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Clinical Aspects of Gastrointestinal Food Allergy in Childhood

Scott H. Sicherer, MD

ABSTRACT. Gastrointestinal food allergies are a spectrum of disorders that result from adverse immune responses to dietary antigens. The named disorders include immediate gastrointestinal hypersensitivity (anaphylaxis), oral allergy syndrome, allergic eosinophilic esophagitis, gastritis, and gastroenterocolitis; dietary protein enterocolitis, proctitis, and enteropathy; and celiac disease. Additional disorders sometimes attributed to food allergy include colic, gastroesophageal reflux, and constipation. The pediatrician faces several challenges in dealing with these disorders because diagnosis requires differentiating allergic disorders from many other causes of similar symptoms, and therapy requires identification of causal foods, application of therapeutic diets and/or medications, and monitoring for resolution of these disorders. This review catalogs the spectrum of gastrointestinal food allergies that affect children and provides a framework for a rational approach to diagnosis and management. *Pediatrics* 2003;111:1609–1616; *gastrointestinal allergy, food allergy, food hypersensitivity, oral tolerance, mucosal immunology.*

ABBREVIATIONS. IgE, immunoglobulin E; RAST, radioallergen sorbent test; GER, gastroesophageal reflux; CMA, cow milk allergy.

The gastrointestinal tract is capable of displaying a relatively narrow repertoire of symptoms and signs in response to disease: pain, nausea, vomiting, and diarrhea. If there is malabsorption or protein loss, then additional manifestations of edema and poor growth may ensue. The challenge for the pediatrician is to determine the cause of symptoms from a wide spectrum of disorders of diverse causes spanning infection, inflammation (Crohn's disease, ulcerative colitis), anatomic problems (pyloric stenosis), malignancy, and metabolic disorders of various types. Among the causes to consider when evaluating gastrointestinal complaints are those among the broad category of adverse reactions to foods. Numerous food components can trigger symptoms; for example, bacterial toxins cause food poisoning, dietary fats may elicit symptoms in those with disorders of lipid digestion (biliary disease), and lactose may elicit symptoms in those with primary or secondary

deficiency of lactase. In contrast to the variety of adverse food reactions caused by toxins, pharmacologic agents (eg, caffeine), and intolerance, food-allergic disorders are attributable to adverse immune responses to dietary proteins and account for numerous gastrointestinal disorders of childhood. This review catalogs the clinical manifestations, pathophysiology, treatment, and natural course of a variety of named gastrointestinal food hypersensitivity disorders that affect infants and children (Table 1)^{1,2} and also discusses several other disorders sometimes attributable to food allergy. A general approach to diagnosis and management is provided.

DISORDERS THAT PRIMARILY AFFECT INFANTS

Dietary Protein-Induced Proctitis/Proctocolitis

Infants with dietary protein-induced proctitis/proctocolitis seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool.^{3,4} Blood loss is usually minimal, and anemia is rare. The disorder manifests in the first several months of life, with a mean age at diagnosis of 2 months.^{5,6} The differential diagnosis includes causes such as infection and anal fissures. The lack of systemic symptoms, vomiting, diarrhea, and growth failure help to differentiate this disorder from other gastrointestinal food allergies that may also include colitis. Cow milk proteins and, less commonly, soy protein are the common triggers. Most infants present while being breastfed^{3,7–9} and are symptomatic as a result of maternally ingested proteins excreted in breast milk. The disorder has also been noted in infants who take casein hydrolysates.¹⁰ Endoscopic examination is often deferred but may show focal to diffuse colitis with edema and erosions. Biopsy reveals an eosinophilic infiltration and occasionally lymphonodular hyperplasia.^{11,12}

The mechanism underlying the disorder is unknown, but it is not associated with immunoglobulin E (IgE) antibody (prick skin tests/radioallergen sorbent tests [RASTs] are characteristically negative). Presumptive evidence to secure the diagnosis is obtained through a response to dietary elimination of the causal food protein. For breastfed infants, maternal restriction of cow milk (and more rarely other foods such as soy or egg) is required.³ If maternal dietary manipulations fail to resolve the bleeding and alternative diagnoses are excluded (by culture, biopsy, etc), then the physician may consider a trial of a hypoallergenic formula (eg, casein hydrolysate). However, there are currently no data to address the outcome of continued breastfeeding despite mild bleeding in an otherwise healthy-seeming infant. For

