

Nutrition in Clinical Practice

<http://ncp.sagepub.com/>

Gastrointestinal Manifestations of Food Allergies in Pediatric Patients

Manuel Garcia-Careaga and John A. Kerner, Jr

Nutr Clin Pract 2005 20: 526

DOI: 10.1177/0115426505020005526

The online version of this article can be found at:

<http://ncp.sagepub.com/content/20/5/526>

Published by:



<http://www.sagepublications.com>

On behalf of:



[The American Society for Parenteral & Enteral Nutrition](#)

Additional services and information for *Nutrition in Clinical Practice* can be found at:

Email Alerts: <http://ncp.sagepub.com/cgi/alerts>

Subscriptions: <http://ncp.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Gastrointestinal Manifestations of Food Allergies in Pediatric Patients

Manuel Garcia-Careaga, MD; and John A. Kerner, Jr, MD

Department of Pediatrics, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Lucile Packard Children's Hospital, Stanford University Medical Center, Stanford, California

ABSTRACT: Foods that account for 90% of allergic reactions in children are cow's milk protein, eggs, peanut, soy, tree nuts, fish, and wheat. Food allergy can manifest as urticaria/angioedema, anaphylaxis, atopic dermatitis, respiratory symptoms, or a gastrointestinal (GI) disorder. GI allergic manifestations can be classified as immunoglobulin E (IgE) mediated (immediate GI hypersensitivity and oral allergy syndrome); "mixed" GI allergy syndromes (involving some IgE components and some non-IgE or T-cell-mediated components) include eosinophilic esophagitis and eosinophilic gastroenteritis. Non-IgE-mediated or T-cell-mediated allergic GI disorders include dietary protein enteropathy, protein-induced enterocolitis, and proctitis. All these conditions share a common denominator: the response of the immune system to a specific protein leading to pathologic inflammatory changes in the GI tract. This immunological response can elicit symptoms such as diarrhea, vomiting, dysphagia, constipation, or GI blood loss, symptoms consistent with a GI disorder. The detection of food allergies can be accomplished by the use of radioallergosorbent (RAST) testing and skin prick tests in helping to assess the IgE-mediated disorders. Patch tests may help evaluate delayed hypersensitivity reactions. Treatment of GI allergic disorders ranges from strict dietary elimination of offending food(s), use of protein hydrolysates, and use of L-amino acid-based formula when protein hydrolysates fail. Treatment with topical (for eosinophilic esophagitis) or systemic steroids is used if all dietary measures are unsuccessful. Maternal breast feeding or the use from birth of hydrolysate formulas (extensive or partial hydrolysates) may be efficacious in the prevention of atopic disease in "high-risk" families (with at least 1 parent or sibling with a history of atopic disease).

Definitions

Food allergies are, by definition, the result of a pathologic immune reaction to a food protein. In contrast, an adverse food reaction is the occurrence of an ill effect as a result of the intake of food, which could be the result of an immunologic- or a nonimmunologic-related response (Table 1).

Food intolerances of nonimmunologic etiology could be secondary to an enzyme deficiency such as disaccharidase deficiency, galactosemia, hereditary fructose intolerance, favism, pancreatic insufficiency, and phenylketonuria. The most common adverse food reaction as a result of an enzyme deficiency is lactose intolerance, which affects approximately 6% of the US population but as much as 90% of some ethnic groups.¹ Adverse food reactions could also be secondary to a pharmacologic effect like those seen with food dyes; preservatives; bacterial, fungal, and seafood toxins; pesticides; metabisulfites; monosodium glutamate; caffeine; and heavy metals. Food poisoning is another common cause of an adverse reaction to food, with the most common offending organisms being bacteria like *Staphylococcus*, *Salmonella*, *Campylobacter*, *E. coli*, and *Shigella*. Other less common food poisoning etiologies include parasites like *Giardia lamblia* and viral hepatitis.

Overview of Gastrointestinal (GI) Food Allergies

It has been estimated that about 25% of the US population believe they have experienced a food allergy, although the actual incidence suggests a rate closer to 2%–8% in young infants and approximately 2% in the adult population. Marklund et al² assessed health-related quality of life among 1488 adolescents with emphasis on food hypersensitivities. They found that 64% of the respondents reported an allergic-type process to defined substances and 51% reported allergic disease like asthma, eczema, and rhinoconjunctivitis. A total of 19% reported food hypersensitivity (these were self-reported and not necessarily medically confirmed). The authors' questionnaires suggest that food allergies in the adolescent group may have a more

Correspondence: John Alan Kerner, Jr, MD, Professor of Pediatrics, Director of Nutrition, Stanford University Medical Center, 750 Welch Road, Suite 116, Palo Alto, CA 94304. Electronic mail may be sent to jkerner@stanfordmed.org.

0884-5336/05/2005-0526\$03.00/0

Nutrition in Clinical Practice 20:526–535, October 2005

Copyright © 2005 American Society for Parenteral and Enteral Nutrition

Table 1
Food intolerance

Adverse reaction to food: any untoward reaction
I. Food allergy/hypersensitivity (immunologic response)
II. Food intolerance (nonimmunologic)
a. Enzyme Deficiency (eg, disaccharidase deficiency, galactosemia, hereditary fructose intolerance)
b. Toxins (shellfish, staphylococcus, mushrooms)
c. Pharmacologic (metabisulfites in wine and salad: bronchospasm; wine, MSG: headache; caffeine: arrhythmia)

MSG, monosodium glutamate.

far-reaching consequence than just the organic component; they may also affect psychosocial health. Factors that have been associated with an increased risk for developing food allergy-associated GI disease are age <3 years, acute reaction close to eating a particular food, atopic dermatitis, bronchial asthma, and family history of atopy.³ Atopy is the tendency to develop immediate-type (IgE) hypersensitivity reactions: atopic eczema, food allergy, asthma, allergic rhinitis. There is a genetic predisposition to synthesize IgE antibodies (inappropriately) against environmental antigens.

