

Food Allergies and Intolerances: A Clinical Approach to the Diagnosis and Management of Adverse Reactions to Food

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Food allergy is an aberrant immunological response to food antigen, which can result in potentially life-threatening reactions. It is often challenging to differentiate food allergy from other adverse reactions to food because their presentations can be indistinguishable. The purpose of this article is to give an overview of the classification, evaluation, and management of adverse food reactions, key differentiating features of food allergy, roles and limitations of various food allergy testing, and promising areas of emerging research. Case studies are used to highlight some of the clinical pearls in diagnosing and managing food-related diseases.

Keywords: Irritable Bowel Syndrome; Nonceliac Gluten Sensitivity; FODMAP; Food Allergy Testing.

Over the last 2 decades, up to 20% of the population in industrialized nations have reported an abnormal physical response to food ingestion, also known as an adverse reaction to food (ARF).¹⁻³ While such responses may be due to immunologic or nonallergic processes, the underlying etiology may be indistinguishable to both patients and providers. In a meta-analysis of patients reporting adverse reactions to food, 35% of subjects self-reported food allergy (FA), while only 3.5% of subjects reached a diagnosis of food allergy confirmed by oral food challenge testing.⁴⁻⁶ Owing to the potentially life-threatening reactions in a subset of patients with food allergies, practitioners must be able to reliably distinguish between the various forms of ARFs. Here, we will cover common clinical scenarios and the approach to management.

CASE 1

A 20-year-old male patient with a history of eczema presents with complaints of hives and diarrhea after eating soy-based products. He shares results from an online company offering IgG food allergy testing and mediator release testing. The tests were positive for multiple foods, which he is struggling to eliminate from his diet. How would you advise him?

Approach to the patient

The patient's reproducible symptoms of hives and diarrhea, shortly after ingestion of soy, are concerning for a

possible IgE-mediated allergy to soy. Although the commercially available mediator release testing showed positivity to multiple foods, this test is not currently recommended for use, and without symptoms, the test results may be reflective of allergen sensitization without food allergy.⁷ He should be referred to a board-certified allergist.

Food allergy

The term food allergy refers to the immunologically driven development of adverse symptoms after ingestion of a food antigen.⁸ Historically, firm prevalence data have been lacking. However, commensurate with most allergic conditions, the incidence of food allergies appears to be increasing worldwide in recent years, with the prevalence of food allergy in both adults and children now reported to be about 10%.^{4,9} Ninety percent of food allergies are attributed to 8 foods: milk, eggs, peanuts, tree nuts, fish, shellfish, wheat, and soy.¹⁰ Over time, a subset of children develop tolerance to milk, egg, wheat, and soy by adolescence, and can consume the previously allergenic food without symptoms. Unfortunately, peanut, tree nut, and seafood allergies typically persist.¹¹ While the literature on the natural history of adult food allergies is limited, a retrospective study of 171 cases of adult onset food allergy noted peak age of onset in the 30s, with shellfish, tree nut, fish, and soy being the most common allergies.¹²

Pathophysiology of IgE-mediated food allergies. In a healthy state, the gut must absorb beneficial nutrients, while guarding against potentially harmful toxins and foreign proteins. The innate immune system and local mechanisms serve as a first line of defense via digestive enzymes, stomach acid, IgA secretion, epithelial tight junctions, and antimicrobial peptides, such as defensins and cathelicidins.^{13,14} For the <2% of proteins absorbed

Abbreviations used in this paper: ARF, adverse reaction to food; DC, dendritic cell; EoE, eosinophilic esophagitis; FA, food allergy; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IL, interleukin; MCAS, mast cell activation syndrome; NCGS, nonceliac gluten sensitivity; NCWS, nonceliac wheat sensitivity; OAS, oral allergy syndrome; sIgE, serum IgE; SPT, skin prick testing.

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in allergenic form, the immune response is naturally dampened by a process termed oral tolerance. After ingestion and digestion of food, gut epithelial cells transport peptides to the mucosa or mucosal dendritic cells (DCs) directly sample the antigen. DCs then present the antigen on major histocompatibility complex class II to naïve T cells, in which expression of co-stimulatory molecules determines the immune response. However, intestinal antigen presenting cells have relatively low expression of co-stimulatory molecules such as CD80 and CD86, which interact with CD28 on T cells.¹⁵ Without further costimulatory proteins, antigen presentation through major histocompatibility complex class II proteins induces T cell anergy or deletion, thus leading to the hyporesponsiveness of the gut immune system. Several T cell subtypes contribute to downregulation of both immune responses. For instance, Th3 cells secrete transforming growth factor β , which promotes IgA production in B cells and Tr1 cells secrete IL-10, which promotes antigen-specific anergy in T cells.^{16,17}