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TABLE 1. Named Gastrointestinal Food-Allergic Disorders of Infancy and Childhood

Disorder	Key Symptoms/Signs/Features
IgE antibody mediated, acute onset Immediate gastrointestinal hypersensitivity	Acute onset nausea, emesis, pain; diarrhea may follow; foods: milk, egg, wheat, soy, peanut, tree nuts, seafood
Oral allergy syndrome	Pruritus, mild edema confined to oral cavity caused by IgE antibodies originally induced by pollen sensitization that react with homologous proteins in certain uncooked fruits/vegetables
IgE antibody associated in some cases/cell mediated, delayed-onset/chronic Eosinophilic gastroenteropathies	Symptoms vary upon site(s)/degree of eosinophilic inflammation; esophageal: dysphagia, pain; generalized: ascites, weight loss, protein losing enteropathy, edema, obstruction; multiple foods
Cell-mediated, delayed-onset/chronic Dietary protein enterocolitis	Chronic exposure: emesis, diarrhea, poor growth, lethargy; reexposure after restriction: emesis, diarrhea, hypotension (15%) $\approx$ 2 h after ingestion; foods: milk, soy, grains
Dietary protein proctitis	Mucousy, bloody stools; causes: breast milk with maternal cow milk ingestion, cow milk
Dietary protein enteropathy Celiac disease	Malabsorption, edema, emesis, poor growth, usually caused by cow milk Malabsorption, diarrhea, response to gluten, HLA-DQ2 associated

cow milk- or soy formula-fed infants, substitution with a protein hydrolysate formula generally leads to cessation of bleeding. An amino acid-based formula may be needed in those who have prolonged bleeding while taking an extensive hydrolysate.^{10,13} Bleeding is expected to resolve within 72 hours of dietary exclusion of the causal protein. Continued bleeding may be an indication for referral for more invasive testing (ie, biopsy) and monitoring for anemia. The disorder should resolve by age 1 or 2 years, and the causal food protein can be gradually added back to the diet at that time with monitoring for visible blood. The disorder is not IgE antibody mediated, so unless additional atopic disease develops in the patient, testing for IgE antibodies to the causal protein is not needed.

Dietary Protein Enteropathy

Dietary protein enteropathy is characterized by protracted diarrhea and vomiting (in two thirds) with resulting malabsorption and failure to thrive with onset most commonly in infancy.^{14–18} Protein-losing enteropathy may lead to edema, abdominal distension, and sometimes anemia. The differential diagnosis must consider other causes of enteropathy (eg, infectious, metabolic, lymphangiectasia, Celiac disease). The disorder is caused by an immune response most commonly to cow milk protein, but soy, cereal grains, egg, and seafood have also been implicated. Diagnosis is based on the combined findings from endoscopy/biopsy, allergen elimination, and challenge. Biopsy reveals variable small bowel villus injury, increased crypt length, intraepithelial lymphocytes, and few eosinophils. The immune mechanisms seem to involve T cell responses¹⁹ and are not associated with IgE antibodies. Although features are shared with Celiac disease, this enteropathy is unlike Celiac disease because resolution generally occurs in 1–2 years and there is no increased threat of future malignancy.¹⁶ Dietary protein enteropathy may persist into later childhood,²⁰ but the frequency of persistence of the disorder into adulthood is unknown.