Various manifestations of allergic disease many times do present in a characteristic sequence (eg, atopic dermatitis → allergic rhinitis → asthma). This sequence has been referred to as the "atopic or allergic march."⁴

A meta-analysis carried out in 1999 of all available studies on the age of onset of the "allergic march" found that during the first year of life in atopic children, there was the onset of atopic dermatitis in 79.8%, cow's milk allergy (CMA) in 72.7%, egg allergy in 71%, and fish allergy in 51.3%. Of those developing bronchial asthma, 41.8% manifested it in the first year of life, 49.3% in the second year, and by the eighth year, 92.5% of atopic children. Allergic rhinitis started in 35% of the infants in the first year of life and in 59% by 5 years of age. These data indicate that allergy develops early in life in those predisposed, and any early intervention and strategies for prevention could have a significant impact.⁵

Few foods account for 90% of the reactions seen in children. The most commonly seen food allergens in children are cow's milk protein (2% of children), eggs (1.3% of children), peanut (0.5% of children), soy, tree nuts, fish, and wheat.¹ In older pediatric patients, the list expands to include berries and chocolate.⁶ Most common food allergens in adults are peanuts, tree nuts, fish, and shellfish.

Patients who develop a GI food allergy could present with urticaria, angioedema, anaphylaxis, atopic dermatitis, diarrhea, GI bleeding, abdominal pain, or respiratory symptoms.

The development of a food allergy requires an immunological reaction directed to a food antigen. In order for this to occur, it is necessary that the food be

digested, absorbed into the systemic circulation, processed, and then presented to a competent immune system.¹

The GI Barrier

The GI tract is a very specialized organ, rich in lymphoid tissue containing macrophages, immunoglobulins, mast cells, intraepithelial lymphocytes, and helper and suppressor T-cells at the subepithelial level (gut-associated lymphoid tissue, or GALT). This well-organized system of cells and their products acts as the mucosal barrier, guarding the body against intrusive antigens.⁷

There are also nonspecific factors that aid in protecting the GI tract from antigenic intrusions, which starts at the moment of food intake. The digestion and breakdown of proteins starts in the oral cavity, continues in the stomach with the help of hydrochloric acid and pepsin, and in the small bowel in the presence of pancreatic proteases. In addition to the enzymatic breakdown of protein, other nonspecific barriers help in reducing the antigenic stimulation of the intestinal mucosa, and these include the inherent GI motility, GI secretions (water, electrolytes, mucus, and defensins), the epithelial barrier, the microvillous membrane, and, at the level of the enterocyte, the lysosomes.⁷

The intestinal mucosa is the gatekeeper, preventing the penetration of macromolecules that could be potentially harmful (Figure 1). The intestinal surface is directly exposed to an environment rich in antigenic load and unique in the sense that its main role is that of suppression rather than active immune response.⁸

Immunologic Reactions

Given the exposure to antigenic material, it is also in the intestinal mucosa, where allergic reactions could be initiated. Two types of immunoallergic reactions have been described in the development of GI allergies: the IgE-mediated reaction, and the T-cell-mediated reaction, also known as non-IgE-mediated.

The IgE-mediated reaction is also known as an immediate onset allergic reaction (type I). In a type I reaction, the IgE antibodies bind to the mast cells in the GI tract, skin, and lungs, causing a release of mediators when they are exposed to determinate antigens.⁹ Circulating IgE also binds and activates basophils, eosinophils, and macrophages. The process involves the sensitization to the offending antigen; when that antigen is reintroduced into the diet, it activates the immune system, with the food antigen binding to the cell surface of the IgE molecule triggering the release of histamine, prostaglandins, leukotrienes, and cytokines.

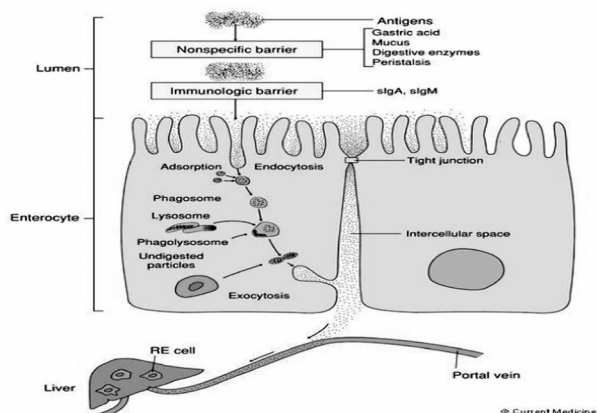


Figure 1. Components of mucosal barrier of gastrointestinal tract. Reprinted from *Gastroenterology*. Sanderson IR, Walker WA. Uptake and transport of macromolecules by the intestine: possible role in clinical disorders (an update). Pages 622–639, © 1993, with permission from The American Gastroenterological Association.

Type III reactions involve the formation of auto-immune complexes with IgG antibodies and activation of the complement cascade. The appearance of symptoms is not immediate and may occur 1–20 hours after the exposure.

A type IV reaction, also known as delayed-onset allergic reaction, is caused by T-cell lymphocyte activation; hence, a T-cell-mediated hypersensitivity. As a result of this sensitization, interleukins 4 and 5 are produced, causing an inflammatory response. Patients exhibiting a delayed hypersensitivity reaction have shown an imbalance in the production of interleukin 4 and γ -interferon.¹⁰

A type II reaction has been reported only rarely in food allergy. Conditions associated with this type of immunologic response (antibody mediated) are autoimmune hemolytic anemia and Goodpasture's syndrome.