In allergic responses, DCs and epithelial cells begin to express costimulatory molecules and prime lymphocytes for cytokine-producing Th2 effector cells or IgE-producing plasma cells. The immune response and Th1/Th2 balance varies depending on the form of co-stimulation, type of DCs involved and cytokine response. For example, CD80/CD28 co-stimulation and myeloid DCs favor Th1 responses, while CD86/CD28 co-stimulation and lymphoid DCs favors Th2 type responses. Several cytokines including IL-13 and IL-4 enhance the switch from IgA production to IgE synthesis.^{18,19} Food-specific IgE antibodies bind to receptors on mast cells that crosslink to adjacent receptor-bound IgE antibodies. At sufficient levels and duration, this binding stimulates the release of histamines, cytokines, and other inflammatory molecules that lead mast cells to play an instrumental role in the allergic response.²⁰ The loss of oral tolerance, along with changes in mucosal barriers and the gut microbiome, allows for immunologic hypersensitivity and allergic reactions via IgE-mediated, non-IgE-mediated, or mixed mechanisms.

Symptoms. Classically, IgE-mediated hypersensitivity reactions involve the immediate onset of symptoms such as cough, chest tightness, wheezing, hives, nausea, vomiting, diarrhea, bloating, dermatitis, angioedema, and life-threatening anaphylaxis (Table 1). Up to 50% of affected patients manifest primarily with gastrointestinal (GI) symptoms. Of these symptoms, immediate vomiting is the most common GI symptom for IgE-mediated reactions.²¹

Diagnosis. Identifying the patient with food allergy can be challenging, as symptoms may be nonspecific and causality difficult to establish. A thorough history is needed to guide further testing and exclude alternative diagnoses. Relevant factors to assess include: symptoms and suspected allergen, number of occurrences, quantity of food ingested, method of food preparation, relationship to exercise, relationship to alcohol

ingestion, duration of symptoms, presence of symptoms without food ingestion, and proximity of symptoms to exposure.

IgE-mediated food allergies typically present within minutes of ingestion, whereas food intolerances may present hours later. Eczema exacerbation may be seen hours after ingestion of a food allergen.²² Alpha-gal (ie, galactose-alpha-1,3-galactose) allergy, discussed later in the paper, may present with symptoms 3–6 hours after meat ingestion, several months after a tick bite.^{23,24} If symptoms are not concerning for a life-threatening reaction, a food diary or allergen-specific elimination diet followed by reintroduction or provocation can be considered in order to establish a correlative relationship. This is different from an oral challenge, which is allergist-guided and discussed later in the paper.

FA should be considered in patients with IgE-mediated symptoms, adults with eosinophilic esophagitis (EoE) and select older children with moderate to severe atopic dermatitis, EoE, or enteropathy because these are associated with food allergy and early sensitization.^{25,26} In addition, studies suggest that higher suspicion for food allergy may be warranted in patients with eosinophilic GI disorder or inflammatory bowel disease.^{27,28} There is no evidence suggesting that the prevalence of food allergy is higher in patients with celiac disease.²⁹ When attempting to distinguish between a food allergy and food intolerance, respiratory, cutaneous, ocular, and cardiovascular symptoms are more suggestive of an allergic process and should prompt further workup. Once a food allergy is suspected by history, patients should be referred to a board-certified allergist for further evaluation.

Available allergy testing. Numerous food allergy tests are now available online via direct-to-consumer advertising. However, many of these tests are costly and have limited supporting evidence. The double-blinded oral food challenge is the gold standard for diagnosis and challenges the patient with escalating doses of the suspected food allergen while monitoring for clinical symptoms. However, the test is not readily available, is often expensive and may lead to severe reactions. In 2010, the National Institute of Allergy and Infectious Diseases released guidelines for food allergy diagnosis and management.³⁰ In accordance with these guidelines, our allergy practice assesses the risk of reaction based on clinical history, allergen-specific IgE testing, or skin prick testing (SPT). If the risk of reaction is moderate, we will perform a supervised oral challenge for definitive diagnosis. If the risk is very low, we may recommend the patient to reintroduce suspected trigger foods at home. Other available tests are not recommended by the National Institute of Allergy and Infectious Diseases guidelines due to lack of standardization or lack of validation. These include intradermal tests, total serum IgE, allergen-specific IgG or IgG4, hair mineral analysis, applied kinesiology, electrodermal test, facial thermography, and endoscopic allergen provocation (Table 2).

Table 1. Symptoms of Adverse Reactions to Food by System

Disease	Signs/Symptoms	Crohn's	UC	IBS	SIBO	GERD	Celiac	EoE	FPIES	OAS	IgE—Food Allergy
Gastrointestinal	Abdominal pain	X	X	X	X	X	X	X	X		X
	Bloating			X	X		X		X		X
	Blood in stool	X	X								
	Chest pain					X		X			X
	Constipation			X							
	Diarrhea	X	X	X	X		X		X		X
	Dysphagia	X				X		X			
	Fecal incontinence	X	X								X
	Fecal urgency	X	X								X
	Flatulence	X	X	X	X		X				
	Food impaction							X			
	Heartburn/reflux					X		X			
	Nausea/vomiting	X				X		X	X		X
	Regurgitation					X		X			
Skin	Angioedema/urticaria										X
	Pruritus										X
	Oral ulcers	X	X								
	Oral itching + swelling									X	X
	Ocular pruritus/periorbital edema										X
	Nasal congestion/rhinorrhea/sneezing										X
	Wheezing, dyspnea										X
Miscellaneous	Hypotension		X						X		X
	Fatigue	X	X				X		X		
	Weight loss/FTT	X	X				X	X	X		
	Joint pain	X	X				X				

EoE, eosinophilic esophagitis; FPIES, food protein-induced enterocolitis syndrome; FTT, ●●●; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; OAS, oral allergy syndrome; SIBO, small intestinal bacterial overgrowth; UC, ulcerative colitis.