Dietary Protein Enterocolitis

The symptoms observed in infants with dietary protein enterocolitis seem similar to but more severe than those observed in protein enteropathy.^{21–23} Because both the small and large bowel are involved, the term “enterocolitis” is used. The disorder must be differentiated from nonallergic causes of enterocolitis (eg, infection, neonatal enterocolitis). Cow milk protein is the most common cause, but approximately half of patients also react to soy. A variety of additional foods have been implicated, including rice, oat and other cereal grains, and poultry.^{12,24,25} During chronic or intermittent ingestion of the causal food protein, infants may experience such severe vomiting and diarrhea that dehydration, lethargy, acidosis, and methemoglobinemia may result,²⁶ and infants may seem septic with high peripheral blood polymorphonuclear leukocyte counts. Resolution of symptoms occurs after appropriate dietary exclusion. A distinct feature of this disorder is that reintroduction of the causal protein leads to a delayed ($\sim$ 2 hours) onset of dramatic symptoms that has been used to confirm the diagnosis by oral food challenge.^{21,22,27} Confirmation of the allergy includes a negative search for other causes; improvement when not ingesting the causal protein; a positive oral challenge resulting in vomiting/diarrhea; and evidence of gastrointestinal inflammation through stool examination for blood, eosinophils, and a rise in the peripheral polymorphonuclear leukocyte count over 3500 cells/mL.²² Caution is needed when performing oral food challenges because approximately 20% of reactions lead to shock.²³ The diagnosis is usually made without biopsy, but colonic biopsies in symptomatic patients reveal crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells; small bowel biopsies reveal edema, acute inflammation, and mild villous injury.^{27–31} The mechanism underlying this disorder seems to involve a milk-specific T cell response with elaboration of the cytokine tumor necrosis factor- α that may also account for some of the systemic symptoms.^{32–34} That

several foods are often involved may reflect a more global problem in immune tolerance for these infants. The disorder is not associated with IgE antibody (but a small subset of patients may eventually establish IgE antibody responses).²³ Considering the high rate of co-allergy to cow milk and soy, treatment with a hypoallergenic formula (casein hydrolysate) is suggested and usually effective (if not, then an amino acid-based formula can be used). It may be advisable to delay the introduction of other allergenic foods, especially grains, in these children. Treatment of acute reactions (reexposure) may require fluid resuscitation, and administration of steroids has been suggested.²³ Most infants outgrow the allergy by age 2 or 3 years, but some seem to maintain hypersensitivity into childhood.³⁵ Because resolution must be proved through oral challenges that can induce severe reactions, evaluation must be undertaken cautiously under supervision in a controlled setting, usually with intravenous access in place.

Additional Disorders Related Primarily to Cow Milk Hypersensitivity

Gastroesophageal Reflux

On the basis of studies using cow milk elimination and challenge, it is clear that a subset of infantile gastroesophageal reflux (GER) is attributable to cow milk allergy (CMA).^{36–41} The magnitude of the problem is not well-defined; it has been estimated that in 16% to 42% of infants, GER is attributable to CMA.^{37,39,40} Risk factors for milk's being causal seem to include esophagitis, malabsorption, diarrhea, and atopic dermatitis. Thus, for many infants with cow milk-associated GER, the reflux is not an isolated symptom. One group^{38–40} identified that in infants with CMA-induced GER, the pH probe shows a "phasic" pattern with a gradual and prolonged fall in pH after milk ingestion. This is in contrast to the pH probe pattern seen with typical GER in which there are multiple, random, sharp decreases in pH. However, the phasic pattern has not been demonstrated by other investigators.⁴² Taking the studies together, it is evident that CMA accounts for GER in some infants, but other causes must also be considered (eg, obstruction, metabolic disorders, and other inflammatory disorders). Particularly when there are additional symptoms of CMA and/or poor responses to other measures (medications), a trial elimination diet may be warranted.

Infantile Colic

There is some evidence that infantile colic is associated with CMA, but the strength of the relationship is not well-defined. Infants who are experiencing symptoms of CMA have a high rate (44%) of colic, and hypoallergenic formulas are more efficacious for colic than antacids or low-lactose formula.^{43,44} However, the role of allergy as opposed to other causes among those with colic and without other symptoms of food allergy remains controversial and in need of additional study. For example, there does not seem to be an increased rate of atopy in infants with col-

ic.⁴⁵ In regard to trials of therapy, a meta-analysis of 27 trials identified through Medline and the Cochrane Controlled Trials Register concluded that infantile colic should preferably be treated by reduced stimulation (effect size 0.48) and a 1-week trial of substitution of cow milk formula with hypoallergenic formula (effect size 0.22 based on 2 studies).⁴⁴ The formula suggested by these authors for substitution was an hydrolysate because the data are less convincing or incomplete for soy and low-lactose formula. They suggested a trial of milk exclusion in the diet of lactating mothers.