Another type of immune response is that of tolerance. Tolerance to an antigen is the result of the absence of a reaction between the immune system and the circulating antigen. Most people acquire tolerance to food antigens.

In essence, the GI allergy syndromes could be primarily IgE mediated (reaginic), mixed IgE/non-reaginic, and nonreaginic/non-IgE-mediated. The IgE-mediated food hypersensitivity causes an immediate GI reaction, leading to nausea, abdominal pain, and emesis.

Food allergies can cause multiple or isolated symptoms, with the most common being diarrhea, vomiting, and abdominal pain. Unfortunately, a myriad of other pathologic conditions can elicit the same response from the GI tract, making it difficult for the physician to sort the diagnosis out from an extensive differential diagnosis list.

IgE-Mediated GI Disorders

Immediate Hypersensitivity Disorders

The primarily IgE-mediated reaction, immediate GI hypersensitivity reaction, could present at any time of life, although the usual age of onset is seen from infancy to childhood. As the word implies, it could occur within minutes of the ingestion of the food protein or could present within a few hours. Most commonly implicated proteins are milk, soy, egg, peanut, shellfish, and cereal. The rapid onset of presentation is the diagnostic clue for a type I hypersensitivity reaction. The patient can develop nausea, vomiting, diarrhea, colic, or just plain abdominal pain. Vomiting may be intermittent. In those patients with longstanding exposure who have acquired partial desensitization to the food antigen, the vomiting may be followed by anorexia, poor weight gain, abdominal pain, and colic.¹

Type I hypersensitivity reactions, as they become systemic, can affect the lungs and the skin, producing reactive airways, rhinoconjunctivitis or generalized acute urticaria, skin flushing, or angioedema. These patients may develop life-threatening bronchospasm and anaphylactic shock. The treatment for this condition is the strict avoidance of the offending protein. The patient may need to have epinephrine administered to avert life-threatening complications. The natural history of this condition is that around 80% of cases resolve over several years, except for those with peanut and shellfish allergy.

Oral Allergy Syndrome

Another manifestation of IgE hypersensitivity reaction is the oral allergy syndrome, also known as pollen-food allergy syndrome. This reaction is mostly limited to the oral cavity, and it rarely manifests systemic symptoms. It is usually characterized by itching, burning, erythema, or tingling of the lips, tongue, palate or oropharynx. The most common implicated proteins are those of fresh fruit and vegetables. These plant proteins can cross-react with airborne allergens, like birch, ragweed, and mugwort pollens. Patients with birch allergy may react to the ingestion of raw apples, pears, celery, hazelnuts, kiwi, potatoes, and carrots. Allergy to ragweed may cross-react when exposed to fresh melon and bananas. Patients allergic to grass pollen may cross-react when ingesting raw tomatoes.¹¹ The reaction is caused by a heat-labile antigen that is rendered inactive when cooked. The treatment consists of avoidance of the fruit and with the cooking of the vegetables. This condition can persist into adulthood.

Mixed-IgE/Nonreaginic Allergy Syndromes

Eosinophilic Gastroenteritis

The eosinophilic gastroenteropathies comprise a group of disorders characterized by an intense eosinophilic infiltration of the esophagus, stomach, or

small bowel mucosa. It can present as early as infancy and finds its peak in the second and third decade of life.¹² The depth of eosinophilic infiltration in the organ wall relates to the manifestation of symptoms and their severity.

The etiology of eosinophilic gastroenteropathy is not well understood. A relation with food sensitivity can be found in some patients but not in others. In those with no identifiable relationship to food, the initiating factor is not determined in most. The diagnosis of eosinophilic enteropathy can only be made after excluding other pathologic conditions that can trigger an eosinophilic response, in conjunction with histologic (biopsy) findings indicating tissue eosinophilia. In eosinophilic gastroenteropathy, it is believed that the pathologic response involves T-cell- and IgE-mediated mechanisms.¹

In eosinophilic gastroenteritis, the gastric antrum and small bowel are frequent sites of the eosinophilic infiltration. There are 3 categories of the disorder: (1) mucosal, (2) muscular, and (3) serosal.

- In the mucosal form, there is nausea, vomiting, abdominal pain and diarrhea; it may be associated with occult blood loss, iron deficiency anemia, protein losing enteropathy, and failure to thrive;
- In the muscular (transmural) form, there may be obstructive symptoms, mimicking pyloric stenosis or thickening of the gastric outlet.
- In the serosal form, patients may present with ascites and abdominal pain.

Treatment includes elimination of pathogenic foods; if that fails, some give a trial of an elemental diet; oral cromolyn may also be added. If the above measures fail, corticosteroids can induce a remission. The patients frequently flare on corticosteroid tapering, and they may require repeated courses or continuous low-dose corticosteroids.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic inflammatory condition affecting the esophagus. It is a member of the family of eosinophilic gastroenteropathies. Teitelbaum et al¹³ demonstrated increased presence of CD3 and CD8 lymphocytes in the esophagus of children with eosinophilic esophagitis. These cells stimulate T-cell proliferation and production of eosinophil chemotactic agents such as eotaxin, attracting more of these cells that, after their activation, will produce cytotoxic substances. These agents can also cause smooth-muscle contraction producing dysphagia, abdominal pain, or respiratory symptoms.