However, a recent study has shown that endoscopic allergen provocation is a promising test for esophageal sensitization in patients with EoE and may deserve further exploration.³¹

As a rule, the diagnosis of food allergy requires both the presence of symptoms and confirmatory testing. Allergen sensitization is defined as the presence of allergen-specific serum IgE (sIgE) and can be measured directly in serum or indirectly by wheal formation. Increasing wheal size or sIgE levels may correlate with likelihood of allergy; however, a positive test result may indicate allergen sensitization without true food allergy.^{30,32} The absence of correlating symptoms renders testing nondiagnostic. Such disparate findings should trigger alternative diagnoses, such as food intolerance,

non-IgE-mediated allergies, or alternative allergens (Figure 1).

Non-IgE-mediated food allergies. It is important to note that the term *food allergy* is often synonymous with IgE-mediated allergies. However, non-IgE-mediated reactions, namely EoE, eosinophilic GI disorder, and celiac disease, have entered the spotlight over the past few decades and may present with more chronic and less temporally related symptoms. Similarly, food protein-induced allergic proctocolitis and food protein-induced enterocolitis syndrome are non-IgE mediated, mixed reactions that occur in children. Of these processes, the role of allergy testing has recently been studied in EoE. In one study, up to 60% of EoE patients tested had a positive sIgE to food and delayed

Table 2. Available Food Allergy Testing

Test	How It Works	Pros	Cons
Recommended			
Oral food challenge	Oral challenge with escalating allergen dose until response seen	Double-blind study is gold standard	Expensive, inconvenient, potential severe allergic reaction
Skin prick test	Allergen introduced subcutaneously Detects presence of sIgE bound to subcutaneous mast cells	High sensitivity, high negative predictive value	Low positive predictive value, low specificity
Allergen-specific IgE	Fluorescent enzyme-labeled antibody assay measuring sIgE	Absolute sIgE levels may correlate directly with likelihood of clinical reaction	Results from different assays may not be comparable More expensive
Patch testing	Allergen containing chambers lined on adhesive tape strips applied to intact skin and reaction checked 48–72 h later	May be useful for evaluation for triggers for EoE but not FA in EoE	Used primarily in research settings Variable sensitivity and specificity
Elimination diet	Elimination of 6 foods: eggs, soy, cow's milk, wheat, seafood, peanut/tree nuts	Can be therapeutic and diagnostic in EoE	Can lead to nutritional deficiency if used long term
Not recommended			
Intradermal tests	Intradermal injection of food allergen	Higher sensitivity than SPT for IgE-mediated FA	Not performed due to higher risk of systemic adverse effects (ie, anaphylaxis)
Total serum IgE	Detects IgE	N/A	Insufficient sensitivity and specificity
Unvalidated			
Allergen-specific IgG	Detects IgG, which is marker of exposure (and also tolerance) to food	N/A	High false positive rate May not be elevated in patients with true IgE allergy

Uncommon tests are basophil histamine release, electrodermal test, facial thermography, lymphocyte stimulation, gastric juice analysis, endoscopic allergen provocation, hair mineral analysis, and applied kinesiology.
EoE, eosinophilic esophagitis; FA, food allergy; N/A, not applicable; sIgE, serum IgE.

reactions to food antigens by atopy patch tests.³³ In our allergy practice, we do an empirical food elimination diet rather than SPT or patch test–guided elimination. However, a recent technical review on the management of patients with EoE indicated that allergy test–guided elimination diet may be considered within the context of other management options.³⁴

Uncommon forms of food allergies. Uncommon forms of food allergies, namely meat allergy and food-dependent exercise-induced anaphylaxis, may go unrecognized by the gastroenterologist due to a lack of familiarity. Alpha-gal syndrome is a recently described, tick-induced allergy to red meat and innards. Transmitted by the Lone Star tick, alpha-gal is a molecule known to be immunogenic in humans. Upon ingestion of red meat, sensitized patients develop a type I reaction to alpha-gal due to glycan-specific IgG and IgE responses.^{23,35} Prevalence of IgE sensitization to alpha-gal has been reported to be up to 20% in tick endemic populations in regions such as Virginia, North Carolina,

and Tennessee.^{24,36,37} However, there is no prevalence data of true meat allergy in the United States.

