

Food Sensitivities

Fact Versus Fiction



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KEYWORDS

• Food allergy • Food intolerances • Food sensitivities • Wheat • Gluten

KEY POINTS

- There is an overestimation of food allergies, resulting in parents eliminating unnecessarily foods from their children's diet.
- Not all adverse reactions to foods are allergies; diagnosis of a food allergy must follow well-defined criteria.
- Many tests are available to the public that purport detection of food intolerances, but they have no scientific validation whatsoever and should not be used.
- The term non-celiac gluten sensitivity is a misnomer and should be abandoned in favor of non-celiac wheat intolerance, an entity suffering from lack of biomarkers and still not convincingly described in children.

INTRODUCTION

Adverse reactions to foods are increasing in prevalence and are often attributed to allergy. Up to one-third of parents report 1 or more food reactions in their children that they may interpret as allergies.¹ However, not all of these are true intolerances and may result in avoidance of foods that could otherwise be reintroduced into the diet. It must be stressed that food-related disorders can lead to a spectrum of clinical manifestations and degrees of severity, but only some of them are related to allergy. In fact, a true food allergy is defined as an “adverse *immune* response that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food.”² Other conditions causing adverse food reactions include congenital or acquired disorders of digestive-absorptive processes, such as lactose intolerance, toxic or pharmacologic reactions, and autoimmune reactions, such as celiac disease (CD). Thus, the noncommitting term “food intolerance” should be used to include all forms

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Abbreviations	
AAP	American Academy of Pediatrics
ATI	Amylase-trypsin inhibitors
CD	Celiac disease
EPIT	Epicutaneous
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides and polyols
FPIES	Food protein-induced enterocolitis syndrome
IBS	Irritable bowel syndrome
NAS	National Academies of Sciences, Engineering, and Medicine
NCGS	Non-celiac gluten sensitivity
NCWI	Non-celiac wheat intolerance
NIAID	National Institute of Allergy and Infectious Disease
OFC	Oral food challenge
SPT	Skin prick testing
VAS	Visual analog score

of adverse reactions due to ingested foods until an adverse reaction is proven to be due to an immune-mediated process (Table 1).

The National Institute of Allergy and Infectious Disease (NIAID) published guidelines for the diagnosis and management of food allergies in 2010 and has been a mainstay in the clinician’s approach to food allergies and intolerances.² A more recent report published in 2017 by the National Academies of Sciences, Engineering, and Medicine (NAS), entitled “Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy,” provides further guidance for the diagnosis, treatment, and prevention of food allergies. The report is based on a study performed by 15 international experts with evidence base including

Table 1 Classification of food intolerances with gastrointestinal manifestations		
Type	Pathogenesis	Main Clinical Entities
Immune-mediated (food allergy)	Immunoglobulin (Ig)E mediated	Immediate gastrointestinal hypersensitivity
	Non-IgE mediated	Oral allergy syndrome Food protein–induced Proctocolitis Enterocolitis (FPIES) Enteropathy
	Occasionally IgE mediated	Eosinophilic esophagitis Eosinophilic gastroenteropathy
Unknown, likely mixed, pathogenesis		Non-celiac gluten sensitivity
Autoimmune	Innate as well as adaptive immunity	Celiac disease
Nonimmune mediated	Disorders of digestive-absorptive processes	Glucose-galactose malabsorption Lactase deficiency Sucrase-isomaltase deficiency Enterokinase deficiency
		Toxic or pharmacologic reactions
		Food poisoning Tyramine (aged cheeses) Histamine (strawberries, caffeine)
		Theobromine (chocolate, tea)
	Idiosyncratic reactions	Food additive Food colorants

literature reviews and assessment of published guidelines and practice parameters.³ Both of these documents provide fundamental points that are discussed throughout this article.