DISORDERS THAT AFFECT BOTH INFANTS AND CHILDREN

Immediate Gastrointestinal Hypersensitivity

Symptoms of immediate gastrointestinal hypersensitivity are acute—usually within minutes or up to 1 to 2 hours—and include nausea, vomiting, and abdominal pain usually within minutes of ingestion. Diarrhea may follow several hours after the initial symptoms. Unlike the disorders described above, this disorder is mediated by IgE antibody directed to food proteins. These IgE antibodies provide a mechanism for food-specific mediator release (eg, histamine) from mast cells. Although immediate, IgE-mediated gastrointestinal reactions may occur without other systemic symptoms; they are more commonly associated with reactions in other organ systems, such as during systemic anaphylaxis in patients with other atopic diseases. For example, children with atopic dermatitis undergoing oral food challenges with foods to which they have specific IgE antibody will sometimes manifest only gastrointestinal symptoms.^{46,47} In addition to a suggestive history, allergy prick skin tests and RASTs to the causal protein will be positive. The usual offenders are milk, egg, peanut, soy, wheat, and seafood. Similar to other IgE-dependent allergic disorders, allergy to milk, egg, wheat, and soy generally resolves, whereas allergies to peanuts, tree nuts, and seafood are more likely to persist.

Eosinophilic Gastroenteropathies (Eosinophilic Esophagitis, Gastroenterocolitis, and Gastritis)

This heterogeneous group of eosinophilic gastroenteropathies has in common an eosinophilic inflammation of the gut. The nomenclature used to describe particular disorders relates to the locations of eosinophilia; the depth and severity of eosinophilic inflammation influences the symptoms. Named subtypes include allergic eosinophilic gastritis, allergic eosinophilic gastroenterocolitis, and allergic eosinophilic esophagitis. The symptoms caused by these disorders overlap those caused by many other pathologic gastrointestinal processes: postprandial nausea, dysphagia, abdominal pain, vomiting, and diarrhea, and if inflammation is very dense, obstruction can result. Small bowel involvement may result in protein-losing enteropathy and weight loss. Serosal involvement can induce eosinophilic ascites. The disorder requires confirmation of an eosinophilic infiltration of the gut by biopsy (sometimes patchy)

and elimination of other causes of eosinophilia, such as parasites, inflammatory bowel disease, and vasculitis. All age groups may be affected, and the disorder has been diagnosed in preterm infants with symptoms that overlap those of necrotizing enterocolitis.⁴⁸ Peripheral eosinophilia is sometimes observed (~50% of patients).^{49,50} The pathophysiologic basis of the disorder has remained elusive, and the role of allergens is debated. At least a subset of those with the disorder are food responsive and reactive to the usual causative agents (eg, milk, egg, wheat, soy) but with an increased degree of multiple food allergies. In patients with food-responsive eosinophilic gastroenteropathies, the pathophysiological mechanisms seem to include both cell-mediated and IgE antibody-mediated forms.

