a careful history and performing a PE, as noted previously, to exclude medical conditions that could mimic the sensitivity. Although there is some controversy regarding commercially available sensitivity testing, the majority of evidence indicates that IgG antibodies are not associated with reactions to food and, in fact, are protective against allergic reactions. Increasing IgG levels are found in patients with natural resolution of milk allergy and in patients undergoing oral immunotherapy (OIT).[63] It is important to educate patients that no validated test exists to diagnose most food sensitivities, except for lactose, fructose, and sucrase-isomaltose. Specifically, cytotoxic assays (adding whole blood to food), electrodermal tests to measure skin conductivity, iris pigment evaluation (iridology), muscle strength changes after food ingestion (kinesiology), facial thermography, and hair, nail, and gastric juice analysis are all unvalidated tests and should

not be performed. Data provided from these tests are scientifically unsound and potentially misleading; as well, testing can be expensive and cause distress in patients.

Treatment

Management of food allergies is based on a 2-pronged approach: avoidance and preparation. Both of these strategies depend on comprehensive patient education. Patients should be educated on interpreting labeled manufactured food products for advisory warnings of common food allergens.[64] Patients and their families should be familiar with the signs and symptoms of anaphylaxis and construct an emergency action plan.[65] Patients should educate pertinent personnel, such as teachers, caregivers of children, and staff at restaurants, of food allergies. Additionally, proper use of intramuscular (IM) epinephrine autoinjectors should be understood by the adult patient, caregivers of pediatric patients, and other close family members.

Once symptoms of anaphylaxis are recognized following exposure to a food allergen, IM epinephrine should be administered immediately. Early treatment with epinephrine within the first 6 minutes after allergen exposure has been shown to be more effective at improving edema, urticaria, bronchospasm, hypotension, and gastrointestinal distress, as well as preventing death, as compared to late administration defined as 20 or more minutes after exposure.[66] Epinephrine injection is given at a dose of 0.3 mg for patients greater than or equal to 30 kg (66 lb) or 0.15 mg for patients 15 to 30 kg (33 to 66 lb) and can be repeated as needed after 5 to 15 minutes.[67] Vigilance for refractory anaphylactic symptoms and prompt medical attention should be prioritized because of the chance of a biphasic reaction.[68] Recurrence of symptoms between 1 and 78 hours after resolution of the initial event, the biphasic reaction, can occur in 1% to 20% of patients.[69]

There are no alternative therapies to epinephrine; however, there are adjunctive therapies that can help ameliorate localized symptoms. Inhaled bronchodilators can improve bronchospasm recalcitrant to IM epinephrine. Importantly, bronchodilators do not impact airway edema and therefore are not a replacement for epinephrine. Antihistamines against histamine-type-1 receptors can help improve pruritus and urticaria.[70] However, the sedative effects of first-generation antihistamines may impair patient monitoring of anaphylactic symptoms. Second-generation antihistamines may improve dermatologic symptoms without the cognitive and psychomotor dampening associated with first-generation antihistamines.[71] Hypotension can be addressed by placing the patient in a recumbent position with the lower extremities elevated to optimize perfusion of vital organs.[72]

Allergen-specific immunotherapy (AIT) provides patients with an opportunity to minimize reaction severity to accidental exposure to food allergens.[73] Currently, 3 routes of allergen administration are under investigation as a treatment for food allergy: OIT, sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Whether by ingestion with OIT, held under the tongue for a period of time with SLIT, or dermatologic exposure with a patch with EPIT, the objective of each method is to provide desensitization via continuous allergen exposure.[74] In comparison to SLIT and EPIT, OIT allows exposure to significantly larger allergen doses to the point that patients may be able to tolerate gram amounts of allergenic foods.[75] However, OIT is associated with higher rates of adverse events, including skin, mucosal, and respiratory symptoms compared with SLIT and EPIT.[76] Currently, only OIT is available on a commercial basis, although access to this therapy is often limited for patients as it is not offered by all practicing allergists.

Although OIT, SLIT, and EPIT have established a role for desensitization in the management of food allergies, concern for durability of these therapies has been raised. A double-blind, randomized, placebo-controlled study of 55 children with egg allergy found that 75% of participants in the treatment arm achieved allergen desensitization after 22 months of OIT.[77] After 2 months without OIT, only 28% of participants in the treatment arm remained desensitized and passed the oral food challenge. Interestingly, those participants passed a subsequent oral food challenge 1 year later after discontinuing OIT. This suggests that the majority of patients will require long-term OIT to sustain desensitization; however, a minority of patients can achieve sustained tolerance after desensitization therapy with OIT.