Allergic eosinophilic esophagitis can produce symptoms indistinguishable from gastroesophageal reflux disease. The age of onset ranges from infancy to adolescence. These patients may present with emesis, failure to thrive, food refusal, abdominal pain, irritability, dysphagia (with esophageal stric-

ture), and sleep pattern disturbance. The esophageal and gastric inflammation does not respond well to H-2 blockers. When tested, their serum IgE is found to be normal or slightly elevated, and significant peripheral eosinophilia has only been observed in about 50% of cases.^{14,15} Finally, the diagnosis will need to be confirmed with a tissue biopsy to document the pathologic mucosal infiltration with eosinophils (>20 eosinophils per high-power field).

Proteins that have been incriminated in allergic eosinophilic esophagitis are cow's milk, wheat, soy, peanut, and egg.¹⁶ Often, there are multiple antigens responsible for the reaction, and there is poor correlation with skin testing in helping to identify them.

The treatment of allergic eosinophilic esophagitis includes the use of hydrolyzed protein formula in the infant, with around an 80% response. The use of elemental diets with L-amino acid formulas has yielded excellent results. Patients have responded to elemental diets even in absence of any identifiable food allergy. Dietary manipulation can in fact decrease the severity of the inflammation, but this has been shown not to be curative in all cases.^{17,18} Should dietary restriction not prove to be satisfactory, a trial of prednisone, methylprednisolone, or inhaled steroids that are swallowed has been proven to be efficacious.^{18,19}

Other Eosinophilic Gastroenteropathies (Eosinophilic Gastritis and Gastroenterocolitis)

Allergic eosinophilic gastritis and enterocolitis can present with symptoms of abdominal pain, anorexia, early satiety, failure to thrive, pyloric stenosis, bleeding, anemia, protein-losing enteropathy, colitis, intestinal obstruction, pseudo-Crohn's disease, intestinal perforation, and eosinophilic ascites.²⁰⁻²² In about 70% of cases, atopy is identified, and laboratory tests show elevated IgE and peripheral eosinophilia. The age of onset ranges from infancy to adolescence, and the most commonly implicated foods are cow's milk, egg, corn, cod, and soy. Often a single antigen is identified and skin testing has been found to have a specificity of approximately 50% in these cases.

These disorders are characterized by marked eosinophilic infiltration of the mucosa and submucosa of the esophagus, stomach antrum, duodenum, and the colon. Response to acid blocking medication, like H-2 blockers or proton pump inhibitors has little or no effect. Intervention with restriction of the offending protein is successful in about 50% of those affected; treatment with hydrolyzed formula seems to be very effective in those younger than 2 years of age. Response to L-amino acid-based formulas is excellent. In patients not responding to dietary protein restriction, a trial of low-dose systemic corticosteroids yields good therapeutic results. About 75% of those affected will experience resolution of symp-

toms over several years, and in the other 25%, their disease will extend into the adult years.

The long-term prognosis of eosinophilic enteropathies is unknown in the pediatric population.²³ In adult patients with eosinophilic esophagitis (treated separately in this document, although still considered an eosinophilic enteropathy), the persistence of symptoms is the common rule, with dysphagia the prevalent problem. During a mean of 7.2 years' follow-up of adult patients with eosinophilic esophagitis, dysphagia persisted, but there was not an associated increase risk of malignancy or premalignant lesions. It is necessary that a long-term follow-up of these patients be done to assess whether there is a risk of malignancy associated with this condition.²⁴

Non-IgE-Mediated GI Disorders

Proctocolitis

Proctocolitis, as a result of cow's milk protein allergy, is usually seen during the first 6 months of life. The infant presents with a history of mucousy bloody stools. It could be specks of blood mixed with the stools or a more significant presence of blood. Up to 60% of the cases occur in breastfed infants. It also can manifest in formula-fed infants and in patients fed soy formulations.²⁵ Although extensively hydrolyzed formulas are used as the first line of therapy, allergic reactions to these formulas have been rarely described.²⁶ In patients who have such an allergic reaction, treatment with an amino acid-based (non-allergenic) formula results in resolution of symptoms. Management of breastfed infants is more difficult. Restriction of cow's milk (and, more rarely, other foods such as soy or egg) from the mother's diet usually results in resolution of symptoms. The formulas stated above are required if maternal dietary restriction fails.

Although the diagnosis is almost always reached on clinical grounds, if confirmation of the disease is sought, a flexible sigmoidoscopy can be performed. The gross finding, on endoscopic mucosal inspection, usually reveals patchy erythematous lesions, edema of the mucosa and friability, and may be accompanied by lymphonodular hyperplasia, which could be limited to the rectum and sigmoid colon, but it can also involve the entire colonic mucosa.

Biopsies obtained from the mucosa of the rectum or colon show the presence of an abnormally high number of eosinophils infiltrating the mucosa and penetrating as deep as the muscularis mucosa.²⁵

Cow's milk protein proctitis/proctocolitis is a disease of infancy and will resolve after elimination of the offending protein. The disorder should resolve between the ages of 6–9 months and 1–2 years.