Perhaps the most common type of eosinophilic gastroenteropathy and most difficult to diagnose and manage is allergic eosinophilic esophagitis. This disorder is particularly challenging to diagnose because the symptoms overlap those of GER. Patients with allergic eosinophilic esophagitis have a predominance of dysphagia (~85%), and there is an overrepresentation of young, atopic male patients.^{51–55} Although symptoms overlap those of GER, in some patients reflux is absent on pH probe. Some authors have evaluated the number of eosinophils per high-power field as a means to differentiate this disorder from GER, and when the numbers exceed 7, especially when they are >24, allergic and/or intrinsic eosinophilic inflammation is likely.^{52,56–61} In this scenario, medical treatment for GER may fail, but anti-inflammatory medications such as oral steroids have proved efficacious.⁶¹ The ability of dietary management to ameliorate the inflammation has been proved⁶² but is not universally curative.⁵² Orenstein et al⁵² documented positive prick skin tests or RASTs in 13 of 19 children with eosinophilic esophagitis (median: 7 foods). Dietary elimination was undertaken in 12 of the 13 with positive tests. Of 10 who were compliant with the diet, all were believed to benefit with resolution of symptoms. Seven of the patients had concomitant therapies (steroid, 3; anti-reflux medications, 2; cromolyn, 1; or fundoplication, 1); however, lapses in the diet were accompanied by recurrence of symptoms in the months after diagnosis despite the other therapies. In a study that specifically addressed the role of food allergy in children with eosinophilic esophagitis, Kelly et al⁶² evaluated patients for whom standard GER treatment or fundoplication failed (6 patients) and who had persistent eosinophilia on esophageal biopsy. These patients were placed on a very restricted diet (1–2 solid foods, eg, apple, corn) and an amino acid-based formula. Eight of 10 patients became symptom-free, and 2 had significant reduction in symptoms within 2 to 6 weeks after starting the dietary program. The patients also demonstrated a decline in the median numbers of eosinophils from 40 to 0.5/high-power field. The causal foods were primarily milk, soy, egg, peanut, and wheat. The correlation of causal foods with positive skin test results was poor, and improved diagnostic methods are under investigation.⁶³ Oral steroids have been effective, including

case reports of high-dose inhaled/swallowed steroids (eg, the off-label use of inhaled steroids sprayed into the mouth and swallowed),⁶⁴ and additional anti-inflammatory therapies such as cromolyn⁵² and leukotriene antagonists have been tried but require additional study.^{65,66} A trial of an elemental diet may prove beneficial in many of these patients,⁶⁷ but the process of identifying causal allergens is time-consuming and often frustrating. If there is a response to elimination diets—which entails at least 6 weeks on the diet and may require a biopsy to confirm—then foods are slowly added back into the diet. The onset of symptoms after addition of a problematic food may be delayed, adding to the diagnostic difficulties.

The natural course of the allergic eosinophilic gastroenteropathies is not well-defined. For at least some patients, the disorder seems to be long-lived and can continue (or present) through adulthood with a waxing and waning course with an element of improvement over time.⁴⁹

DISORDERS THAT GENERALLY PRESENT OUTSIDE INFANCY

Oral Allergy Syndrome (Pollen-Food Syndrome)

Individuals with oral allergy syndrome, an IgE antibody-mediated disorder, experience prompt oral pruritus and sometimes angioedema of the lips, tongue, and palate when ingesting certain fresh fruits and vegetables.⁶⁸ The expression of this allergic response requires initial sensitization via the respiratory route to pollens that contain proteins that are homologous to those found in particular fruits and vegetables. Individuals with this syndrome, therefore, usually have a history of seasonal allergic rhinitis (hayfever). Examples of the associated pollens and foods include reactions to melons in individuals with ragweed allergy and reactions to apples, peaches, and cherries in those with birch pollen allergy. The proteins are labile, and cooked forms of the fruits and vegetables generally do not induce symptoms. Similarly, it is assumed that systemic reactions are averted because the proteins are easily digested. However, ~9% of individuals experience symptoms beyond the mouth, and 1% to 2% experience severe reactions.⁶⁹ Allergy skin tests using fresh extracts of the implicated food are characteristically positive.

Celiac Disease

Celiac disease represents an immune response to a food protein (gluten) and therefore may be considered a food-allergic disorder.^{70,71} Symptoms include vomiting, diarrhea, anorexia, and growth failure. Initial symptoms may present in the first year of life, but characteristic clinical features usually manifest after age 1 year. The disorder is caused by gliadin-specific T cell responses enhanced by deamidated gliadin produced by tissue transglutaminase. Antigen presentation is central as >95% of patients are HLA DQ2. The symptoms include protein-losing enteropathy and growth failure. A full discussion of diagnosis and management is beyond the scope of this review.

