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Diseases of the Gastrointestinal Tract of Children Caused by Immune Reactions to Foods

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Adverse reactions to foods are most common in infants and young children, and frequently present as gastrointestinal (GI) symptoms including abdominal pain, vomiting, diarrhea, and failure to thrive. Up to 8% of infants will experience adverse food reactions, as shown in a prospective study of 480 newborns followed for 3 years in an American general pediatric practice [1]. In addition, parents reported reactions to fruits and fruit juices in 75 infants (16%), and complaints were confirmed in 56 (12%) by open challenges; 23% to orange, 23% to tomato, 12% to apple, 7% to grape, and 35% to other fruits. A number of prospective studies have evaluated the prevalence of cow milk allergy in young infants. Overall, it appears that about 2.5% of infants experience cow milk allergy in the first years of life [1-4] and that nearly 85% of sensitive infants lose their reactivity by their third birthday [5]. In the series reported, over half of the adverse reactions detected in infants involve reactions of the GI tract.

Gastrointestinal Food Intolerances

While immune-mediated reactions will be the primary focus of this discussion, food intolerances and other disorders may present with similar findings (table 1). Postinfectious malabsorption syndromes are among the most frequent causes of food intolerance. Infectious agents can induce mucosal injury, resulting in malabsorption secondary to villous atrophy, secondary disaccharidase deficiency, bile salt deconjugation, and increased enteric protein losses. While any infectious process can provoke these secondary carbohydrate malabsorption disorders, certain virus (e.g. *Rotavirus*), parasites (e.g. *Giardia*, *Cryptosporidium*), and bacteria

Table 1. Disorders which lead to chronic GI symptoms and must be differentiated from food hypersensitivities

Food intolerances

Postinfectious malabsorption (secondary disaccharidase deficiency, villous atrophy, bile salt deconjugation)

Viral – *Rotavirus*

Parasitic – *Giardia*, *Cryptosporidium*

Bacterial – *Shigella*, *Clostridium difficile*

Metabolic disorders

Transient fructose and/or sorbitol malabsorption

Primary carbohydrate malabsorption – lactase deficiency, sucrase deficiency

Hypo- or abetalipoproteinemia

Acrodermatitis enteropathica

Bacterial enterotoxins

Vibrio cholerae, toxigenic *Escherichia coli*, *Clostridium difficile*

Other disorders

Cystic fibrosis

Chronic inflammatory bowel disease

'Chronic nonspecific diarrhea of infancy'

Tumors – neuroblastoma (catecholamines or vasoactive inhibitory peptide),

Zollinger-Ellison syndrome (gastrin)

Anatomical abnormalities

Intestinal lymphangiectasia

Short bowel syndrome

Hirschsprung's disease (especially with enterocolitis)

Ileal stenosis

(e.g. *Shigella*, *Clostridium difficile*) are most frequently implicated. Primary metabolic disorders are quite rare, but include carbohydrate malabsorption (lactose intolerance, sucrose intolerance), hypo- or abetalipoproteinemia, and acrodermatitis enteropathica. Carbohydrate malabsorption should be suspected when reducing (lactose) or nonreducing (sucrose) sugars are detected in the stool, and can be confirmed by tolerance tests or hydrogen breath tests [6]. Transient fructose and sorbitol intolerance are not uncommon in the first few years of life, and frequently present as chronic diarrhea with a marked perianal, 'scalded' appearing rash due to the acidic diarrhea, and occasionally failure to thrive [7, 8]. Cystic fibrosis, which occurs in 0.04% of live births, should be considered in any child with poor weight gain or weight loss, and steatorrhea. The diagnosis should be suspected in the presence of a low fecal trypsin concentration and confirmed with a sweat test. Inflammatory bowel disease (ulcerative colitis and Crohn's disease) is rare in young children and tends to peak at 12–16 years of age. It should be suspected whenever chronic diarrhea occurs in the presence of abdominal pain, hematochezia, fever,