Management of food sensitivities relies solely on avoidance. Again, this strategy depends on patient education on interpreting labeled manufactured food products for advisory warnings of common food allergens.[64] Because of the lack of immune reaction, ingestion of foods associated with adverse symptoms will not result in harm or sequelae.[78] Therefore, these foods can be ingested up to the point of abdominal pain, bloating, diarrhea, or other uncomfortable results. Importantly, patients should be screened for eating disorders such as avoidant/restrictive food intake disorder, a condition describing patients who restrict their diet owing to concerns of aversive consequences of eating.[79]

Conclusion

Food allergies are often a nebulous concept to both the public and health care providers. Given the global increase in the prevalence of food allergies, the need for further research and education on the various presentations,

diagnostic modalities, and treatment strategies for food allergies is critical. Importantly, the potential harm to patients associated with deficiencies in knowledge of the evidence-based methods of identification and management of food allergies presents a significant risk of compounding the already heavy burden of affected individuals. Repercussions of incomplete understanding of the diagnostic process are particularly hazardous, as true food allergies may be missed and left untreated. Failure to delineate a food allergy from a food sensitivity can further impair quality of life, as inappropriate interventions such as hair or stool testing and elimination diets can result in increased financial costs or nutritional concerns, respectively.

Historically, the foundation of food allergy and sensitivity management has been avoidance. Although this approach can be successful, it requires persistent vigilance that can significantly impact quality of life, as inadvertent ingestion of food allergens is always possible. AIT with oral, sublingual, and epicutaneous desensitization methods has addressed a previously unmet need in the management of food allergies. AIT serves as a tool to help patients prevent anaphylaxis from accidental exposure. However, strict adherence to AIT is required to gain protection from food allergens. Additionally, questions of AIT durability are still being investigated.

The impact of food allergies and sensitivities on patients and the health care system warrants further robust investigation into diagnostic and therapeutic techniques that can further optimize patient outcomes.

Disclosures

The authors do not have any relevant conflicts of interest to disclose.

References

1. Warren CM, Sehgal S, Sicherer SH, Gupta RS. Epidemiology and the growing epidemic of food allergy in children and adults across the globe. *Curr Allergy Asthma Rep*. 2024;24(3):95-106.
2. Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J. Too clean, or not too clean: the hygiene hypothesis and home hygiene. *Clin Exp Allergy*. 2006;36(4):402-425.
3. Vlieg-Boerstra B, Groetch M, Vassilopoulou E, et al. The immune-supportive diet in allergy management: a narrative review and proposal. *Allergy*. 2023;78(6):1441-1458.
4. Okoshi K, Sakurai K, Yamamoto M, et al; Japan Environment and Children's Study group. Maternal antibiotic exposure and childhood allergies: the Japan Environment and Children's Study. *J Allergy Clin Immunol Glob*. 2023;2(4):100137.
5. Riggioni C, Ricci C, Moya B, et al. Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy. *Allergy*. 2024;79(2):324-352.
6. Burks AW. Peanut allergy. *Lancet*. 2008;371(9623):1538-1546.
7. Gargano D, Appanna R, Santonicola A, et al. Food allergy and intolerance: a narrative review on nutritional concerns. *Nutrients*. 2021;13(5):1638.
8. Anvari S, Miller J, Yeh CY, Davis CM. IgE-mediated food allergy. *Clin Rev Allergy Immunol*. 2019;57(2):244-260.
9. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S116-S125.
10. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. 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(6 suppl):S1-S58.
11. Lomer MC. Review article: the aetiology, diagnosis, mechanisms and clinical evidence for food intolerance. *Aliment Pharmacol Ther*. 2015;41(3):262-275.
12. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146(1):67-75.e5.
13. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol*. 2010;126(6):1105-1118.
14. van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria. *Nat Rev Dis Primers*. 2021;7(1):36.
15. Barone H, Bliksrud YT, Elgen IB, et al. Tyrosinemia type 1 and symptoms of ADHD: biochemical mechanisms and implications for treatment and prognosis. *Am J Med Genet B Neuropsychiatr Genet*. 2020;183(2):95-105.
16. Hasan T, Arora R, Bansal AK, Bhattacharya R, Sharma GS, Singh LR. Disturbed homocysteine metabolism is associated with cancer. *Exp Mol Med*. 2019;51(2):1-13.
17. Demirbas D, Coelho AI, Rubio-Gozalbo ME, Berry GT. Hereditary galactosemia. *Metabolism*. 2018;83:188-196.
18. Altun I, Kiykim A, Zubarioglu T, et al. Altered immune response in organic acidemia. *Pediatr Int*. 2022;64(1):e15082.
19. Abril AG, Villa TG, Barros-Velázquez J, et al. *Staphylococcus aureus* exotoxins and their detection in the dairy industry and mastitis. *Toxins (Basel)*. 2020;12(9):537.
20. Rushing BR, Selim MI. Aflatoxin B1: a review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. *Food Chem Toxicol*. 2019;124:81-100.
21. Thottumkara AP, Parsons WH, Du Bois J. Saxitoxin. *Angew Chem Int Ed Engl*. 2014;53(23):5760-5784.
22. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open*. 2019;2(1):e185630.
23. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *J Allergy Clin Immunol*. 2013;132(5):1216-1219.e5.
24. Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. *Allergy Asthma Proc*. 2015;36(6):458-467.
25. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133(2):291-307.
26. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *J Allergy Clin Immunol*. 2010;125(3):683-686.
27. Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129(4):906-920.
28. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125(6):1322-1326.
29. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatr Int*. 2010;52(5):820-824.
30. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol*. 2011;127(3):623-30.e1.
31. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. *Ann Allergy Asthma Immunol*. 2014;112(3):222-229.e3.
32. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;(121):1-8.
33. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr*. 2011;158(4):578-583.e1.
34. Warren CM, Jiang J, Gupta RS. Epidemiology and burden of food allergy. *Curr Allergy Asthma Rep*. 2020;20(2):6.
35. Hultquist H, Dyer A, Jiang J, Gupta R, Warren C. Phenotypic characterization of childhood- and adult-onset food allergy among adults in the United States. *J Allergy Clin Immunol Glob*. 2022;1(4):257-264.
36. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. *Gastroenterology*. 2015;148(6):1120-31.e4.
37. Noval Rivas M, Chatila TA. Regulatory T cells in allergic diseases. *J Allergy Clin Immunol*. 2016;138(3):639-652.
38. Tirumalasetty J, Barshow S, Kost L, et al. Peanut allergy: risk factors, immune mechanisms, and best practices for oral immunotherapy success. *Expert Rev Clin*