Food Protein-Induced Enterocolitis Syndrome

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe manifestation of a food hypersensitivity reaction. It has been associated not

only with cow's milk protein and soy but to other solid foods like turkey, lentils, rice, oat, barley, and vegetables. The offending vegetables have included sweet potatoes, squash, string beans, and peas. Symptoms may appear during the first month of life and can be seen in association with faltering of growth. Symptoms occur with a median time of appearance of 2 hours after ingestion of the protein and include vomiting, diarrhea, lethargy, and dehydration. The severity of this reaction can lead to acidemia, methemoglobinemia, and shock.^{27–29}

The immune mechanism responsible for the reaction appears to be T-cell mediated. There has been no association with IgE antibodies, and at the level of the affected tissue there is a diffuse inflammation with predominant plasma cell infiltrate, crypt abscess formation, villous injury, and in some cases it leads to focal erosive gastritis and esophagitis with prominent eosinophilia infiltrating the tissue.²⁵ Treatment is with a hypoallergenic formula (casein hydrolysate), which is usually effective (if not, an amino acid-based formula can be used). Most infants outgrow the allergy by age 2 or 3 years, and some seem to maintain hypersensitivity into childhood.¹⁶

Dietary Food Enteropathy

Dietary food enteropathy presents in infancy with symptoms of diarrhea, vomiting, and failure to gain weight. This disorder can ultimately lead to a state of protein-losing enteropathy, edema, and GI blood loss. Reaction to cow's milk protein is the most common etiology, although other proteins like soy, egg, fish, and cereal grains have been associated with this condition. As with the previous 2 disorders, it is mediated by a T-cell-mediated immune reaction, and IgE antibodies do not play a role. Diagnosis is based on the combined findings from endoscopy/biopsy, allergen elimination, and challenge. Biopsy reveals variable small bowel villus injury, increased crypt length, and intraepithelial lymphocytes. Treatment is dietary restriction of the offending allergen. Dietary food enteropathy usually resolves during the first 2 years of life, although it may persist into the childhood years.¹⁶ For a comparison between these 3 entities, please refer to Table 2.

Constipation

Allergy to cow's milk has been associated with the development of constipation. The inflammation that develops as a result of an allergic response could lead to the formation of an anal fissure, causing painful defecation. The response to the painful act can lead to a retentive pattern. Anal lesions will disappear after discontinuation of cow's milk and reappear after rechallenge in a significant number of patients. In the study by Iacono et al,³⁰ specific IgE antibodies to cow's milk were found in 31 out of 44 patients with constipation. The presence of other

Table 2
Non-IgE-mediated gastrointestinal disorders

	Enteropathy	FPIES	Proctitis
Age at onset	1–18 mo	2d–6 mo	2d–3 mo
Duration	18–36 mo	9–36 mo	6–9 mo
Presentation	Indolent	Acute	Acute, mild
FTT	Moderate/severe	Moderate	No
Irritability	Mild	Moderate	Minimal
Emesis	Mild	Moderate	No
Diarrhea	Moderate	Severe	Mild
Rectal bleeding	Minimal	Moderate	Mild/moderate
Fecal PMN's	No	Common	Common
Anemia	Moderate	Moderate	Mild
Main etiology	Cow's milk	Cow's milk	Breast milk
Other etiology	Soy, wheat, egg, cod	Hydrolyzed casein, rice, nut	Soy, corn, egg

Duration, once the offending allergen is removed; FPIES, food protein-induced enterocolitis syndrome; FTT, failure to thrive; PMNs, polymorphonuclear cells.

signs of CMA, like bronchospasm, dermatitis, and rhinitis, increases the chance that constipation will respond to a cow's milk-free diet.³⁰

Celiac Disease

Celiac disease, or gluten enteropathy, is an immune response to the gliadin component found in wheat, rye, and barley (gliadin in oats is no longer implicated by most experts). Celiac disease is considered a multifactorial disease in which not only the exposure to gliadin is necessary but also the presence of a genetic susceptibility as well. Gluten enteropathy is a T-cell-mediated chronic inflammatory process with an autoimmune component and can manifest with extraintestinal manifestations as well.³¹

The prevalence of celiac disease in the general unselected population of North America and Western Europe ranged from 152 to 2670 per 100,000. Among the studies conducted in the United States, the prevalence ranged from 1:320 (only child population in this group) to 1:105.³² The resolution of the inflammation and symptoms occurs upon complete avoidance of products containing gliadin.

Lymphonodular Hyperplasia

The significance of lymphonodular hyperplasia, in relation to a pathologic process, is not clear. The small and large intestine is an organ rich in lymphoid tissue. Aggregation of lymphoid follicles, also known as Peyer's patches, will give rise to submucosal nodules. It is thought that the appearance of lymphoid nodules corresponds to an enhanced immunological response. Its gross appearance in colonoscopy or upper endoscopy is that of small raised nodules. Sometimes it can give a cobblestone appearance to the mucosa. During colonoscopy and distal ileal intubation, it is not uncommon to find prominent lymphoid hyperplasia, which is very frequently regarded as a normal finding. Also,

aphthoid erosions can be seen throughout the colonic mucosa in a patchy distribution.

Kokkonen and Kaurttunen³³ conducted a retrospective analysis of 140 children using colonoscopy and upper endoscopy and review of the histopathology and clinical symptomatology. They concluded that lymphonodular hyperplasia of the colon and terminal ileum is not an innocent finding as previously thought, having a significant correlation with food allergy as a result of an up-regulated immune response. Lymphonodular hyperplasia is not an exclusive finding of food allergy; other entities like inflammatory bowel disease can have the same findings on endoscopy. The authors pointed to the fact that the true prevalence of lymphonodular hyperplasia in the general population without symptoms is unknown.³³

Another study has shown an association between the presence of lymphonodular hyperplasia and abnormalities in Th1 and Th2 function in non-IgE food allergy. More studies in this area are needed to better understand this association.³⁴

Lymphonodular hyperplasia has been incriminated as a disorder causing diarrhea, low-grade GI bleeding, anemia, abdominal pain, and protein-losing enteropathy. Its onset can occur in infancy, causing proctitis, and in the toddler age group can present with low-grade colitis. In most cases, the etiology is idiopathic, and in others, a relation with cow's milk, soy, and even hydrolyzed formula has been found. Resolution of symptoms is anticipated with puberty.