Table 2. GI food hypersensitivities in children

IgE-mediated food hypersensitivities
Oral allergy syndrome
GI anaphylaxis
Allergic eosinophilic gastroenteritis (subset)
Infantile colic (subset)
Non-IgE-mediated food hypersensitivities
Food-induced enterocolitis syndrome
Food-induced colitis syndrome
Food-induced malabsorption syndrome
Celiac disease
Allergic eosinophilic gastroenteritis
? Inflammatory bowel disease (subset)

poor growth, weight loss, arthritis or arthralgias, canker sores, and/or erythema nodosum [9]. Diagnosis of these disorders can be made with roentgenographic and/or endoscopic studies. Rarely anatomical disorders will lead to chronic diarrhea. These may include intestinal lymphangiectasia, short bowel syndrome, ileal stenosis, or Hirschsprung's disease, especially with enterocolitis secondary to infection (e.g. *Staphylococcus aureus*).

Gastrointestinal Food Hypersensitivities

GI hypersensitivity reactions in children may be the result of IgE- or non-IgE-mediated mechanisms (table 2). Vomiting, diarrhea, and failure to thrive are the most frequent presenting symptoms. Although IgE-mediated reactions generally occur more rapidly than non-IgE-mediated reactions, an apparent 'down-regulation' (partial desensitization) of the IgE-mediated response may lead to 'delayed' or even 'inapparent' reactions in some infants, i.e., an infant may not vomit with every feeding.

IgE-Mediated Gastrointestinal Food Hypersensitivities

GI anaphylaxis is a form of IgE-mediated GI hypersensitivity which may involve only the GI tract in young infants, but often accompanies allergic manifestations in other target organs in older children. IgE-mediated GI allergy results in a variety of symptoms, which generally develop within minutes to 2 h of eating the responsible food allergen and consist of nausea, abdominal pain (especially colicky cramps), vomiting, and/or diarrhea [10, 11]. The continued ingestion of a food allergen in a sensitive child seems to induce partial desensitization

of GI mast cells resulting in less pronounced symptoms. For example, children with atopic dermatitis and food allergy rarely have GI complaints, except possibly for poor appetite ('picky eater'), but oral challenge following allergen elimination frequently results in abdominal cramps and vomiting. Lactulose absorption, a measure of gut wall integrity, has been shown to be abnormal in such patients [12]. GI anaphylaxis is suspected by clinical history and prick skin testing, and confirmed by eliminating the suspected food allergen from the diet for up to 2 weeks to demonstrate resolution of symptoms, and then eliciting clinical symptoms by oral food challenge. Double-blind, placebo-controlled oral food challenges will provoke classical symptoms if the allergen has been strictly eliminated from the patient's diet for 10–14 days.

Prior to the identification of IgE, reagin-mediated reactions of the GI tract were investigated in a series of studies by Walzer and co-workers [13–17] utilizing passive sensitization. Sera from food allergic patients were injected into rectal, colonic, and ileal mucosal tissue in normal volunteers and patients with ileostomies and colostomies. Following the ingestion of the responsible food allergen, the passively sensitized site was noted to become pale, and then rapidly became edematous and hyperemic with marked mucus secretion [15]. These studies established that food allergens are rapidly absorbed and transported by way of the circulation to intestinal and extraintestinal mast cells.

Early radiographic studies of GI anaphylaxis demonstrated hypertonicity of the transverse and pelvic colon, and hypotonicity of the cecum and ascending colon following allergen ingestion in a sensitized patient [18]. Gastric retention, hypermotility of the intestine, and colonic spasm was demonstrated in 4 food-allergic patients after administering barium mixtures containing specific allergens [19]. In a study of 12 food-allergic children, fluoroscopy and a single-blind protocol were utilized to compare the effect of barium contrast with and without food allergen [20]. Gastric hypotonia and retention of the allergen test meal with prominent pylorospasm, and increased or decreased peristaltic activity of the intestines were noted.