FOOD ALLERGY

Prevalence

The true prevalence of food allergies is difficult to define for several reasons, including that most studies focus on only the most common foods, although more than 170 foods have been identified in causing IgE-mediated reactions.² The definition of food allergy often varies in prevalence studies, as well as whether the diagnosis was self-reported versus identified by testing. These, among many other factors, limit the reliability of prevalence estimates and the recent report from the NAS could not give definitive prevalence data for the United States. However, a review published in the *Journal of the American Medical Association* in 2010 estimated that food allergy affects more than 1% to 2% and less than 10% of the US population,⁴ and a study published in *Pediatrics* determined 8% of children have food allergy as identified by parental report.⁵ It is known that self-reported allergies likely overestimate prevalence,⁶ thus it is imperative to use the gold standard oral food challenge (OFC), which has not been used in US studies since the 1980s.⁷ A study using skin prick testing (SPT) followed by OFC in Melbourne, Australia, identified the prevalence of food allergies at age 1 year to be 11% and at age 4 to be 3.8%.⁸

IMMUNOGLOBULIN E-MEDIATED FOOD ALLERGY

Myth: "The Immunoglobulin E Allergy Testing Was Positive for Wheat, Eggs, Milk, and Corn, Therefore the Patient Is Allergic to These Foods"

A positive immunoglobulin (Ig)E test shows sensitivity to that allergen, but does not imply clinical relevance. The most common food allergens in the United States include cow's milk, egg, peanut, tree nuts, wheat, shellfish, and soy. Cow's milk proteins followed by soybean proteins are the most common cause of food allergy during infancy, whereas egg protein allergy is most common in school-aged children.⁹ Most food allergies have a high rate of resolution. For example, more than 50% of children with a milk allergy will have resolution by ages 5 to 10 years.¹⁰ Egg, wheat, and soy allergies all have nearly 50% resolution by age 9.¹⁰ Allergies to peanuts and tree nuts are less likely to resolve, with only 20% resolution by age 4 for peanuts and only 10% resolution of tree nut allergies.¹⁰ Allergy to seeds, fish, and shellfish are also considered persistent. Achieving tolerance to allergens is likely associated with an increased amount of T regulatory cells and reduction of allergen-specific IgE.¹¹ A family history of atopy and atopic dermatitis are well-known risk factors for the development of IgE-mediated food allergies. Other risk factors include male sex, race/ethnicity (increased in Asian and black children compared with white children), and genetics.¹² Numerous theories regarding environmental risk factors for food allergy have been proposed, such as the hygiene hypothesis, the allergen avoidance hypothesis, dual allergen exposure hypothesis, and nutritional immunomodulation hypothesis with variable levels of evidence.¹² Other speculations for allergy risk factors that lack firm data include obesity, processed foods, food additives, and genetically modified foods.³

Clinical Presentation

IgE-mediated reactions typically have a rapid onset within minutes to hours of ingestion of the offending agent. Numerous organ systems can be involved, including

the gastrointestinal tract, skin, lungs, and heart. Gastrointestinal manifestations, such as abdominal pain, nausea, vomiting, and diarrhea are the most common presentation in children (50% to 80%). Skin involvement, such as erythema, itching, and urticaria, is the second most common presentation in children (20% to 40%) followed by respiratory symptoms of cough, wheezing, and rhinorrhea (4% to 25%).¹³

Food allergy should be suspected when symptoms occur within minutes to hours of ingestion of a specific food, especially if it occurs on more than one occasion.² Allergy testing also should be considered for infants and children with severe atopic dermatitis, allergic proctocolitis, enterocolitis, enteropathy, and eosinophilic esophagitis. Food allergy is not a typical trigger of chronic asthma or chronic rhinitis so this should not prompt allergy testing.⁷

Diagnosis

The medical history is key to diagnosis and can help identify the likelihood of a food allergy, hone pertinent test selection, and suggest alternative etiologies for symptomatology. The diagnosis of food allergies is challenging, as there is not a uniform set of criteria to follow.⁴ In addition to the clinical history, laboratory studies and an OFC are often necessary to confirm a diagnosis. The NIAID guidelines recommend SPTs and serum IgE (sIgE) testing to assist in identifying IgE-mediated food reactions. These tests typically have high sensitivity but poor specificity, thus they should be used in the context of the clinical history and possible food challenge, as positive tests alone are not diagnostic.^{14,15} This is demonstrated in a study of 44 children avoiding foods because of positive allergy test results. After 111 OFCs, 93% were found to be tolerant to the avoided foods.¹⁶ Nearly 40% of primary care physicians incorrectly interpreted positive sIgE blood tests or SPTs as sufficient for diagnosis of allergy.¹⁷ With this in mind, physicians should be discouraged from ordering “panels” of food tests without the appropriate rationale. Component testing, which measures sIgE to specific proteins in foods, can improve the specificity of testing. For example, a protein in peanuts called Ara h 2 is associated with clinical reactions and is a more specific identifier of true peanut allergy.¹⁸ A recent systematic review¹⁹ concluded that selected components of cow’s milk, hen’s egg, peanut, hazelnut, and shrimp allergen showed high specificity, but lower sensitivity. However, few studies exist for each component, and studies vary widely regarding the cutoff values used, making it challenging to synthesize findings across studies.