Chronic Constipation

Cow milk intolerance has been suggested as a cause of chronic constipation in older infants and toddlers.⁷²⁻⁷⁵ Considering potential selection bias and paucity of studies, it is difficult to know what percentage of constipated children may be cow milk responsive. Among small groups of selected patients, responsiveness was 28% to 68%.^{74,75} There may be an immunologic basis because investigators have demonstrated a higher rate of atopic disease, rectal mucosal inflammation, and IgE antibodies in the milk-responsive group.⁷⁴ In these studies, substitution with soy or other foods may have also had a nonimmunologic laxative effect. No specific recommendations have been made, but prudence may suggest that a trial of dietary elimination of cow milk be undertaken for recalcitrant constipation unresponsive to other therapies. Additional studies are needed to confirm the specific associations.

APPROACH TO DIAGNOSIS AND MANAGEMENT

Additional reviews in this series address the general scheme for the diagnosis and management of food allergy in infants and children. What is emphasized here are the features that may indicate to the pediatrician that food hypersensitivity may be a cause of observed gastrointestinal disease. The pediatrician who is evaluating an infant or child with symptoms/signs of gastrointestinal disease must determine the cause from among a wide variety of possibilities, including infection, metabolic disorder, anatomic disorders, etc. Adverse responses to ingestants remains 1 of the possibilities, and within this broad category one must consider both immunologic (allergic) and nonimmunologic (intolerance, pharmacologic effects, food poisoning, etc) causes.

A recent consensus workshop (Workshop on the Classification of Gastrointestinal Diseases of Infants and Children, November 1998, Washington, DC)¹ considered a variety of factors in establishing a diagnosis of food allergy in gastrointestinal disorders. These elements are summarized in Table 2 and take into consideration the variety of clinical manifestations of food-allergic disorders and the overlap with non-food-allergic disorders. Consequently, 1 single recommendation cannot be made for diagnosing gastrointestinal food allergy, and proof of underlying immunologic mechanisms is lacking for most of the described disorders, except for those mediated by food-specific IgE antibodies. It should also be acknowledged that symptoms often overlap (eg, vomiting and diarrhea) and patients may not always fit neatly into 1 category (eg, proctitis as differentiated from a very mild manifestation of enterocolitis).

Co-consideration of the features indicating a high likelihood of allergic gastrointestinal disease (Table 2), along with an appreciation for the named food-allergic disorders that affect the gut (Table 1), provides an essential starting point for the evaluation of the role of food allergy in gastrointestinal disease. For immediate reactions that are likely to be IgE antibody-mediated, ancillary tests such as prick skin tests or RASTs are helpful in verifying suspicions

TABLE 2. Elements Suggesting Food Allergy as a Cause of Gastrointestinal Disease

1) Temporal relationship of characteristic symptoms to particular foods
2) Exclusion of anatomical, metabolic, infectious and other inflammatory causes
3) Pathologic findings consistent with an allergic cause (e.g., eosinophilia)
4) Confirmation of a relationship between ingestion of the specific dietary protein and symptoms by clinical challenges or repeated exposures
5) Evidence of the food specific IgE antibody in settings of IgE-mediated disease
6) Associated atopic disease (atopic dermatitis, asthma)
7) Failure to respond to conventional therapies aimed at anatomical, functional, metabolic or infectious causes
8) Improvement in symptoms with elimination of the causal dietary protein(s)
9) Clinical response to treatments of allergic inflammation (i.e.-corticosteroids)
10) Similarities to clinical syndromes either proven or presumed to be caused by immunologic mechanisms
11) Lack of other explanations for the clinical allergic-like reaction

Adapted from Sampson and Anderson.¹

obtained in the history. In some cases, oral food challenges may be needed for additional verification. However, the majority of gastrointestinal food hypersensitivity disorders are not mediated by IgE antibody, and so the evaluation is much more dependent on the results of elimination diets, selected oral food challenges, and biopsies as indicated. Unlike the evaluation for food allergy in skin or respiratory disease, for gastrointestinal food allergy a number of ancillary tests, often administered by gastroenterologists and allergists, may be needed to determine the diagnosis (Table 3). Additional tests that may have value, such as patch testing with foods,⁶³ are under study. Patch testing with foods involves the placement of a food extract under occlusion on the skin for 24 hours with observation at 24 and 48 hours after removal for erythema and papules indicated a delayed-type hypersensitivity response. More study is needed before such tests can be generally recommended. Table 4 summarizes features that are helpful for the evaluation of specific clinical disorders. Table 5 summarizes clinical circumstances that suggest consideration for food allergy as a cause.