Food challenges under endoscopy were first reported in 1942. Six patients with gastrointestinal food allergy, 4 patients with asthma symptoms exacerbated by food ingestion, and 3 controls were evaluated by gastroscopy [21]. A small amount of food allergen was placed on the gastric mucosa through the gastroscope and the mucosa was re-visualized 30 min later. The gastric mucosa of patients with GI allergy was markedly hyperemic and edematous with patches of thick gray mucous and scattered petechiae, similar to what Walzer [15] described in passively sensitized intestinal mucosa. More recently, larger numbers of patients were studied with the flexible gastroscope (intra-gastral provocation under endoscopic control) and have confirmed these earlier observations [22]. In addition, intestinal biopsies demonstrated a significant decrease in stainable mast cells and tissue histamine content following a positive food challenge.

Studies of IgE-mediated food hypersensitivity in rats have provided a useful model of GI anaphylaxis. Ovalbumin-sensitized rats were used to investigate the effects of repeated daily ingestion of a food allergen (ovalbumin) [23]. Serum rat mast cell protease II (RMCP II) levels increased to over 15 times normal levels following the ovalbumin challenge on the first day, and ranged between 2 and 5 times normal on 4 subsequent challenge days. Eliminating ovalbumin for 9 days before re-feeding sensitized animals resulted in increased serum RMCP II levels, but to only 5 times normal concentrations. This study provided *in vivo* evidence of desensitization, with the initial allergen challenge leading to a marked mast cell activation followed by a period of partial desensitization. Subsequent exposures to allergen, even after short periods of avoidance, provoked smaller (but significant) amounts of mast cell mediator release. These studies are consistent with the 'blunting' of distinct allergic symptoms in food-sensitive individuals regularly ingesting food allergens and support the practice of complete food allergen avoidance for 10–14 days in order to elicit a distinctive response to oral food challenges in man. The rat model also has been used to study the therapeutic effects of cromolyn sodium, and H₁ and H₂ antihistamines have been examined in the rodent model. Premedicating the animals failed to block the allergic response [24], which is consistent with the lack of therapeutic effect in man.

Allergic eosinophilic gastroenteritis (AEG) is a disorder distinguished clinically by postprandial nausea and vomiting, abdominal pain, diarrhea (occasionally steatorrhea), and failure to thrive in young infants or weight loss in older children and adults. Biopsies of the GI tract reveal an eosinophilic infiltrate which may involve the mucosal, muscular, and/or serosal layers of the stomach or small intestine [25–28]. Symptoms are exacerbated by foods in about one-half of patients with the mucosal form; patients are generally atopic with elevated serum IgE concentrations, positive prick skin tests to a variety of foods and inhalants and peripheral blood eosinophilia [25]. Some infants develop iron deficiency anemia and generalized edema secondary to hypoalbuminemia which occurs secondary to protein-losing enteropathy, not infrequently in the presence of minimal GI symptoms such as occasional vomiting and diarrhea [26, 29]. In young infants, AEG also may present as pyloric stenosis with outlet obstruction and postprandial, projectile emesis [30].

The *diagnosis* of this subset of AEG is based on a suggestive history and a biopsy demonstrating the characteristic eosinophilic infiltration [27]. Eosinophilic infiltrates are often patchy so multiple biopsies (up to 8) are recommended to rule out AEG [31]. Laboratory studies consistent with this diagnosis include peripheral eosinophilia, Charcot-Leyden crystals in the stools, positive prick skin tests to foods, abnormal absorption studies (e.g. *D*-xylose, mannitol/lactulose), and occasionally anemia and hypoalbuminemia. Identification and elimination of the responsible food allergen from the diet for 3–8 weeks may be nec-

essary to bring about resolution of symptoms and 3–4 months for normalization of intestinal histology. Specific foods provoking AEG may be determined by blinded food challenges. Some patients with IgE antibodies to specific foods develop anaphylactic symptoms during oral food challenges, so appropriate equipment and personnel to treat anaphylaxis should be available.