Immunol. 2023;19(7):785-795.
39. Lee CJ, McGill SK. Food allergies and alpha-gal syndrome for the gastroenterologist. *Curr Gastroenterol Rep*. 2023;25(2):21-30.
40. Unhapipatpong C, Julanon N, Krikeerati T, Vichara-Anont I, Sompornrattanaphan M. Adult IgE-mediated food allergy is on the rise: a review of phenotypes, pathophysiologic mechanisms, diagnosis, and advances in management. *Asian Pac J Allergy Immunol.* 2022;40(4):308-320.
41. Jansson-Knodell CL, Rubio-Tapia A. Gluten-related disorders from bench to bedside. *Clin Gastroenterol Hepatol.* 2024;22(4):693-704.e1.
42. Silvester JA, Therrien A, Kelly CP. Celiac disease: fallacies and facts. *Am J Gastroenterol*. 2021;116(6):1148-1155.
43. Hudec M, Riegerová K, Pala J, Kútna V, Černá M, O Leary VB. Celiac disease defined by over-sensitivity to gliadin activation and superior antigen presentation of dendritic cells. *Int J Mol Sci.* 2021;22(18):9982.
44. Hartono S, Zidan E, Sitaula P, Brooks JP. Pearls and pitfalls in food protein-induced enterocolitis syndrome (FPIES). *Allergy Asthma Proc*. 2023;44(5):368-373.
45. Mennini M, Fiocchi AG, Cafarotti A, et al. Food protein-induced allergic proctocolitis in infants: literature review and proposal of a management protocol. *World Allergy Organ J.* 2020;13(10):100471.
46. Agyemang A, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a comprehensive review. *Clin Rev Allergy Immunol.* 2019;57(2):261-271.
47. Low EE, Dellon ES. Review article: emerging insights into the epidemiology, pathophysiology, diagnostic and therapeutic aspects of eosinophilic oesophagitis and other eosinophilic gastrointestinal diseases. *Aliment Pharmacol Ther*. 2024;59(3):322-340.
48. Burris AD, Burris J, Järvinen KM. Cow's milk protein allergy in term and preterm infant: clinical manifestations, immunologic pathophysiology, and management strategies. *Neoreviews.* 2020;21(12):e795-e808.
49. Viswanathan L, Rao SSC. Intestinal disaccharidase deficiency in adults: evaluation and treatment. *Curr Gastroenterol Rep.* 2023;25(6):134-139.
50. Thomas EG, Thomas DJ. Mimics of allergy and angioedema. *Immunol Allergy Clin North Am.* 2023;43(3):553-568.
51. Mullins ME. Ciguatera fish poisoning in the age of discovery and the age of enlightenment. *Clin Toxicol (Phila).* 2022;60(3):392-396.
52. Kumar P, Mahato DK, Kamle M, Mohanta TK, Kang SG. Aflatoxins: a global concern for food safety, human health and their management. *Front Microbiol*. 2017;7:2170.
53. Argudín MA, Mendoza MC, Rodicio MR. Food poisoning and *Staphylococcus aureus* enterotoxins. *Toxins (Basel).* 2010;2(7):1751-1773.
54. Cermak SA, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. *J Am Diet Assoc*. 2010;110(2):238-246.
55. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. 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(6)(suppl):S1-S58.
56. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al; EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy.* 2014;69(8):1008-1025.
57. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V; EPAAC Study Group. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy*. 2008;38(1):161-168.