Diagnosis And Management

The evaluation of children with food allergies starts with the process of a thorough history and complete physical examination. The physician must analyze the presenting symptom or symptoms and their relation to food. The temporal relation of the reaction after exposure to food is of paramount

importance. Approaches to diagnosis of GI food allergies are depicted in Table 3. The IgE-mediated reactions are easier to detect and diagnose, but unfortunately, the non-IgE-mediated food allergies present a challenge for the clinician. Specific immunological testing is not available for many of the categories of non-IgE-mediated food allergy reaction. The exclusion of other pathologic conditions, whether infectious, noninfectious inflammatory, metabolic, endocrine, or anatomical, is frequently necessary.

In regard to laboratory testing, when the problem is that of an IgE-mediated sensitivity reactions, RAST (radioallergosorbent test) testing and skin prick tests could help in the confirmation of the suspected diagnosis. In some instances, a direct challenge with the food protein is necessary. With skin testing and RAST panels, false negatives are uncommon and, therefore, have a good negative predictive value. On the other hand, false positives are common and have a poor positive predictive value.

In the case of non-IgE-mediated reactions, other nonspecific laboratory tests can be done. These include stool examination for presence of blood, eosinophils, and white blood cells. The atopy patch test is a promising resource to identify non-IgE-mediated reactions. It involves the cutaneous exposure to a food protein for as long as 48 hours. A positive reaction indicates a delayed hypersensitivity reaction. The pitfall with this test is that at the moment there are no standardized methods of application and interpreting the results. The patch itself can cause changes in the skin as a result of prolonged contact irritation.¹¹

An upper GI endoscopy or colonoscopy with biopsies could be helpful in suggesting the presence of a non-IgE-mediated disorder.

The gold standard for diagnosis of food-related allergies is the double-blind placebo control challenge. Other tests, like single blind or open challenges, can also be helpful. In a double-blind challenge, the patient undergoes an elimination diet for at least 7 days. The patient should not be taking medications, specifically those that can blunt or ameliorate an allergic response. The challenge should be undertaken in a facility where the child can be under constant supervision, and medications to avert a life-threatening reaction should be immediately accessible. The child will initially receive a small dose of the suspected allergy-causing protein and then continue gradually increasing the amount of antigen over time until reaching a maximum without reaction.¹ The period of observation may take as long as 4 hours for the non-IgE-mediated reactions, although some may manifest the reaction after >24 hours after exposure.

The treatment for food allergies is the avoidance of the offending antigen. It sounds simple but in reality it is not, because hidden antigens in foods will represent a challenge for these patients, and elimination diets may lead to malnutrition or dietary deficiencies.¹ A meticulous attention to food

labels is mandatory with special attention to "hidden food." How to read food labels is part of the parental education in order to prevent cross-contamination of products (eg, the same mill may be used to process wheat and corn). Joshi showed that most parents were unable to identify allergens in food labels. He also found that only 7% of 60 parents were able to identify milk protein in 14 sample labels.³⁵ The Food Allergy and Anaphylaxis Network (Fairfax, VA; 1-800-929-4040; <http://www.foodallergy.org>) is an excellent resource for parents caring for the food-allergic child.

Some patients will need to take extensive hydrolyzed formulas or L-amino acid-based preparations to maintain adequate nutrition and health. Oral systemic corticosteroids may be needed in the more severe cases. For patients who are at risk of developing a life-threatening anaphylactic reaction, the parents and the child need to receive training in how to avoid, and if exposed, how to recognize a reaction early enough to administer injectable epinephrine.

Therapy in infants often requires selection of an alternative formula. In infants with IgE-mediated CMA, most (86%) will tolerate a soy formula,³⁶ but the rate of tolerance is lower (50%) for most of the cell-mediated disorders.²⁸ Infants with true CMA would be expected also to react to partially hydrolyzed formula, lactose-free cow's milk-based formula, and most mammalian milks (eg, sheep, goat),³⁷ so none of these is a good alternative. In most cases (>95%), infants with CMA will tolerate extensively hydrolyzed cow's 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.³⁸⁻⁴⁰

Prevention is the mother of all cures. Meta-analyses of existing studies suggest a beneficial role for breast-feeding high-risk infants for the first 3-6 months of life in the prevention of atopic disease.^{41,42} At this time, there are no conclusive studies indicating that the manipulation of the mother's diet during pregnancy or while breastfeeding or the restriction of allergenic foods from the infant's diet will prevent the development of food allergy. There is also some evidence that regular intake of peanuts by the pregnant mother may increase the chance of a child developing a peanut allergy.⁴³

A large ongoing study in Germany comparing the use of various hypoallergenic infant formulas with cow's milk formulas as a supplement to breast-feeding or as a weaning formula in high-risk infants suggests that extensively hydrolyzed casein formula or partially hydrolyzed whey formula might be useful in the prevention of some atopic disease and food allergy,⁴⁴ as suggested by a recent meta-analysis.⁴⁵

In the year 2000, The American Academy of Pediatrics Committee on Nutrition published their recommendations for food allergy prevention (Table 4). Their prevention guidelines were directed to the high-risk infant (at high risk for food allergy), and there were no limitations imposed on the mother's

