

Gastrointestinal Food Allergies: Do They Exist?

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Gastrointestinal (GI) symptoms are often attributed to adverse reactions to foods (ARF), but it is not always clear whether such reactions are caused by food allergy. A reaction to food proteins that is mediated by immunologic events is referred to as food allergy or food hypersensitivity. One of the most common types of food allergy is the IgE-mediated immediate hypersensitivity reaction to foods, which can give rise to dermatologic and respiratory tract symptoms in addition to GI complaints. Other GI forms of food allergy include food protein-induced enterocolitis or gastroenteropathy, celiac disease, and some cases of eosinophilic gastroenteritis. Because most patients complaining of adverse reactions to food have non-immune mechanisms for their complaints, it is important to distinguish the various types of ARF, as their management may differ substantially. Recent advances in the field of food allergy provide opportunities to improve diagnostic methods and develop new modalities for management that will complement the current practice of allergen avoidance.

Introduction

Adverse reactions to foods (ARF) have been reported in 20% to 25% of the general population, with some studies suggesting that as many as 45% of individuals complain of ARF. Many of the complaints are gastrointestinal (GI) in nature, including dyspepsia, heartburn, abdominal pain, diarrhea, and even rectal bleeding. Only a small proportion of ARF is caused by food allergic mechanisms, with most reactions attributed to non-immune mechanisms (Table 1). The most common form of GI food allergy results from immediate hypersensitivity to ingested food antigens. Celiac disease and food protein-induced enterocolitis syndromes are also classified as food allergies although other immunologic mechanisms are involved in these conditions. The majority of ARF is not immune-mediated and includes toxic, infectious, pharmacologic, metabolic, psychological and physiologic reactions to foods or food additives. This article, which focuses on GI

reactions to food, provides an overview of food allergy, highlighting recent developments in the field. The reader is referred to a number of other recent reviews that cover the topic of food allergy [1,2•,3•], as well as those that focus on gastrointestinal food allergy [4••,5••].

Food Allergy

Allergy has been considered an important environmental disease [6], with reactions to food allergens now recognized as the major cause of anaphylaxis and death from anaphylactic reactions [2•,7•]. The prevalence of food allergy is estimated to be as high as 5% to 8% in children in the first 2 years of life, with a lower frequency (1% to 2%) in adults and children over the age of 10 years. Food allergy is more common in atopic individuals, who often have a family history of atopic eczema, asthma, and food allergy. Cow's milk, eggs, peanuts and other nuts, soy, and wheat proteins are among the most common causes of food allergy in early childhood, whereas peanuts, fish, shellfish, and tree nuts are the most common food allergens in adolescence and adult life. Two percent to 2.5% of young children are allergic to cow's milk, less than 2% to eggs, and a smaller percentage to soy protein. A recent survey indicates that 0.6% of the US population is allergic to peanuts and another 0.5% to 0.6% to tree nuts [8]. Children may "outgrow" their food allergies, yet retain in vivo (skin-prick test) and in vitro (radioallergosorbent test) reactions to these foods and develop airway reactivity to inhalant allergens. Antigen-related factors may be involved in this age-based recovery, because clinical reactions to eggs, milk, soy protein, and wheat are lost, whereas those to peanuts, tree nuts, fish, and shellfish persist. A recent study challenges the currently accepted belief that sensitivity to peanuts persists into adult life because some children in this study did lose sensitivity over time [9•].

Surveys indicate that 40% to 70% of patients with food allergies report GI symptoms, which include nausea, vomiting, abdominal pain, bloating, and diarrhea (Table 2) [10–12]. These reactions may be immediate or delayed. The oral allergy syndrome, often triggered by certain fresh fruits and vegetables that cross-react with pollen allergens, manifests as swelling of the lips and tongue and is categorized as a GI food allergy. Other manifestations of food allergy include urticaria, eczema [13], rhinitis, asthma, otitis [14], and anaphylaxis [15•]. Whether food allergy causes arthritis,