Food-dependent exercise induced anaphylaxis is rare and manifests when physical exertion takes place within a few hours of food allergen ingestion. Symptoms typically do not occur in the absence of exercise.³⁸ To date, the pathophysiology remains largely unknown, but has been speculated to be the result of mast cell degranulation with alterations in plasma pH and blood flow redistribution.³⁹

Oral allergy syndrome (OAS) is a hypersensitivity to plant-based foods, typically presenting with oropharyngeal itching, tingling, or swelling. It is the most common form of food allergy, with an estimated prevalence of 5%–8%.⁴⁰ In OAS, cross-reactivity with pollen protein in a previously sensitized patient induces an allergic response immediately after ingestion of a food allergen. Symptoms typically occur after the ingestion of raw fruits or vegetables and rarely include anaphylaxis. The involved protein is heat labile; therefore, patients

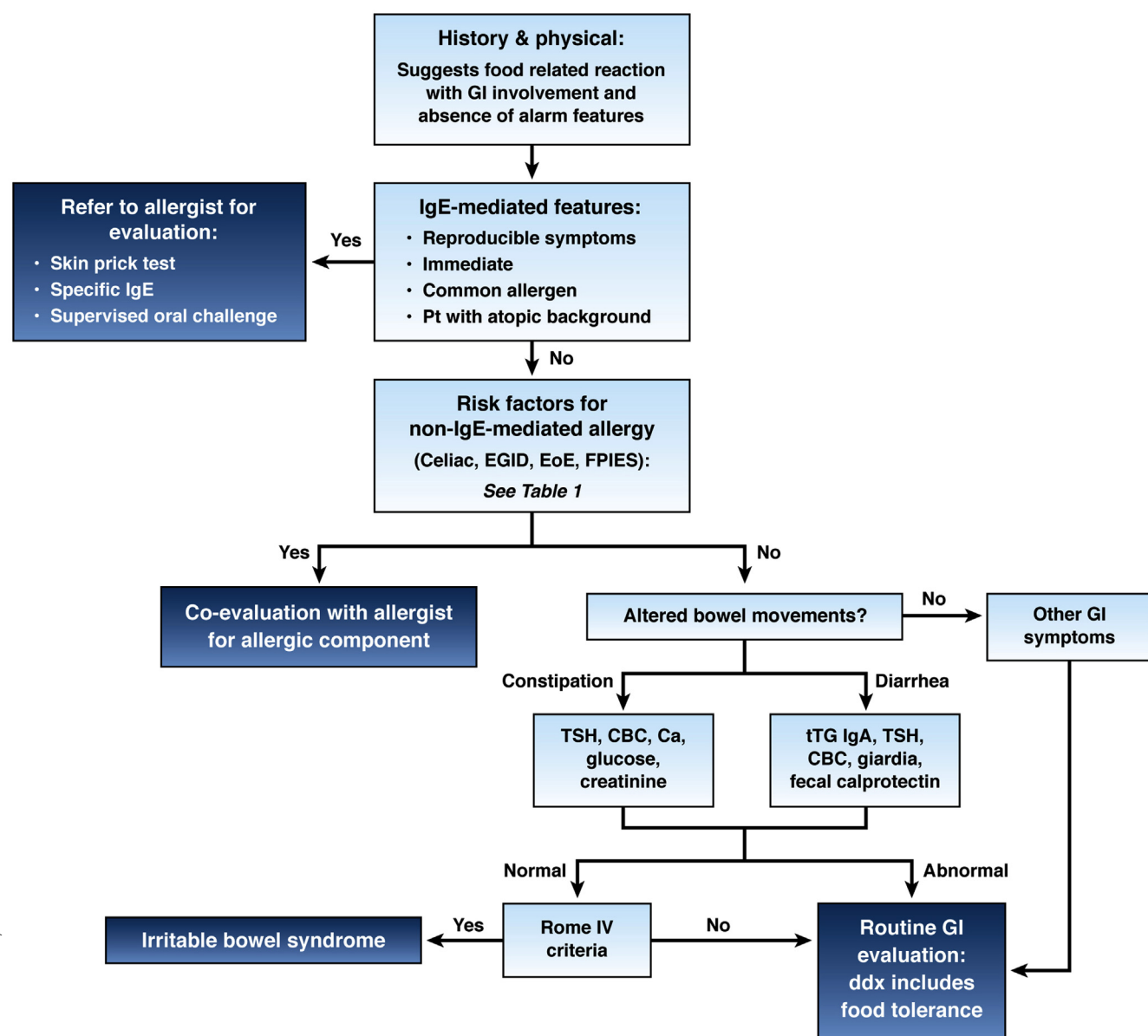


Figure 1. Diagnostic algorithm and coordination of care management for patients presenting with an adverse reaction to food. CBC, complete blood count; EGID, eosinophilic GI disorder; FPIES, food protein-induced enterocolitis syndrome; tTG, tissue transglutaminase; TSH, thyroid-stimulating factor.

are able to tolerate the heated food, such as apple pie, but develop oral symptoms with the raw form, such as apple. This classic presentation triggers suspicion for OAS. OAS occurs in over 50% of patients with pollen allergies, specifically birch tree, ragweed, and grass pollen.⁴⁰