Table 3
Gastrointestinal food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Pollen-food allergy syndrome (oral allergy syndrome)	IgE mediated	Mild pruritis, tingling, or angioedema of the lips, palate, tongue, or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms	Clinical history and positive SPT responses to relevant food proteins (prick-plus-prick method); $\pm$ oral challenge—positive with fresh food, negative with cooked food
Gastrointestinal anaphylaxis	IgE mediated	Rapid onset of nausea, abdominal pain, cramps, vomiting, or diarrhea; other target organ responses (ie, skin, respiratory tract) often involved	Clinical history and positive SPT responses or RAST results; $\pm$ oral challenge
Allergic eosinophilic esophagitis	IgE mediated or cell mediated	Gastroesophageal reflux or excessive spitting up or emesis, dysphagia, intermittent abdominal pain, irritability, sleep disturbance, failure to respond to conventional reflux medications	Clinical history, SPTs, endoscopy and biopsy, elimination diet and challenge
Allergic eosinophilic gastroenteritis	IgE mediated or cell mediated	Recurrent abdominal pain, irritability, early satiety, intermittent vomiting, FTT, or weight loss	Clinical history, SPTs, endoscopy and biopsy, elimination diet and challenge
Food protein-induced proctocolitis	Cell mediated	Gross or occult blood in stool; typically thriving; usually presents in first few months of life	SPT responses negative; elimination of food protein—clearing of most bleeding in 72 h; $\pm$ endoscopy and biopsy; challenge induces bleeding within 72 h
Food protein-induced enterocolitis	Cell mediated	Protracted vomiting and diarrhea ($\pm$ blood) not infrequently with dehydration; abdominal distention, FTT; vomiting typically delayed 1–3 h after feeding	SPT responses negative; elimination of food protein—clearing of symptoms in 24–72 h, challenge—recurrent vomiting within 1–2 h, $\sim$ 15% have hypotension
Food protein-induced enteropathy, celiac disease (gluten-sensitive enteropathy)	Cell mediated	Diarrhea or steatorrhea, abdominal distention and flatulence, weight loss or FTT, $\pm$ nausea and vomiting, oral ulcers	Endoscopy and biopsy IgA; elimination diet with resolution of symptoms and food challenge; celiac: IgA anti-tissue transglutaminase antibodies and antitransglutaminase antibodies

Used with permission from *J Allergy Clin Immunol*. 2003;111(suppl):S540–547.

FTT, failure to thrive; IgA, immunoglobulin A; SPT, skin prick test; RAST, radioallergen sorbent test.

Reprinted from the *Journal of Allergy and Clinical Immunology*, Vol. 111. Sampson HA, Food Allergy, pp 5540–5547, © 2003, with permission from The American Academy of Allergy, Asthma and Immunology.

Table 4
Prevention of food allergy⁴⁶

American Academy of Pediatrics 2000 recommendations for prevention of food allergy
Prevention limited to high-risk infants
No dietary restrictions during pregnancy, with the possible exception of peanut
Exclusive breastfeeding until 6 mo
Eliminate peanuts and nuts from lactation diet (consider elimination of eggs, cow's milk, fish)
Supplemental calcium and vitamins during restricted-lactation diets
If bottle-fed, use hypoallergenic formula (extensive, or possibly partial, hydrolysate)
Least allergenic solid foods at 6 mo; cow's milk at 12 mo; eggs at 24 mo; peanuts, nuts, and fish at 36 mo

nutrient intake, with the exception of avoiding eating tree nuts and peanuts during the lactation period. If the high-risk child is offered infant formulas, the choice of a hydrolyzed formula (either an extensive or partial hydrolysate) is preferable.

With the exception of celiac disease and some food allergies that can persist into adulthood (eg, shellfish and peanuts), the vast majority of food allergies disappear over time.

Conclusion

In essence, gastrointestinal food hypersensitivities can cause symptoms from mouth to anus. These symptoms may be as subtle as mild pruritus, tingling of tongue and palate, to nausea, vomiting, diarrhea, dysphagia, failure to thrive, gastrointestinal blood loss, and the most ominous: anaphylaxis. Food allergies have become an increasing source of concern among both the lay public and health caregivers. We now have a better understanding of the different processes involved in the development of an allergic reaction, making recognition and treatment choices easier for the physician. Anaphylaxis due to an IgE-mediated immune reaction is a life-threatening event. The nonreaginic or T-cell-mediated allergic conditions can also have a significant, chronic, and deleterious effect in the health of an individual. Understanding these conditions and their differences is of paramount importance to be able to select the most appropriate therapy or combination of therapies. Of no less importance is the education of patients with food allergies. This education should be delivered in clear terms in an effort to avoid potentially fatal reactions or chronic debilitating disease.

Acknowledgments

The work was supported in part by the Carl and Patricia Dierkes Endowed Fund for Nutrition and Home Care.