Table 1. Classification of adverse reactions to food or food additives

Food allergy or food hypersensitivity
Immediate hypersensitivity reactions
Allergic eosinophilic gastroenteritis
Food protein–induced enterocolitis syndromes
Celiac disease
Food intolerance (non-immune mechanisms)
Food toxicity or food poisoning
Pharmacologic reactions
Metabolic reactions
Idiosyncratic reactions
Psychological reactions
Physiologic reactions

Table 2. Manifestations of food allergy

GI presentations (in 40% to 70%)
Edema of oropharyngeal mucosa
Nausea and vomiting
Diarrhea
Abdominal pain
Other manifestations
Urticaria, eczema
Asthma, rhinitis, otitis
Anaphylaxis

migraine headaches, and other neurologic manifestations remains controversial. Over 100 fatal cases of food-induced anaphylaxis are estimated to occur each year in the United States [2•], with over 90% of these deaths attributable to exposure to peanuts or tree nuts. Food allergy is now recognized as the leading cause of anaphylactic death in the United States and other developed nations [16], whereas food allergy is not a significant cause of anaphylaxis in developing countries. The diagnosis and current management of food hypersensitivity rest on the identification of specific food antigens responsible for GI and other symptoms, followed by elimination of these antigens from the diet.

Pathogenesis of Food Allergy

The key contributors to the development of food allergy and its manifestations include the host immune response, which is dependent on age and genetic factors, properties of the food protein, and target-organ reactivity [17]. How the gut barrier regulates immune system exposure to food antigens also plays an important role [18]. Detailed discussion of these events is beyond the scope of this article, but a brief summary is provided. Immediate hypersensitivity reactions to foods are a consequence of antigen exposure leading to IgE or sometimes IgG4 antibody production, with attachment to mast cells and basophils. Subsequent exposure to the food antigen induces mast-cell degranulation, with release of mediators that include histamine, eicosanoids, and cytokines. Studies in humans and animal models [19,20] demonstrate that GI mast-cell activation leads

to alterations of gastric acid secretion, mucosal barrier function, fluid and electrolyte exchange, and gut motility. Recent studies in experimental models demonstrate a role for eosinophils in GI food allergy as well as GI reactions to inhaled allergens [21,22••,23••,24••].

Other Immune-mediated Adverse Reactions to Food

Immunologic reactions to food can involve mechanisms other than immediate hypersensitivity. Immune complex formation and complement deposition have been documented in food allergy, particularly food protein–induced enterocolitis syndromes such as cow's milk protein enteropathy. Cell-mediated immune reactions to food antigens also play a role in these diseases and in celiac disease. Food protein–induced enterocolitis syndromes (or gastroenteropathies) present in infancy or early childhood and are most commonly caused by cow's milk protein, followed by soy protein and, less commonly, eggs, fish, and other food antigens [25]. Clinical manifestations include diarrhea, vomiting, anemia, bleeding, and failure to thrive. Allergic gastroenteropathy is also described in preterm infants [26]. As with patients with other food allergies, these patients are managed by elimination of the specific food antigen until the disease resolves with age. It is common practice to switch infants with enterocolitis from a cow's milk–based formula to a soy protein–derived formula, but because over half react to soy protein, continued problems may result from the development of soy protein–induced enterocolitis. Hypoallergenic or elemental feeds are often necessary in such patients.

Celiac disease is one of the best-recognized entities resulting from an immunologic reaction to food [27]. Dietary ingestion of gluten found in wheat, rye, barley, and oats induces an enteropathy in genetically susceptible individuals. Removal of gluten from the diet restores normal small bowel function and appearance, with improvement in symptoms that can range from diarrhea, weight loss, and failure to thrive to the more common but less often recognized complaints of fatigue, dyspepsia, neurologic dysfunction, and musculoskeletal problems. As with other immune-mediated ARE, elimination of the offending food substance (gluten) is the primary method of management in celiac disease. However, unlike other food proteins that induce enteropathy, gluten must be eliminated from the diet on a life-long basis in celiac disease.