The gold standard for allergy diagnosis is a double-blind placebo-controlled food challenge; however, due to expense and lengthy time requirements, it is rarely used in clinical practice.²⁰ More typically, unmasked OFCs are performed in the clinical setting. Both the NAS report and NIAID guidelines advise against the use of many non-validated tests that have, however, gained some popularity. These include food allergy patch testing (atopy patch test), measurement of total IgE, and the basophil activation test. Other tests not recommended and considered “unproven and nonstandardized” for diagnosing food allergy are listed in **Box 1**.

Treatment

The mainstay of treatment for IgE-mediated food allergies remains avoidance of the causing allergen. This must occur in numerous settings including home, school, restaurants, and travel, and families should have a written allergy and anaphylaxis emergency plan.²¹ Intramuscular epinephrine should be administered as a first line for emergent treatment for food allergy anaphylaxis.^{3,22} Antihistamines and steroids also may be used in the case of inadvertent ingestion of allergens. Two additional topics were outlined in the recent NAS report pertinent to the pediatric population: the need for

Box 1**Tests not recommended in the diagnosis of food allergy**

- Allergen-specific immunoglobulin (Ig)A, IgG, or IgG4
- Provocation neutralization
- Immune complexes
- Human leukocyte antigen screening
- Lymphocyte stimulation
- Facial thermography
- Gastric juice analysis
- Endoscopic allergen provocation
- Hair analysis
- Applied kinesiology
- Cytotoxic assays
- Electrodermal testing
- Mediator release assays
- Bioresonance
- Iridology

Data from Sicherer SH, Allen K, Lack G, et al. Critical issues in food allergy: a National Academies consensus report. Pediatrics 2017;140(2):3. with permission.

nutritional monitoring for children avoiding foods due to allergy, and attention to psychosocial aspects of food allergy management, including the increased risk of bullying.⁷ Immunotherapy is not currently recommended by any of the major allergy guidelines; however, it continues to be aggressively explored. Immunotherapy involves giving gradually increasing doses of specific allergens to induce desensitization and ultimately tolerance.²³ This can be accomplished via oral (OIT), sublingual (SLIT), or epicutaneous (EPIT) routes. OIT appears to be more effective than SLIT and EPIT but with more side effects, including allergic reactions and increased risk of eosinophilic esophagitis. Although there are no currently approved therapies for food allergies, 2 commercial products are in the third phase of clinical trials.²³

Prevention of Food Allergy

Recommendations for the prevention of food allergy have changed in the past few decades. Previously allergen avoidance during pregnancy, breastfeeding, and infancy was encouraged; however, these myths have been dispelled. There are now numerous studies suggesting early oral exposure may result in the induction of tolerance.

Maternal dietary restriction and breastfeeding

The American Academy of Pediatrics (AAP), NAS, and NIAID all discourage eliminating allergenic food from the diet of pregnant or lactating women, as there is no supportive evidence that this is beneficial in preventing food allergy even in at-risk infants.^{2,3,24} There is also no significant evidence for a protective effect of breastfeeding for at-risk infants. However, all 3 entities in addition to the World Health Organization promote nursing of all infants through the first 6 months of life.^{2,3,24}

Timing and introduction of complementary foods

There is evidence that very early (during the first 2–3 months of life) introduction of potential allergens put infants at an increased risk for allergy formation; however, there are no convincing data that delaying introduction of solid foods beyond 4 to 6 months of age has any protective effect on the development of food allergy. In the Learning Early About Peanut (LEAP) trial, infants at high risk of peanut allergy (severe eczema or egg allergy) were randomized to receive or avoid peanut to the age of 5 years. The children sensitized to peanut had a peanut allergy rate of 10.6% compared with those in the avoidance group who had peanut allergy rate of 35.3% ($P = .004$; relative risk reduction 70%).²⁵ The AAP, NAS, and NIAID guidelines all recommend early introduction of peanuts in infants at high risk. Delaying the introduction of egg, cow milk, and wheat seems to have no benefits, so it is suggested that there is a potential benefit for introducing these foods in the first year of life when developmentally ready.³ Although delaying introduction of these other allergens is not necessary, it is still unclear if early introduction (4–6 months of age) to at-risk infants is beneficial. Two recent randomized control trials investigating egg introduction to at-risk infants had differing outcomes: one study showed a reduced sensitization at 1 year to those exposed early and the other study showed no change in the risk of future egg allergy.^{26,27}