Occasionally, patients with suspected mast cell activation syndrome (MCAS) may be referred to a gastroenterologist due to associated GI symptoms. MCAS affects multiple organs and may manifest with GI symptoms such as cramping, nausea, vomiting, or diarrhea.⁴¹ This group of diseases is classified into primary, secondary, or idiopathic MCAS. Primary MCAS results from intrinsic overproduction or abnormal function of mast cells, whereas patients with secondary MCAS have

normal mast cell quantity and function, but symptoms may be triggered by an IgE-mediated food allergy. Idiopathic MCAS is diagnosed in the absence of other identifiable causes.⁴¹ Patients presenting with suspected MCAS should first be evaluated for other GI etiology, and then referred to an allergist to rule out secondary MCAS. Management most commonly includes treatment with H1 and H2 antihistamines, cromolyn sodium, or anti-IgE therapy.^{42,43} Leukotriene antagonists may be used as a second line of therapy in some cases.^{41,42}

Because gastroenterologists are often sought for care after a nondiagnostic evaluation by primary care physicians, dentists, and otolaryngologists, high clinical suspicion for these presentations should be maintained in the correct patient population or clinical context.

Food allergy management. After a food allergy is identified, allergen avoidance is the mainstay of treatment. To assist in the identification and elimination of allergens, the Food Allergen Labeling and Consumer Protection Act of 2004 mandated the disclosure of any of the 8 major food allergens using their common names to keep manufacturers from misleading customers.⁴⁴ Similarly, to assist in the elimination of allergens in genetically modified foods, genetically modified foods must undergo molecular and physiochemical comparison with known allergens during food production.⁴⁵ To date, there have been no reported allergic reactions to genetically modified foods.

Failure of a patient to improve with allergen avoidance may suggest cross-contamination in food preparation and unintentional exposures, including skin contact and inhalation of aerosolized protein. Food allergens or aeroallergens that share structural similarity may cross-react and trigger an immune response, as is commonly seen with shellfish and different tree nuts. Because patients may require removal of several foods or nutrient-rich foods such as milk, nutritional monitoring, and instruction from a registered dietitian nutritionist should be considered.

To date, pharmacological management of food allergies is largely limited to treatment of anaphylaxis and symptom management with antihistamines, corticosteroids, and bronchodilators. Epinephrine injection is the recommended treatment for anaphylaxis, with several delivery systems available on the market for self-administration ([Supplementary Table 1](#)). Diagnostic criteria for anaphylaxis and indication for epinephrine administration has been described elsewhere.⁴⁶ In addition, allergy-specific oral immunotherapy has shown promising results. This technique uses small amounts of allergen or cross-reactive allergens to desensitize the patient; however, it is unclear if sustained unresponsiveness to the allergen will develop with long-term treatment. Recently, the Food and Drug Administration approved a commercial product called Palforzia for the use of peanut immunotherapy in patients 4–17 years of age.⁴⁷ Immune altering drugs, such as anti-IgE therapy in peanut allergy, have been described in patients with severe cases but are not currently recommended.⁴⁸

CASE 2

A 50-year-old woman presents with complaints of worsened diarrhea after eating food. She has been unable to identify triggers, as seemingly unrelated foods cause symptoms. She has previously had an extensive GI workup of symptoms, including esophagogastroduodenoscopy and colonoscopy, and has been diagnosed with irritable bowel syndrome with diarrhea (IBS-D). She would like to know which dietary changes would best manage her symptoms.

Approach to the patient

Reassurance—the patient's presentation is suggestive of a functional GI disorder, which may be associated with ARFs. While symptoms of food intolerances or ARFs may impair quality of life, they are generally not life-threatening. In addition to standard IBS treatments, she may benefit from a low-FODMAP diet with strict removal of high-FODMAP foods for a few weeks, followed by a slow rechallenge phase. It is important to avoid unnecessary restrictions, which increase the risk of nutritional deficiencies and inappropriate food phobias.

Non-immune-mediated adverse food reactions

The majority of adverse reactions to food can be attributed to nonallergic processes, such as food intolerances, pharmacologic reactions, and toxic reactions. In otherwise healthy patients, a physiologic response to food may generate disconcerting symptoms. For instance, fatty food, chocolate, peppermint, red wine, and orange juice may decrease lower esophageal sphincter pressure and worsen reflux symptoms. Similarly, legumes, onions, and bran fiber naturally lead to gas production and may cause bloating. Adverse reactions may also be caused by chemical and irritant effects of food (eg, gustatory rhinitis from spicy food), pharmacologic food reactions from tryptamine and food additives, metabolic disorders such as lactose intolerance and toxic effects from food poisoning ([Figure 2](#)).^{49,50}

About 60% of patients with functional GI disorders (FGIDs) report food-related symptoms.⁵¹ Interestingly, studies are now beginning to elucidate the roles of carbohydrates, dietary proteins and animal fats in IBS and may even suggest histological effects of food in IBS patients.⁵² Many of these studies were conducted using the Rome III criteria for IBS, which has since been updated by Rome IV.^{53,54} In a study by Fritscher-Ravens et al,⁵⁵ IBS patients who were introduced to cow's milk protein, wheat, and soy were noted to have changes in the density of intraepithelial lymphocytes, epithelial leaks, and mucosal sloughing on endomicroscopy and biopsies. Carroccio et al,⁵⁶ while attempting to find a cytologic assay to identify food hypersensitivity in patients with IBS like symptoms, found that 20% of patients had food hypersensitivity to cow's milk or wheat, as diagnosed by double-blind food challenges. In these patients, symptom scores improved when placed on an elimination diet. This early data suggest that perhaps the relationship between the allergic diathesis and IBS is more complex than initially believed.