Food allergy is thought to play a role in some patients with eosinophilic gastroenteritis, a relatively rare condition characterized by eosinophilic infiltration of the gut and peripheral eosinophilia. Approximately half the patients with eosinophilic gastroenteritis have atopic features, including food allergy. Strategies to identify and eliminate food antigens should be followed, as in other food-allergic conditions, but often other measures, particularly treatment with corticosteroids, are necessary to manage patients with eosinophilic gastroenteritis.

Non-immune Adverse Reactions to Food

Food toxicity or food poisoning results from microbial contamination of food, causing primarily GI manifestations due to preformed toxins (eg, staphylococcal enterotoxin) or replication of enteric pathogens (*Campylobacter*, *Salmonella*, and *Shigella* spp, *Escherichia coli*). These reactions can be distinguished from other ARF because they usually do not recur and have fairly characteristic presentations. Occasionally, the self-limited infection may result in a postinfectious irritable bowel syndrome (IBS). Patients with recurrent infectious GI illnesses should be evaluated for immunodeficiencies such as IgA deficiency, which occurs at a frequency of one individual in 600. IgA-deficient patients are also reported to have a greater incidence of food allergies, and a recent study suggests that low levels of IgA in breast milk may predispose infants to the development of cow's milk allergy [28].

Anaphylactoid or pseudo-allergic reactions to food result from foods that mimic the effects of mast-cell degranulation but do not involve IgE antibodies. Strawberries and shellfish may cause this type of ARF. As with true food allergy, patients exhibiting such reactions should be instructed to avoid the offending food substance. Pharmacologic reactions to food or food additives represent a relatively common type of ARF, although most of these reactions cause symptoms outside of the GI tract. Histamine found in certain cheeses or in scombroid fish such as tuna can cause headaches and diffuse erythema of the skin. Certain individuals develop migraine headaches after ingesting various foodstuffs, including those rich in amines. Sulfites, tartrazine, and monosodium glutamate (MSG) have all been associated with asthma, and MSG can cause a characteristic syndrome consisting of a burning or warm sensation, chest tightness, headache, and gastric discomfort shortly after its ingestion.

Globally, lactose intolerance is the most common adverse reaction to a specific food. Most cases result from declining levels of intestinal lactase activity in later childhood and adult life, although rare congenital deficiencies can occur. Symptoms of lactase insufficiency are usually dose related and include bloating, flatulence, and diarrhea. Secondary lactase deficiency can result from viral gastroenteritis, radiation enteritis, Crohn's disease, and celiac sprue.

In certain individuals, reactions to food may be psychological. This is a difficult type of adverse reaction to diagnose because the mechanisms giving rise to such reactions are poorly understood. An individual who experienced a severe food poisoning reaction may avoid the culprit food for fear of further reactions. Children forced to eat certain foods under adverse circumstances (ie, as a form of child abuse) may experience symptoms of anxiety or fear when ingesting the food later in life. There is also some evidence that hypersensitivity reactions to food may be triggered through central neural mechanisms, so that eventually, just the thought of ingesting the food can trigger allergic symptoms in the absence of antigen.

Table 3. GI disorders and adverse reactions to food

GI food allergy
Food protein–induced enterocolitis syndromes
Celiac disease
Eosinophilic gastroenteritis
Lactose intolerance
Gastroesophageal reflux disease
Nonulcer dyspepsia
Irritable bowel syndrome
Inflammatory bowel disease

Perhaps the most common form of ARF results from physiologic reactions to food components or additives. For example, it is well known that starches found in legumes serve as substrate for gas production by colonic flora. Many other foods are associated with "gas," including cabbage, bran fiber, and other vegetables and grains. Other foods and food additives affect the lower esophageal sphincter, whereas foods high in fat delay gastric emptying, resulting in symptoms of heartburn and dyspepsia. Physiologic reactions to foods are often noted by patients with functional bowel disease, many of whom exhibit heightened endocrine, motor, and sensory responses to normal digestive events. It is important to determine whether a specific food intolerance exists in this group of patients, because elimination of the offending food or foods can provide some benefit.