Hydrolyzed formulas

There are conflicting studies and recommendations regarding the benefits of using partially and extensively hydrolyzed formulas in lieu of cow milk in the first 4 to 6 months in infants with high risk of developing atopic disease. A recent systemic review and meta-analysis failed to find a beneficial effect of these formulas on allergy.²⁸ There is no evidence of preventive effects in low-risk children.²⁹ The NAS committee concluded that there is not enough current evidence to recommend these formulas, which is contrary to the previous AAP Clinical Report in 2008, which suggested there may be a modest benefit in prevention of atopy.^{3,24} The Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy also clearly recommends *against* hydrolyzed (partially or extensively) infant formula for the prevention of allergic disease.³⁰ The European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend only hypoallergenic formulas with a documented preventive effect for high-risk children in the first 4 months of life only.³¹ Overall, it is evident that more research in this area is necessary to draw firm conclusions.

IMMUNE, non-IgE-MEDIATED FOOD ALLERGY

The non-IgE-mediated food allergies more commonly present with gastrointestinal symptoms and are typically subacute or chronic in nature. This category of food allergy encompasses the following disorders: food protein-induced proctitis and proctocolitis, food protein-induced enterocolitis syndrome (FPIES), and food protein-induced enteropathy.

Food Protein-Induced Proctocolitis

Myth: “A child with milk protein-induced proctocolitis as an infant should continue to avoid milk indefinitely”

Food protein-induced proctocolitis is a cell-mediated reaction that tends to occur in exclusively breastfed infants. Food allergens ingested by the mother then appear in the breast milk to produce the reaction. The most typical food implicated is cow's milk (76%); however, it may be caused by egg (16%), soy (6%), or corn (2%) or multiple foods.³² Infants often present in the first month of life with low-grade rectal bleeding. This condition is benign, although may be alarming to new parents. Blood

loss is minimal and typically does not cause anemia. Diagnosis is made clinically, and flexible sigmoidoscopy may be performed for tissue diagnosis for patients with atypical symptoms or who do not respond to treatment. Treatment is avoidance of the provoking allergen. *If left untreated, this condition will resolve spontaneously.* The offending antigen may be reintroduced as early as 6 months of age with 50% of infants tolerating the antigen and 95% tolerating by 9 months of age.³³

Food Protein–Induced Enterocolitis Syndrome

Myth: “If skin and IgE blood tests are negative, there is no allergy”

FPIES is an allergic syndrome that also presents in infants; however, they are generally much sicker than those with proctocolitis. Whereas proctocolitis is common in exclusively breastfed infants, FPIES is uncommon in this population and more typically presents in infants who are formula fed. The mechanism of action is unclear but postulated to be due to ingested food antigens causing local T-cell–mediated inflammation that leads to increased intestinal permeability and fluid shifts.³⁴ The humoral immune response also may be involved. The typical offending agent is cow’s milk and, to a lesser extent, soy. Rice, Oats, and poultry have also been implicated.³⁵ Infants will present in the first month of life with profuse vomiting, diarrhea, and melena or hematochezia. Lethargy, pallor, dehydration, and hypotension are also common. *The diagnosis is made based on the clinical presentation and requires meeting the major criterion of vomiting within 1 to 4 hours after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms in addition to 3 minor criteria.* The minor criteria include additional vomiting, extreme lethargy, marked pallor, need for emergency room visit, need for intravenous fluid, diarrhea, hypotension, and hypothermia.³⁶ A food challenge also may be performed, especially in the setting of a single episode, as viral gastroenteritis is also common at this age. Treatment is based on eliminating the offending food. Most children presenting with cow’s milk and soy FPIES normally become tolerant to the offending food by the age of 3; however, solid food FPIES may have a longer course.