A number of tests are of unproven utility and should not be used. These include measurement of IgG₄ antibody, provocation-neutralization (drops placed under the tongue or injected to diagnose and

TABLE 3. Laboratory Tests Used in the Evaluation of Food Allergy in Gastrointestinal Disorders*

Primary tests for specific IgE antibody to particular foods, as indicated
RAST (radioallergosorbent test)
Prick/puncture skin tests
Adjunctive tests
Endoscopy/biopsy
Absorption studies
Stool analysis (heme, leukocytes, eosinophils)
pH probe

* Tests are selected on the basis of individual disorders/symptom complexes.

TABLE 4. Features and Diagnostic Tests Helpful for Diagnosis

Disorder Under Consideration	Central Diagnostic Tests*	Additional Diagnostic Tests†	Natural Course	Routine for Follow-up
Immediate gastrointestinal hypersensitivity	PST, RAST	OFC	Depends upon food	Repeat PST/RAST, OFC
Oral allergy syndrome	PST	OFC, RAST	Prolonged	PST, RAST, OFC if suspected resolution
Eosinophilic gastroenteropathies	Biopsy, ED	PST, RAST, OFC	Prolonged	Biopsy, OFC, PST, RAST
Dietary protein enterocolitis	ED (OFC)	PST, RAST, OFC, sepsis evaluation	2 y	OFC
Dietary protein proctitis	ED	Usually none, biopsy if recalcitrant, stool culture	1–2 y	Gradual reintroduction
Dietary protein enteropathy	Biopsy, ED	PST, RAST, OFC	2 y	OFC
Milk-induced reflux, colic, or constipation	ED and OFC	pH probe, biopsy, trial reflux medications	Reflux/colic-resolves beyond age 1–2 y	OFC
Celiac disease	Serologies, biopsy		Permanent	Routine health visits

PST indicates prick skin test; ED, elimination diets; OFC, oral food challenge.

* The history is paramount to the diagnosis of all of the disorders.

† May be needed to verify specific foods involved, selected on the basis of various needs (nutrition, ruling out other disorders, etc).

TABLE 5. Summary: Specific Clinical Scenarios That May Warrant Evaluation for Food Allergy or Intolerance

Immediate gastrointestinal responses (oral pruritus, vomiting, diarrhea) after ingestion of particular food(s)
Mucousy/bloody stools in an infant
Malabsorption/protein-losing enteropathy
Subacute/chronic vomiting, diarrhea, or dysphagia
Failure to thrive
Gastrointestinal symptoms in a patient with atopy (eg, atopic dermatitis)
Gastroesophageal reflux disease recalcitrant to typical therapies
Infantile colic poorly responsive to behavioral interventions
Chronic constipation recalcitrant to typical management

treat various symptoms), and applied kinesiology (muscle strength testing).⁷⁶

Therapy in infants often requires selection of an alternative formula. In infants with IgE-mediated CMA, most (~86%) will tolerate a soy formula,⁷⁷ but the rate of tolerance is lower (~50%) for most of the cell-mediated disorders.²³ Infants with true CMA would be expected also to react to partially hydrolyzed formula, lactose-free cow milk-based formula, and most mammalian milks (eg, sheep, goat),⁷⁸ so none of these is a good alternative. In most cases (>95%), infants with CMA will tolerate extensively hydrolyzed cow milk formula, but for the few who continue to react (presumably as a result of residual allergens), an amino acid-based formula is required for therapy.^{10,67,79–81}

Although therapy of gastrointestinal food hypersensitivity disorders includes dietary restriction, the good news is that most of the disorders resolve with time. Hence, a central aspect of management is periodic reevaluation (oral food challenge) for determination of tolerance, a procedure that often requires the specific expertise of an allergist or gastroenterologist if acute or severe reactions are possible. Hopefully, the coming years will bring improved diagnostic, therapeutic, and preventive strategies for better management of these conditions.

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