Gastrointestinal Disorders and Adverse Reactions to Food

Even in the absence of a history of food intolerance, it is commonplace for patients with gastrointestinal disorders to believe that something in their diet has caused their condition and to seek dietary advice from various sources, including gastrointestinal specialists [20]. A significant number of GI conditions are associated with ARF (Table 3), but food plays a causative role in only some of these disorders. For patients with gastroesophageal reflux disease, nonulcer dyspepsia, IBS, and other functional conditions, nonspecific physiologic reactions to food can provoke symptoms. It is generally advisable to instruct these patients to avoid foods that cause symptoms, but non-dietary measures are usually necessary to manage their complaints. However, food protein intolerance or allergy may play a role in infants with gastroesophageal reflux [29]. There is no clear role for hypoallergenic diets in IBS, although a few studies report benefit from such diets, and in rare instances, such measures may be needed to convince a patient that specific dietary factors are not the cause of his or her illness.

Many studies have examined the role of diet in inflammatory bowel disease (IBD), but there is no evidence that specific immune-mediated reactions to food play a role in most patients with either Crohn's disease or ulcerative

Table 4. Approach to patients with suspected food allergies as a cause of GI symptoms

Careful history
Diet diary
Elimination diet
Skin testing
Food antigen challenge
Exclusion
Management of other disorders

colitis. Elemental enteral feeding and parenteral nutrition can assist in the management of patients with IBD, with benefits that appear to be related to improved nutrition and bowel rest rather than removal of specific allergens from the diet. Patients in remission should be encouraged to eat a nutritionally balanced diet without restrictions unless they experience intolerance to specific foods. Patients with IBD are commonly instructed to avoid dairy products, but this is unnecessary, except in patients with symptomatic lactose intolerance or rare instances of cow's milk protein allergy, because such foods are good sources of calcium in a population at increased risk of osteoporosis.

Approach to Patients Complaining of Adverse Reactions to Food

Guidelines for the evaluation of food allergies have recently been published as a medical position statement by the American Gastroenterological Association [30••]. Table 4 outlines an approach to take with such patients. It is essential to obtain a careful history correlating symptoms with specific foods. Most immediate hypersensitivity reactions to food include a set of symptoms that consistently occur minutes to hours after ingesting certain foods. In some individuals, other factors, such as medications or exercise, may modulate the reaction to a specific food. Specificity of the reaction does not always imply a food allergy, because patients with anaphylactoid reactions or lactose intolerance report defined reactions to specific foods. However, the nature of the reaction helps to differentiate lactose intolerance (*ie*, gas, bloating, and diarrhea) from an allergy to cow's milk protein (often urticaria, swelling of the lips and oral mucosa, and/or asthmatic symptoms, in addition to GI symptoms).

If a specific food or group of foods cannot be identified in the initial history, the patient should keep a diet diary for several weeks in an attempt to correlate foods with GI and other symptoms. After certain foods are identified as possible culprits by history or through the diet diary, these items should be eliminated from the diet for several weeks to determine the effect on symptoms. If a benefit is seen, the patient may reintroduce the putative allergen(s) in an attempt to prove the association. Such open food challenges are subject to bias and should be corroborated by another more objective method before permanent

elimination of the foodstuff from the diet, particularly if the patient is young and the food(s) in question represent a major component of the diet (*eg*, eggs, milk, or wheat). If specific foods are not identified by the clinical history or with a diet diary, a hypoallergenic diet, such as that shown in Table 5, may be tried for 2 to 3 weeks. In most cases of adverse GI reactions to foods or food additives, this approach is without benefit, but in cases where a benefit is seen, new foods are gradually introduced in an attempt to identify specific foods that may contribute to the illness. It is important to recognize that the response to the hypoallergenic diet may be falsely interpreted as a negative test because a minority of subjects can react to antigens contained in a typically hypoallergenic diet.