Food Protein–Induced Enteropathy

Food protein–induced enteropathy presents in infants and young children and is the result of a cell-mediated reaction to cow’s milk and soy protein. It is most likely to occur in infants younger than 9 months who have been fed regular cow’s milk instead of formula. The presentation includes a chronic osmotic diarrhea and failure to thrive and can be very similar to CD. Diagnosis is based on clinical features and confirmed with endoscopy and duodenal biopsy, which will reveal distortion of villous architecture that is indistinguishable from CD. The differentiation from CD is based on negative serologies, including anti-tissue transglutaminase and deamidated gliadin peptides. Treatment is avoidance of the allergen and it typically resolves after 2 years of age.³⁷

EOSINOPHILIC GASTROINTESTINAL DISEASE: EOSINOPHILIC ESOPHAGITIS, GASTROENTEROPATHY

Myth: “Food-Specific IgE Testing Determines the Causative Foods for Eosinophilic Gastroenteropathies”

Eosinophilic gastrointestinal disorders (EGIDs) are characterized by eosinophilic infiltration of segments of the intestinal tract in the absence of known causes for eosinophilia.³⁸ Although EGIDs are typically listed under non-IgE food reactions, they have properties of both IgE-mediated food allergy and cellular-mediated hypersensitivity disorders.³⁹ These disorders present with a variety of symptoms depending on the

location and extent of involvement in the gastrointestinal tract and may include difficulty or pain with swallowing, abdominal pain, nausea, vomiting, and weight loss. *Food-specific IgE tests and SPTs may be used to identify foods associated with EGIDs, but alone are not sufficient to make the diagnosis and if negative do not rule out the possibility of eosinophilic gastroenteropathies.*^{2,40} Upper and/or lower endoscopy with mucosal biopsies are necessary for diagnosis in conjunction with the clinical presentation.

Dietary therapy options include elemental diet, which is strict use of amino acid-based formula, targeted diet based on allergy testing, or empiric elimination of the most likely food antigens.⁴¹ Pharmacologic therapy includes topical steroids for both initial and maintenance therapy. Cromolyn, leukotriene receptor antagonists, and immunosuppressive agents are not recommended for treatment.⁴⁰

UNCLEAR, LIKELY MIXED, PATHOGENESIS: NON-CELIAC GLUTEN SENSITIVITY

Myths: “There Is a Test for Gluten Sensitivity; Non-Celiac Gluten Sensitivity Has Been Well Documented in Children Too”

Gluten consumption has been linked to a wide range of disorders, including CD, wheat allergy, dermatitis herpetiformis, gluten ataxia, peripheral neuropathy, and possibly this relatively new entity called “non-celiac gluten sensitivity” (NCGS).

These patients by definition do not meet the criteria for CD or wheat allergy, but report experiencing a number of intestinal and/or extra-intestinal symptoms after consuming gluten-containing foods.⁴² They present neither the autoantibodies nor the enteropathy characteristic of CD. In NCGS, symptoms typically occur soon after ingestion of gluten-containing foods and disappear quickly after elimination of wheat-related foods. On reintroduction of wheat, rapid relapse typically occurs. The clinical manifestations are mostly, but not exclusively, gastrointestinal, and are similar to those of irritable bowel syndrome. In 2015, one of us proposed that “NCGS is a misnomer and probably an umbrella term including various clinical entities.”⁴³ With time, it has become even more clear that indeed this entity encompasses various, distinct populations: whereas a small minority may indeed react to gluten itself, most appear to react to FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), and among them especially fructans, as elegantly demonstrated by Skodje and colleagues⁴⁴ in 2017 (**Fig. 1**). But these patients may also react to a series of proteins found in wheat grouped under the name of ATI (Amylase-Trypsin Inhibitors)⁴⁵; or to wheat with non-IgE-mediated mechanisms⁴⁶; or indeed may simply respond to the placebo/nocebo effect.⁴⁷

It is also important to notice that in spite of numerous reports in the adult literature, this entity has not been adequately demonstrated in children. In fact, after a first report that was an open-label, pilot study likely to be biased,⁴⁸ very recently the same group published a multicenter double-blind, placebo-controlled trial in children⁴⁹: after screening more than 1000 patients and eventually enrolling only 28 eligible children, the investigators found 4 of them to respond to gluten with a VAS (visual analog score) significantly higher after gluten than after placebo. However (**Fig. 2**), also 4 of these children responded to *placebo* with a VAS significantly higher than after gluten, thus making the interpretation quite doubtful at best.