References

1. Spergel JM, Pawlowski NA. Food allergy. *Pediatr Clin North Am*. 2002;49:73–96.
2. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life among adolescents with all conditions, with emphasis on food hypersensitivity. *Health Qual Life Outcomes*. 2004;2:65–80.
3. American Gastroenterology Association Medical Position Statement: evaluation of food allergies. *Gastroenterology*. 2001;120:1023–1025.
4. Hahn E, Bacharier LB. The atopic march: the pattern of allergic disease development in childhood. *Immunol Allergy Clin North Am*. 2005;25:231–246.
5. Cantani A. The growing genetic links and the early onset of atopic diseases in children stress the unique role of the atopic march: a meta-analysis. *J Investig Allergol Clin Immunol*. 1999;9:314–320.
6. Utter SL, Collier SB. Special diets. In: Walker WL, Watkins JB, Duggan C, eds. *Nutrition in Pediatrics*. 3rd ed. Ontario, Canada: BC Decker Inc; 2003:997–1016.
7. Stern M. Allergic enteropathy/food allergy. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric Gastrointestinal Disease*. 3rd ed. Ontario, Canada: BC Decker Inc; 2000:746–762.
8. Lehrer SB, Wilod LG, Bost KL, Sorensen RU. Food allergy: current knowledge and future directions. *Immunol Allergy Clin North Am*. 1999;19:563–581.
9. Stenton GR, Vliagoftis H, Befus D. Role of intestinal mast cells in modulating gastrointestinal pathophysiology. *Ann Allergy Asthma Immunol*. 1998;81:1–15.
10. Andre F, Pene J, Andre C. Interleukin-4 and interferon-gamma production by peripheral blood mononuclear cells from food-allergic patients. *Allergy*. 1996;51:350–355.
11. Sampson HA. Update on food allergy. *J Allergy Clin Immunol*. 2004;113:805–819.
12. Kirschner B. Undetermined colitis and other inflammatory diseases. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR, eds. *Pediatric Gastrointestinal Diseases*. 4th ed. Ontario, Canada: BC Decker Inc; 2004:850–865.
13. Teitelbaum J, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology*. 2002;122:1216–1225.
14. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut*. 1990;31:54–58.
15. Caldwell JH, Mekhjian HS, Hurtubise PE, Beman FN. Eosinophilic gastroenteritis with obstruction: immunological studies of seven patients. *Gastroenterology*. 1978;74:825–828.
16. Sicherer SH. Clinical aspects of gastrointestinal food allergies. *Pediatrics*. 2003;1609–1616.
17. Kelly K, Lazemby A, Rowe P, Yardley JH, Perman JH, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503–1512.
18. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdson L, Kokoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol*. 2000;95:1422–1430.
19. Liacouras CA. Eosinophilic esophagitis in children and adults. *J Pediatr Gastroenterol Nutr*. 2003;37(Suppl):S23–S28.
20. Whittington PF, Whittington GL. Eosinophilic gastroenteropathy in childhood. *J Pediatr Gastroenterol Nutr*. 1988;7:379–385.
21. Khan S, Orenstein S. Eosinophilic gastroenteritis masquerading as pyloric stenosis. *Clin Pediatr*. 2000;39:55–57.
22. Hümmer-Ehret BH, Rohrschneider WK, Oleszczuk-Raschke K, Darge K, Nützenadel W, Tröguer J. Eosinophilic gastroenteritis mimicking idiopathic pyloric stenosis. *Pediatr Radiol*. 1998;28:711–713.
23. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? *Clin Gastroenterol Hepatol*. 2004;2:523–530.
24. Straumann A, Spichtin HP, Grize L, Bucher K, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003;125:1660–1669.

25. Sicherer SH. Enterocolitis, proctocolitis, and enteropathy. In: Leung DYM, Sampson HA, Geha RS, Szefer SJ, eds. *Pediatric Allergy: Principles and Practice*. St. Louis, MO: Mosby; 2003:510–517.
26. Vanderhoof JA, Murray ND, Kaufman SS, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. *J Pediatr*. 1997;131:658–669.
27. Levy Y. Food protein-induced enterocolitis. *Pediatr Allergy Immunol*. 2003;14:325–329.
28. Sicherer SH. Food protein induced enterocolitis syndrome: case presentations and management lessons. *J Allerg Clin Immunol*. 2005;115:149–155.
29. Nowak-Węgrzyn A. Food protein induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003;111:829–835.
30. Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med*. 1998;339:1100–1104.
31. Mäki M, Lohi O. Enteropathy: celiac disease. In: Walker A, Goulet O, Kleinman RE, Sherman P, Shneider BL, Sanderson IR, eds. *Pediatric Gastrointestinal Disease*. 4th ed. Hamilton, Ontario, Canada: BC Decker Inc; 2004:932–943.
32. Dubé C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk western European populations: a systematic review. *Gastroenterology*. 2005;128(4 suppl 1):S57–S67.
33. Kokkonen J, Kaurttunen T. Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? *J Pediatr Gastroenterol Nutr*. 2002;34:42–46.
34. Bellanti JA, Zeligs BJ, Malka-Rais J, Sabra A. Abnormalities of the TH-1 function in non-IgE food allergy, celiac disease, and ileal lymphonodular hyperplasia: a new relationship? *Ann Allergy Asthma Immunol*. 2003;90:84–89.
35. Joshi P, Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food-allergic children. *J Allergy Clin Immunol*. 2002;109:1019–1021.
36. Zeiger RS, Sampson HA, Bock SA, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr*. 1999;134:614–622.
37. Bellioni-Businco B, Paganelli R, Lucenti P, Giampietro PG, Perborn H, Businco L. Allergenicity of goat's milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 1999;103:1191–1194.
38. Kelso JM, Sampson HA. Food protein-induced enterocolitis to casein hydrolysate formulas. *J Allergy Clin Immunol*. 1993;92:909–910.
39. Frisner H, Rosendal A, Barkholt V. Identification of immunogenic maize proteins in a casein hydrolysate formula. *Pediatr Allergy Immunol*. 2000;11:106–110.
40. Isolauri E, Sutas Y, Makinen KS, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *J Pediatr*. 1995;127:550–557.
41. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol*. 2001;45:520–527.
42. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr*. 2001;139:261–266.
43. Frank L, Marian A, Visser M, Weinberg E, Potter PC. Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol*. 1999;10:27–32.
44. von Berg A, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol*. 2003;111:533–540.
45. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd., pgs 1–61.
46. American Academy of Pediatrics Committee on Nutrition: Hypoallergenic infant formulas. *Pediatrics* 2000;106:346–349.