Skin-prick testing provides a readily available and relatively inexpensive means to assess a panel of food allergens in both children and adults. The major limitation of skin testing is its poor positive predictive value (many asymptomatic patients exhibit reactions to food allergens), but a negative test in the absence of antihistamine use strongly suggests that immediate hypersensitivity is an unlikely mechanism for the patient's food-induced complaints. A radioallergosorbent test (RAST) is an alternative to skin testing in very young children, patients with severe atopic dermatitis, and patients reporting anaphylactic reactions to foods or food additives. The limitations of RAST are expense, lower sensitivity, and the relatively limited number of antigens that can be tested, compared with skin testing. A modification of the traditional RAST is reported to be more sensitive than a standard RAST [31]. The basophil histamine release assay can also be used to evaluate allergic reactions to food *in vitro*, but it is largely reserved for research studies [32]. Sublingual and neuromuscular testing for food antigens is not considered acceptable for diagnosis of food allergy. Unless there is clinical evidence of adverse reactions to foods identified by skin testing or *in vitro* methods, these foods do not need to be eliminated from the diet in most instances.

Because reactions to food antigens by RAST or skin testing are neither specific nor sensitive, a double-blind, placebo-controlled food challenge, in which food antigens are administered by nasogastric tube or gelatin capsules, should be performed if possible. This technique is considered the gold standard for diagnosing food allergy but is not widely available. A number of investigators have performed the gastrointestinal equivalent of skin testing by injecting the gastrointestinal mucosa with a panel of antigens and observing for a wheal-and-flare response by endoscopy. This technique was reported as early as the 1930s, with subsequent series describing gastric, duodenal, and most recently, colonic mucosal allergen challenge [33,34]. Although these techniques represent an advance in the field of food hypersensitivity, their incorporation into routine clinical practice has been limited. In contrast, endoscopy and mucosal biopsy techniques remain the major diagnostic method to evaluate other GI immune-mediated reactions to food, including

Table 5. Sample elimination (exclusion or hypoallergenic) diet

Food category*	Allowed	Avoid
Meat and meat alternatives	Lamb Chicken Turkey	Pork Beef Fish Eggs Milk and milk products Seafood
Grains	Rice (Barley) Tapioca Arrowroot	Wheat Oats Corn Rye
Legumes and nuts	Avoid all dried peas, beans, nuts	
Vegetables	All except corn and peas	
Fruits	All except citrus fruits, strawberries, and tomatoes	
Sweeteners	Sugar (cane or beet) Maple syrup Honey	
Fats and oils	Olive oil Safflower oil Shortening	Soy, corn, peanut oils Butter Margarine
Miscellaneous	White vinegar Water (Ginger ale) Salt (Pepper) Fruit juices	Coffee, tea Alcohol Chocolate Colas Spices Chewing gum

*Foods in parentheses () may cause adverse reactions in some individuals. These may be omitted from the trial elimination diet. If an allowed food is one that has caused a reaction in the past, it should also be omitted. While on the trial elimination diet, patients are instructed to keep a record of their symptoms and to note any change from ones on the previous regular diet. If there are symptoms, patients should check to see if there is any relationship to particular foods.

celiac disease, food protein gastroenteropathies, and eosinophilic gastroenteritis. According to a recent report, the histologic finding of lymphoid nodular hyperplasia with normal villi in duodenal biopsies indicates untreated food allergy, and this finding was not present in celiac disease [35].

Management of Food Allergy

The cornerstone of food allergy management is avoidance of the offending allergen. This is particularly important in peanut allergy, where trace amounts of allergen can cause significant reactions. Most fatalities attributed to food allergy have been caused by peanut allergy [36]. Because it is often difficult to prevent accidental exposure to food antigens, patients with a history of anaphylactic reaction should be instructed to carry an epinephrine-containing syringe for emergency administration. Because reactions may be biphasic in nature, patients must be instructed to go to a local emergency facility after the initial symptoms. Individuals who are at increased risk of anaphylaxis include those with a history of anaphylaxis; those with reactions that include respiratory symptoms; those who have ingested peanuts, tree nuts, fish, or seafood; and those taking beta blockers or angiotensin-converting enzyme inhibitors. Patients with food allergies should learn to read and

understand labels for hidden food allergens and to recognize the potential for foods to cross-react with other antigens (*eg*, banana and kiwi with latex, and birch pollen with apple, carrot, and hazelnut). The Food Allergy Network (www.foodallergy.org) is a source of valuable information for those with various types of food allergy. Similarly, it is important for patients with celiac disease to join local foundations and support groups.