In conclusion on NCGS:

- Because gluten is responsible at best for a small fraction of these patients, the term NCGS is a misnomer and should be abandoned to the less committing “non-celiac wheat intolerance” (NCWI).

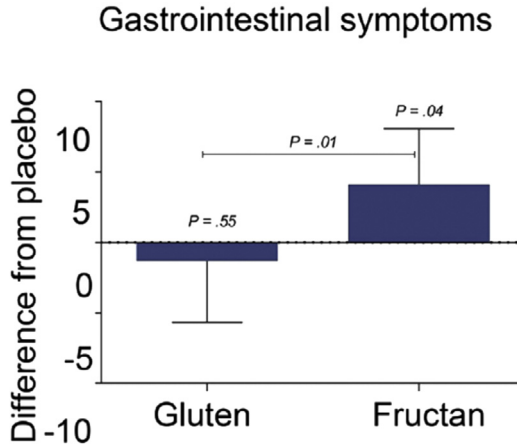


Fig. 1. Mean difference in gluten and fructan response from placebo (95% confidence intervals) for overall Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome (GSRS-IBS). (From Skodje GI, Sarna VK, Minelle IH, et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology* 2018;154(3):534; with permission.)

- It cannot be overemphasized how important it is to first rule out the existence of CD or wheat allergy before considering NCWI.
- To this day, there is no convincing documentation of the existence of NCWI in children.

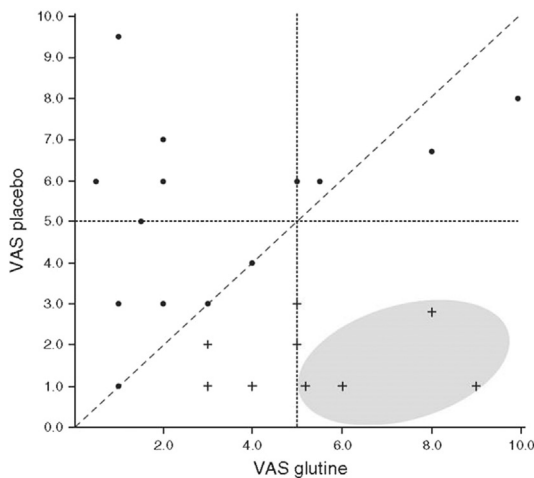


Fig. 2. Distribution of patients according to their VAS while on gluten and placebo; patients on the diagonal line have an equal response to gluten and placebo, children in the lower left quadrant experience a mild degree of overall response (<5) to either gluten or placebo. (Reprinted by permission from Springer Nature: Francavilla R, Cristofori F, Verzillo L, et al. Randomized Double-Blind Placebo-Controlled Crossover Trial for the Diagnosis of Non-Celiac Gluten Sensitivity in Children. *Am J Gastroenterol* 2018;113(3):428.)

Table 2
Diagnostic approach for food intolerances

Condition Suspected	Clinical	Food(s) Involved	Diagnostic Approach
Immediate GI hypersensitivity	Usually infancy to childhood: reactions to offending food within minutes: vomiting, diarrhea, nausea, pain; also rhinoconjunctivitis, skin rash, angioedema	Cow's milk, soy, eggs, peanuts, wheat, shellfish	History, +SPT and/or sIgE
Food protein–induced proctocolitis	Early infancy: streaks of blood and mucus in stools in breastfed, typically healthy infants	Cow's milk, eggs, soy, corn (in mother's diet)	Clinical diagnosis supported by food elimination in mother's diet
Food protein–induced enterocolitis syndrome	Early infancy: vomiting, diarrhea, colitis	Rice, soy, cow's milk, vegetables, fruits, oats, meat, fish	Clinical criteria $\pm$ food challenge
Food protein–induced enteropathy	Infants and toddlers: malabsorption syndrome similar to early-onset celiac disease, hypoalbuminemia	Cow's milk, occasionally soy or egg	Clinical diagnosis supported by duodenal biopsies with patchy villous atrophy
Eosinophilic esophagitis	All ages: asymptomatic, refluxlike symptoms, dysphagia	Cow's milk, soy, eggs, peanuts, wheat, shellfish	Endoscopy with biopsies showing typical changes; SPT, sIgE sometimes useful
Eosinophilic gastroenteropathy	Highly variable symptoms depending on localization and extension of eosinophilic infiltrates	Cow's milk, soy, eggs, peanuts, wheat, shellfish	Endoscopy with biopsies
Gluten sensitivity	Adults with IBS-like symptoms	Fructans; wheat components such as ATI; gluten in a minority	Clinical only: no diagnostic marker available
Celiac disease	All ages. Strictly limited to HLA-DQ2 and/or DQ8 positive subjects. GI and extra-GI symptoms	Gluten	Specific serology+, diagnostic features of duodenal biopsies
Lactose intolerance	Increases with age: abdominal pain, bloating, flatulence, diarrhea	Lactose	Clinical, breath hydrogen testing, rarely duodenal biopsy