Infantile colic is a poorly defined syndrome of paroxysmal fussiness characterized by inconsolable crying, abdominal distention, excessive gas, and drawing up of the legs which generally presents in the first month of life and resolves within 3–6 months [32]. A variety of psychosocial and dietary factors have been implicated in the etiology of infantile colic, but with the lack of a standardized diagnostic criteria and subjective symptoms of relatively short duration, it has been difficult to establish an etiology for this disorder. Double-blind, cross-over trials in bottle-fed and breast-fed infants suggest that IgE-mediated hypersensitivity may be a pathogenic factor in 10–15% of colicky infants [33–35].

The response to brief trials of hypoallergenic formula (extensively hydrolyzed milk-based formula [36]) are used to *diagnose* food-induced colic. Symptoms should resolve when the infant is placed on the hypoallergenic formula and recur when the regular formula or breast-feeding is resumed. For clinical trials, a food-allergic etiology is suggested when two placebo-controlled, blinded, cross-over trials of the suspected allergenic food result in symptoms during the allergen challenges and resolution during the placebo challenges. In the practice setting, a hypoallergenic formula may be tried and if colic resolves, periodic rechallenges should be carried out every 3–4 months to determine whether sensitivity has resolved. Prolonged use of hypoallergenic formulas is rarely necessary.

Non-IgE-Mediated Gastrointestinal Food Hypersensitivity

Food-induced enterocolitis syndrome most frequently presents in young infants during the first 3 months of life with recurrent vomiting and diarrhea, which may progress to dehydration [37, 38]. About one-third of infants with severe diarrhea develop acidosis and transient methemoglobinemia [39]. Cow's milk and/or soy protein are most often responsible for the enterocolitis syndrome, but it also occurs in exclusively breast-fed infants from food proteins passed in maternal breast milk. Enterocolitis also has been reported in older children to egg, wheat, rice, peanut, nuts, chicken and turkey [23, 38, 40]. Occult blood, neutrophils, eosinophils, and reducing substances (malabsorbed sugars) are frequently found in the stools. Prick skin tests to the responsible food allergen are negative. Jejunal biopsies reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells [41]. In vitro studies with peripheral blood mononuclear cells suggest that cytokines released from lym-

phocytes and other cell types directly affect the GI barrier and likely contribute to patient symptoms [42, 43]. A recent study suggested that antigen-induced secretion of TNF- α from local mononuclear cells (i.e. lymphocytes and monocytes) may account for the reaction [44]. Challenge or ingestion of the responsible food allergen generally elicits vomiting within 1–3 h, and may induce anaphylactoid shock (about 15% of cases) [40, 45]. Allergen elimination leads to resolution of symptoms within 24–72 h, although secondary disaccharidase deficiency may persist longer [38, 46].

The *diagnosis* of food-induced enterocolitis may be established by eliminating the suspected allergen from the diet and then challenging the patient with the suspected food allergen. Oral food challenges consist of administering up to 0.6 g/kg body weight of the suspected protein allergen while monitoring symptoms and the peripheral blood white count [38, 46]. Vomiting and diarrhea generally develop within 1–4 h of administering the food challenge and the absolute neutrophil count will increase at least 3,500 cells/mm³ 4–6 h following the development of symptoms, and neutrophils and eosinophils will be present in the stools. Food challenges (or accidental allergen ingestion) may lead to profuse vomiting, dehydration and hypotension, so challenges should be performed in a medical setting. Young infants found sensitive to cow's milk should be placed on a 'hypoallergenic' infant formula (extensively hydrolyzed, e.g. AlimentumTM, NutramigenTM), since up to 50% of these infants will develop similar symptoms to soy formulas [47]. The majority of infants 'outgrow' their sensitivity within 1–2 years, but infants with both cow milk- and soy protein-induced enterocolitis tend to have more prolonged sensitivity, with soy reactivity being most persistent.