To date, there is no evidence that oral desensitization, injection immunotherapy, prophylactic medication, or similar techniques are beneficial in the prevention or modulation of food allergy. Hypoallergenic diets have been recommended during pregnancy and with breast feeding for atopic mothers in order to reduce the incidence of food allergy in their offspring. It is also recommended that foods with a higher allergenic potential should be introduced later into the diets of infants at high risk of developing food allergy to decrease the tendency to develop such an allergy. Formulas with reduced antigenicity include those in which milk proteins are partially hydrolyzed by heat or enzymes, as well as more extensively hydrolyzed preparations. For the 10% of infants that still react to even the more hydrolyzed formulas, amino acid-based preparations should be used [37]. For infants with IgE-mediated cow's milk allergy, there is only a small chance that they will also be allergic to soy

protein, whereas infants with cow's milk protein-induced enteropathy have a greater than 50% likelihood of developing soy protein-induced enterocolitis. Antihistamines, ketotifen, oral cromolyn, and corticosteroids may modify symptoms to food allergens, but their efficacy is unproven. Dietary restrictions for peanut allergy, food allergy associated with anaphylaxis, and celiac disease should be maintained on a long-term basis, whereas such measures can be lessened in other types of food allergy that resolve with time, particularly those presenting in early childhood. As noted previously, skin testing cannot be used to predict loss of clinical reactivity because skin tests may remain positive in a child who no longer has clinical manifestations of food allergy.

Perhaps the most exciting developments are new therapeutic approaches that offer the potential to be applied to food allergy. These include tolerogenic peptides, recombinant epitopes, and anti-IgE and DNA vaccination, as well as neutralizing antibodies or receptor antagonists of Th2 cytokines such as interleukin-4. Methods to genetically or chemically modify the antigenic structures of foods to reduce their allergic potential are also under development. For example, it is known that single amino acid substitutions in the IgE binding site of a peanut allergen can lead to the loss of binding to these epitopes [38,39]. Antibodies specific for the portion of the IgE molecule that binds to receptors on mast cells and basophils have been used in animal models, and clinical trials with asthmatic subjects have shown benefit, establishing the potential for this strategy in food allergy [40]. DNA vaccination to induce host-cell expression of antigenic protein also offers promise as a therapy for food allergy, evidenced by a recent study in a mouse model of peanut allergy. Mice vaccinated orally with DNA coding for a major peanut allergen, Ara h2, complexed with a polysaccharide delivery vehicle, were shown to express the food protein in their GI tract and to exhibit less immunologic and clinical reactivity to subsequent challenge with antigen, compared with control mice [41••].

Conclusions

Adverse reactions to food resulting in gastrointestinal symptoms are common in the general population. Whereas only a minority of individuals have symptoms caused by food allergy, GI food allergies do exist in both children and adults. It is important to recognize cases of food allergy in order to correctly diagnose and manage the small subset of patients with immunologically mediated adverse reactions to food. Potentially fatal reactions to food necessitate careful instruction and monitoring on the part of health-care workers involved with individuals at risk of anaphylaxis. Recent reports of new diagnostic methods and strategies for treatment, including immunologic modulation and hypoallergenic foods, are exciting developments in the field of food allergy.

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This two-part article by one of the leaders in food allergy provides a comprehensive and recent review of the topic. Over 200 references are cited, including many classic studies in the field. The clinical syndromes associated with food allergy are well reviewed in part 1, and a useful algorithm for the diagnostic evaluation is included in part 2.

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- This is the first study to report successful oral DNA vaccination in the quest to modulate gut allergic responses to food. Further studies are needed in animal models with the hope that such approaches may be applied to human food allergy in the future.