Abbreviations: ATI, amylase-trypsin inhibitors; GI, gastrointestinal; IBS, irritable bowel syndrome; sIgE, serum immunoglobulin E; SPT, skin prick testing.

AUTOIMMUNE FOOD INTOLERANCE: CELIAC DISEASE

Myth: “Asymptomatic Patients with Celiac Disease Do Not Need a Gluten-Free Diet”

CD is the most common genetically induced food intolerance and is an autoimmune disorder affecting 1% of the population and occurs in individuals of all ages who express the HLA-Class II haplotypes DQ2 and/or DQ8. Ingestion of gluten and related proteins found in wheat, barley, and rye trigger CD in genetically susceptible individuals. It is characterized by an inflammatory enteropathy that leads to flattening of the small intestinal mucosa through a combined adaptive and innate immune response.^{50,51} There are variable degrees of severity and clinical manifestations. Gastrointestinal symptoms are prominent, especially in younger children, and include abdominal pain, distention, diarrhea, constipation, and rarely in the present day, malnutrition and failure to thrive. Extra-intestinal manifestations include short stature, iron-deficiency anemia, female infertility, and the typical skin finding of dermatitis herpetiformis. Diagnosis of CD involves serologic screening with autoantibodies that are very sensitive and specific: anti-tissue transglutaminase antibodies (tTG), anti-endomysium antibodies (EMA) and deamidated gliadin peptides.⁴² The diagnosis is then typically confirmed by upper endoscopy and obtaining duodenal biopsies, which will show typical histologic changes in the mucosa. *CD is treated by prompt and strict adherence to a life-long gluten-free diet regardless of presenting symptoms.*

NONIMMUNE MEDIATED

Disaccharide Deficiencies: Lactose Intolerance

Myth: “lactose intolerance is the same as a milk allergy”

Among the disaccharidase deficiencies, lactase deficiency is by far the most common, although the exact prevalence is unknown.⁵² Intolerance to lactose (one of the FOD-MAP carbohydrates) is a clinical syndrome in which ingestion of lactose causes symptoms of abdominal pain, bloating, gassiness, and diarrhea. Ingested lactose from dairy-containing foods is broken down by the enzyme lactase on the microvilli surface of the small intestine. *In acquired lactase deficiency, the lactase enzyme is deficient and lactose not absorbed by the small bowel, passing rapidly into the colon. There the lactose is converted to short-chain fatty acids by intestinal bacteria producing fermentation products (including gases such as hydrogen), which cause the typical symptoms.*⁵² *There is no immune reaction, as seen with a milk allergy.* Diagnosis primarily can be made clinically with confirmation by resolution of symptoms after avoiding lactose-containing foods for 5 to 7 days. A lactose breath hydrogen test also may be used to confirm the diagnosis, and in rare cases a small bowel biopsy to determine lactase enzyme activity may be used. Treatment includes dietary lactose restriction or enzyme replacement, which is available over the counter.

SUMMARY

Not all adverse reactions are due to food allergy, and an excellent history is the essential first step in making the proper diagnosis. The clinical history will guide appropriate testing selection, and **Table 2** is a suggested diagnostic approach to food intolerances. A positive sIgE or SPT alone is not sufficient to make a diagnosis: testing indicates sensitization but not necessarily clinical allergy. Finally, it is imperative to keep in mind that patient-reported and parental-reported food allergies are often not substantiated by allergy testing and may prompt investigation of other nonallergy causes of food intolerance.

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