58. Niggemann B, Reibel S, Roehr CC, et al. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol*. 2001;108(6):1053-1058.
59. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. *J Allergy Clin Immunol*. 2009;123(6)(suppl):S365-S383.
60. Breuer K, Heratizadeh A, Wulf A, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy*. 2004;34(5):817-824.
61. Peters RL, Gurrin LC, Allen KJ. The predictive value of skin prick testing for challenge-proven food allergy: a systematic review. *Pediatr Allergy Immunol*. 2012;23(4):347-352.
62. Tripodi S, Businco AD, Alessandri C, Panetta V, Restani P, Matricardi PM. Predicting the outcome of oral food challenges with hen's egg through skin test end-point titration. *Clin Exp Allergy.* 2009;39(8):1225-1233.
63. Kanagaratham C, El Ansari YS, Lewis OL, Oettgen HC. IgE and IgG antibodies as regulators of mast cell and basophil functions in food allergy. *Front Immunol*. 2020;11:603050.
64. Muraro A, Hoffmann-Sommergruber K, Holzhauser T, et al; EAACI Food Allergy and Anaphylaxis Guidelines Group. EAACI Food Allergy and Anaphylaxis Guidelines. Protecting consumers with food allergies: understanding food consumption, meeting regulations and identifying unmet needs. *Allergy*. 2014;69(11):1464-1472.
65. Pistiner M, Mendez-Reyes JE, Eftekhari S, et al. Factors associated with epinephrine use in the treatment of anaphylaxis in infants and toddlers. *J Allergy Clin Immunol Pract.* 2024;12(2):364-371.e1.
66. Ho MH, Wong WH, Chang C. Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol*. 2014;46(3):225-240.
67. EpiPen and EpiPen Jr. Prescribing information. Meridian Medical Technologies; 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019430Orig1s106Lbl.pdf. Accessed August 22, 2024.
68. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;327(6):380-384.
69. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol*. 2005;95(3):217-226.
70. Delli Colli L, Al Ali A, Gabrielli S, et al. Managing anaphylaxis: epinephrine, antihistamines, and corticosteroids: more than 10 years of Cross-Canada Anaphylaxis REgistry data. *Ann Allergy Asthma Immunol.* 2023;131(6):752-758.e1.
71. Simons FE. Advances in H1-antihistamines. *N Engl J Med.* 2004;351(21):2203-2217.
72. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol.* 2003;112(2):451-452.
73. Özdemir PG, Sato S, Yanagida N, Ebisawa M. Oral immunotherapy in food allergy: where are we now? *Allergy Asthma Immunol Res.* 2023;15(2):125-144.
74. Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol.* 2016;137(4):973-982.
75. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. *Nat Rev Immunol*. 2016;16(12):751-765.
76. Feuille E, Nowak-Wegrzyn A. Allergen-specific immunotherapies for food allergy. *Allergy Asthma Immunol Res.* 2018;10(3):189-206.
77. Burks AW, Jones SM, Wood RA, et al; Consortium of Food Allergy Research (CoFAR). Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. 2012;367(3):233-243.
78. Hon E, Gupta SK. Gastrointestinal food allergies and intolerances. *Gastroenterol Clin North Am*. 2021;50(1):41-57.
79. Werlang ME, Sim LA, Lebow JR, Lacy BE. Assessing for eating disorders: a primer for gastroenterologists. *Am J Gastroenterol*. 2021;116(1):68-76.