Not surprisingly, dietary modification can lead to significant symptom improvement in patients with FGIDs. One such diet is the recently popularized low-FODMAP diet. FODMAPs are fermentable oligo-, di-, and monosaccharides and polyols, such as fructose, fructans, sucrose, lactose, and sorbitol, that are poorly absorbed,

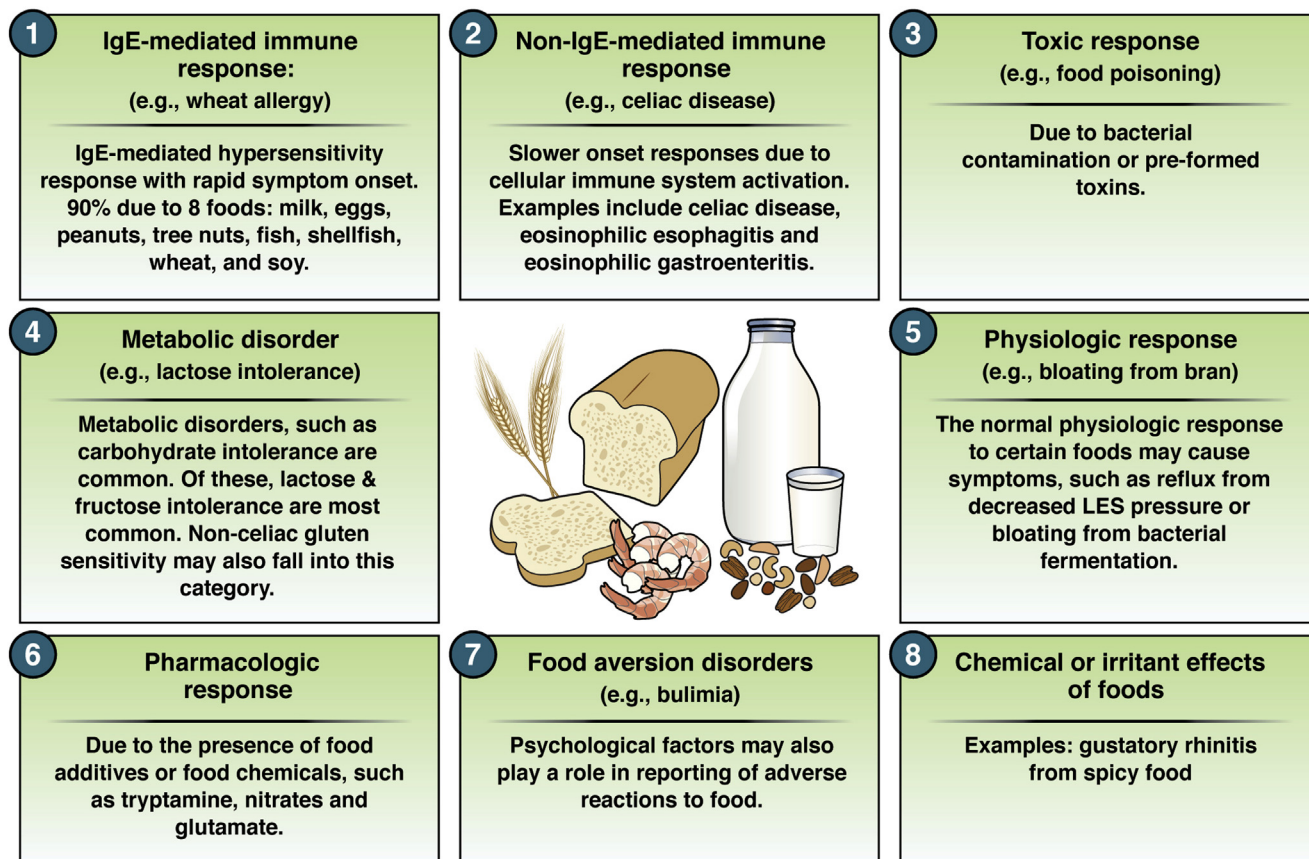


Figure 2. Common causes of adverse reactions to food with examples. LES, lower esophageal sphincter.