Food-induced colitis also presents in the first few months of life and is often secondary to cow milk or soy protein hypersensitivity [48–52], although 45% of the cases occur in exclusively breast-fed infants [53], who develop colitis secondary to food allergens passed in their mothers' breast milk [54]. Food-induced colitis also has been reported secondary to a variety of other foods: egg, wheat, corn, fish, shellfish, and nuts [53]. Infants with this disorder generally do not appear ill, often have normally formed stools, and only come to attention because of the presence of blood (gross or occult) in their stools. Lesions are confined to the large bowel and consist of mucosal edema with infiltration of eosinophils in the epithelium and lamina propria. PMNs are present in severe lesions with crypt destruction [41, 51, 53].

The *diagnosis* of food-induced colitis is established by eliminating the suspected food allergen(s) and oral challenge with 0.6 g/kg body weight of the suspected food. Hematochezia generally resolves within 72 h of strict food allergen elimination, but the resolution of mucosal lesions may take up to 1 month [48, 51, 53]. Sigmoidoscopy findings are variable, revealing areas of patchy mucosal injection to severe friability with small aphthoid ulcerations and bleeding.

Colonic biopsies are characterized by a prominent eosinophilic infiltrate in the surface and crypt epithelia and the lamina propria [41, 51, 53]. Cow milk- and soy protein-induced colitis generally resolve by 2–3 years of age with allergen avoidance [52]. To determine whether symptoms have resolved, small amounts of milk or soy should be cautiously re-introduced after the first year of life [55].

Malabsorption syndromes (excluding celiac disease) generally present in the first several months of life with diarrhea or steatorrhea and poor weight gain [56]. Symptoms may include protracted diarrhea, vomiting in up to two-thirds of patients, and failure to thrive. Increased fecal fat and carbohydrate malabsorption are frequently present. Cow milk sensitivity is the most frequent cause of this syndrome, but sensitivity to soy, egg and wheat (transient celiac disease) have also been reported. Patchy villous atrophy with cellular infiltrate is seen on biopsy [57]. Serum IgA and IgG cow milk-specific antibodies are elevated in patients with cow milk-induced malabsorption, but this is not unique to patients with malabsorption syndrome.

The *diagnosis* is established by excluding the responsible food allergen from the diet and then challenging the patient once symptoms have cleared. A patchy villous atrophy is evident on biopsy, with a prominent mononuclear round cell infiltrate and small number of eosinophils in the epithelium and lamina propria, not unlike celiac disease but generally much less severe [55, 57]. When the responsible food allergen is excluded from the diet, symptoms resolve within several days to weeks, but villous atrophy and increased numbers of eosinophils, activated CD4+ cells in the lamina propria, and CD8+ cells in the intraepithelium [57] may take several weeks to months to revert to normal. Unlike celiac disease, this disorder appears to be transient, but the natural history of this disorder has not been well studied.

Celiac disease is an inherited malabsorption syndrome with more extensive enteropathy. Total villous atrophy and extensive cellular infiltrate are associated with sensitivity to gluten found in wheat, rye, barley and oat. The incidence is reported as 1:4,000, but is as high as 1:300 in Sweden [58]. Approximately 90% of patients with celiac disease are HLA-B8-positive and nearly 80% have the HLA-DW3 antigen (20% or less in normals) [59], supporting the theory of genetic predisposition [60]. However, the striking increase in celiac disease in Sweden over recent years compared to the stable incidence in genetically similar Denmark, strongly incriminates feeding practices in the pathogenesis of this disease as well [60]. Patients often present with diarrhea or steatorrhea, abdominal distention and flatulence, weight loss, and occasionally nausea and vomiting, oral ulcers, and other extraintestinal symptoms. Villous atrophy of the small bowel is a classic feature of celiac patients ingesting gluten, with increased lymphocytes, predominantly of the CD8 cytotoxic/suppressor phenotype, in the intraepithelial space [61]. γ/δ -Bearing T cells are reported to be increased in both the peripheral blood and jejunal