rapidly fermented, and osmotically active. Symptoms arise from fermentation leading to gas production, osmotic diarrhea, microbiota changes, and increased permeability.^{57–59} A randomized control trial in 2014 found that the low-FODMAP diet improved symptoms in patients with IBS.⁶⁰ A meta-analysis of 12 studies in 2017 confirmed these findings.⁶¹ As such, the low-FODMAP diet is a promising tool for symptom management in patients with IBS and potentially other FGIDs. A few studies have described the role of gluten and wheat in symptom generation in IBS and support the role of the gluten-free diet in IBS.⁶² The mechanism of symptom induction is debated, and the studies could not elucidate if symptoms were caused by wheat protein (ie, gluten) or wheat starch (ie, FODMAPs) in gluten-containing products. Nevertheless, given a reported response in a subset of patients to gluten removal, the gluten-free diet could also be considered with the added benefit of dietary adherence when compared with the low-FODMAP diet. Other diets, such as the Paleolithic diet, Candida diet, and histamine-free diet have recently gained popularity; however, there is little to no evidence to support their use.

Patients may bring up leaky gut, a condition thought to be caused by increased permeability of the intestinal wall, which allows toxins from the digestive system into the bloodstream. However, there is no validated

diagnostic criteria and therefore no clinical trials supporting any treatment options. Patients with symptoms believed to be caused by leaky gut should be treated for the underlying disease.⁶³

Gluten-specific reactions. Gluten is a complex of immunogenic, water-soluble proteins stored with starches of grains such as wheat, rye, and barley. From features in *Vogue* to *The New York Times*, the gluten-free diet has become widely popularized and a common concern for patients presenting to GI clinics. In fact, the consumer research firm Mintel reported a 136% growth in the sales of gluten-free foods in 2015, with an estimated \$11.6 billion in sales that year.⁶⁴ While the role of gluten in symptom generation was discovered in 1953 in patients with celiac disease, we now know that gluten-specific complaints are not unique to celiac disease.⁶⁵ A study by Campanella et al,⁶⁶ evaluated 180 patients with a symptom-based diagnosis of celiac disease and found that only 51 patients met biopsy- and antibody-based criteria for diagnosis. In the study, the positive predictive value of symptom improvement after gluten withdrawal was only 36% for celiac disease, suggesting that most symptoms were attributable to a separate process. The differential diagnosis for gluten-related symptoms also includes IgE-mediated wheat allergy and nonceliac gluten sensitivity (NCGS), which differ in pathogenesis, prognosis, and testing. As such, it is important to

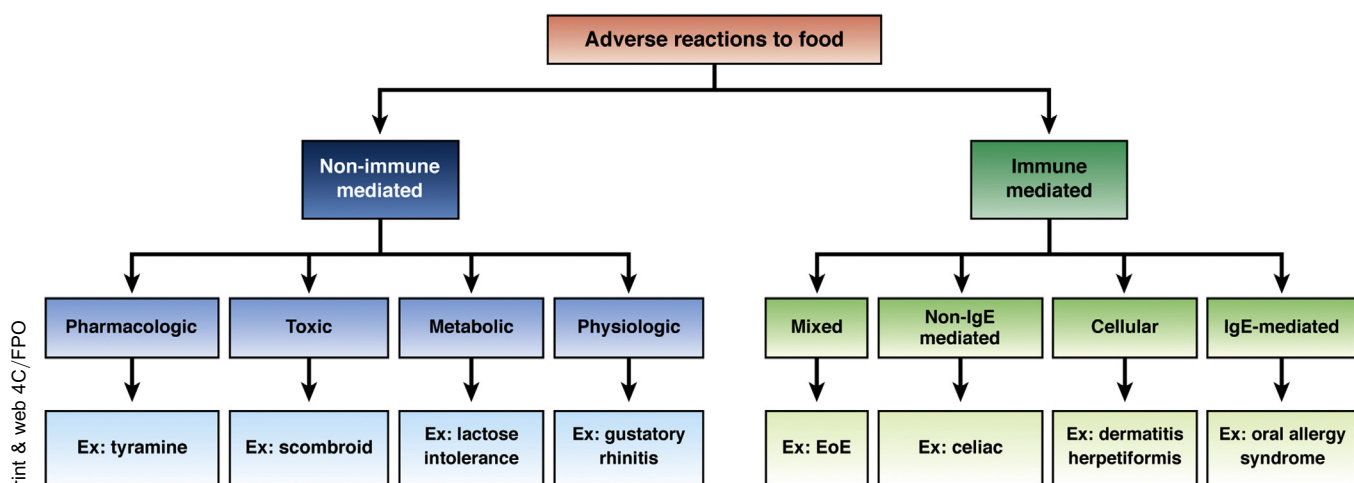


Figure 3. Differentiation between immune-mediated and non-immune-mediated adverse reactions to food.

distinguish celiac disease, a T lymphocyte-mediated immune response, with proven benefit from gluten avoidance, and IgE-mediated wheat allergy from other gluten or wheat related processes.

NCGS or nonceliac gluten wheat sensitivity. Screening tests for celiac disease should be conducted first in all patients with concern for gluten-specific complaints. However, most patients with gluten-specific complaints likely fall into the category of nonceliac wheat sensitivity (NCWS), previously categorized as NCGS. NCWS is a heterogeneous clinical syndrome with morphological and symptomatic changes precipitated by the ingestion of gluten or wheat, despite the absence of celiac disease or wheat allergy.⁶⁷ The syndrome may present with GI or extraintestinal manifestations, such as diarrhea, abdominal discomfort, pain, bloating, flatulence, headache, lethargy, and neurological symptoms including ataxia.⁶⁸

While early studies evaluated the role of gluten in seemingly gluten-related complaints, later studies cast doubt on the role of gluten in symptom generation. A meta-analysis of 10 food challenge studies including 1312 patients labeled with NCGS found that only 16% of patients with NCGS showed a gluten-specific response and 40% reported increased symptoms with placebo. These findings, consistent with previous studies, cast doubt on the role of gluten in NCGS.⁶⁹ A double-blinded, placebo-controlled crossover study by Skodje et al⁷⁰ found that GI symptoms in patients with self-reported NCGS were higher with fructan (wheat starch) in gluten-containing foods than with gluten itself ($P = .049$). These findings, among others, argue that the benefit of the gluten-free diet in these patients may be due to concurrent elimination of other dietary factors, such as wheat starch or nongluten proteins in wheat.⁷¹ Amylase-trypsin inhibitor proteins are nongluten proteins found in wheat that are potent activators of the innate immune system and may be implicated in NCGS or NCWS. As such, the term *nonceliac wheat sensitivity* is likely more accurate than *nonceliac gluten sensitivity*.

To date, the entity remains poorly understood and is thought to represent an overlap between functional GI disorders and celiac disease in symptomatology and perhaps pathophysiology.⁷²⁻⁷⁴ Although there is no evidence of allergic mechanisms, the exact pathophysiology of symptom generation is unknown. The exact incidence of this syndrome is unknown but is likely to be substantially greater than celiac disease. More prospective trials are needed to investigate the utility of a low-FODMAP diet in NCWS patients. Ultimately, patients may choose to follow a strict gluten-free diet based on the severity of symptoms.

Conclusion and Emerging Areas of Research

While adverse food reactions affect many patients globally, food allergies affect a small percentage of the population but can be life-threatening. Clinicians must maintain a high level of suspicion when evaluating a patient with possible adverse reactions to food, to determine if a food allergy is at fault or if the reaction is due to one of several other non-immune-mediated reactions (Figure 3). A detailed history and history directed allergy testing can distinguish food allergy from nonimmune food reactions. Allergen avoidance remains the mainstay of treatment; however, further research is needed regarding pharmacotherapies, such as allergy specific immunostimulation, anti-IgE therapy, and peptide immunotherapy.

For management of food intolerances and sensitivities, many dietary modifications have been introduced, but none more popular than the gluten-free and low-FODMAP diets. Strict gluten avoidance can improve outcomes in patients with celiac disease; however, the benefit is yet to be fully understood in patients with NCWS. NCWS may mimic celiac disease, and further studies are needed to elucidate the pathophysiology, establish diagnostic criteria for the syndrome and

determine the subset of patients who truly benefit from gluten avoidance. As new studies suggest that the benefits of a gluten-free diet may stem from elimination of other dietary factors such as fructan, further research is needed on the role of FODMAPs in symptom generation in NCWS and other FGIDs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1016/j.cgh.2021.01.025>.

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Reprint requests

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Conflicts of Interest

These authors disclose the following: John Leung has served as a consultant for Noble Insights, Shire Pharmaceuticals, Genzyme Corporation, Guidepoint, Eli Lilly, Sophos, and Takeda. Sheila E. Crowe is a co-author of *Celiac Disease for Dummies* and receives royalties from John Wiley & Sons annually; has served on the advisory board for and received honoraria from Ferring; and has served as a Site PI for Celimmune on a placebo-controlled, randomized clinical trial of interleukin (IL)-15 for refractory celiac disease type II and received support for the PI and Clinical Trials Office at University of California San Diego in 2017. The remaining authors disclose no conflicts.

Supplementary Table 1. Available Epinephrine Devices in North America by Dose

Patient Weight	Available Epinephrine Devices
7.5–15 kg (16.5–33 lb)	• Auvi-Q autoinjector (0.1-mg dose)
15–30 kg (33–66 lb)	• EpiPen autoinjector (0.15-mg dose) • Authorized generics of EpiPen (0.15-mg dose) • Adrenaclick autoinjector (0.15-mg dose) • Authorized generics of Adrenaclick (0.15-mg dose) • Auvi-Q autoinjector (0.15-mg dose) • Symjepi prefilled syringe (0.15-mg dose)
30+ kg (66+ lb)	• EpiPen autoinjector (0.3-mg dose) • Authorized generics of EpiPen (0.3-mg dose) • Adrenaclick autoinjector (0.3-mg dose) • Authorized generics of Adrenaclick (0.3-mg dose) • Auvi-Q autoinjector (0.3-mg dose) • Symjepi prefilled syringe (0.3-mg dose)