mucosa [62]. IgM- and IgA-containing B cells are increased in the lamina propria [63] and serum IgA concentration is increased [64]. IgA antibodies to gluten are present in over 80% of adults and children with untreated celiac disease [65]. IgG antibodies to a variety of foods are elevated, presumably secondary to increased food antigen absorption. The immunopathogenesis of this disorder is unknown, but a cell-mediated mechanism appears to be involved [59, 66]. Levels of IgM-, IgG-, and IgA-food antigen-containing immune complexes are increased in celiac patients but do not appear to have any correlation with disease activity [67].

The European Society for Pediatric Gastroenterology and Nutrition proposed revised diagnostic criteria for celiac disease, which require greater dependency on serologic tests [68]. Recent studies showed that infants less than 2 years of age should be screened for IgA antigliadin antibodies [69], whereas older individuals should be first screened for IgA antigliadin antibodies and then confirmed with IgA antiendomysium antibodies [70], and possibly IgA antijejunal antibodies [71]. However, the intestinal biopsy remains the 'gold standard', and a definitive *diagnosis* is dependent on demonstrating biopsy evidence of villous atrophy and inflammatory infiltrate, resolution of biopsy findings after 6–12 weeks of gluten elimination, and recurrence of biopsy changes following gluten challenge [72]. Once the diagnosis of celiac disease is established, gluten-containing foods should be completely excluded from the diet for life, both to control symptoms and avoid the increased risk of malignancy [73].

AEG, as discussed above, is characterized by pronounced infiltration of the stomach and/or small intestinal mucosa, muscular layer, and/or serosa with eosinophils. Clinical symptoms roughly correlate with the degree of eosinophil infiltration of the bowel wall [25, 27, 28]. Infiltration of the mucosal layer with eosinophils generally leads to a syndrome of malabsorption while infiltration of the muscular layer often leads to an obstructive disorder. Subserosal disease generally is characterized by eosinophilic ascites. The immunopathogenic mechanism(s) responsible for AEG is not known, but peripheral blood T cells from these patients secrete excessive IL-4 and IL-5 [74], a finding consistent with the elevated IgE and eosinophilia seen in this disorder. In children, especially with gastroesophageal reflux, food hypersensitivity may be a more common cause of AEG than previously appreciated. Recently a group of 10 children diagnosed with severe gastroesophageal reflux were evaluated. Symptoms consisted of postprandial abdominal pain (colic), early satiety or food refusal, vomiting [frequently marked by thick 'stringy' (egg white-like) mucus], occasionally diarrhea, and failure to thrive were evaluated [75]. All children were refractory to standard reflux medications and 6 of the 10 children had undergone Nissen fundoplication, yet continued to have symptoms (retching instead of vomiting) and failure to thrive. Endoscopy and biopsies of the esophagus, stomach and proximal duodenum were consistent with a diagnosis of AEG. Following 6–8 weeks of an amino

acid-based elemental diet (NeocateTM plus rice) symptoms completely resolved in 8 of 10 children (2 children were markedly improved but continued to have poor appetites) and biopsies revealed marked reduction or clearing of the eosinophilic infiltrate in the esophagus and significant improvement in the grade of basal zone hyperplasia and the lengths of the vascular papillae [75]. Symptoms promptly recurred following challenges with specific foods, e.g. milk, egg, soy.

The *diagnosis* of AEG is based on compatible clinical history and biopsy findings of an eosinophilic infiltration of the gastrointestinal wall. Since the eosinophilic infiltrate is frequently patchy, multiple biopsies are often required. A 6- to 8-week trial on an elemental diet may be warranted in severe cases. A marked reduction in symptoms should occur within 3–6 weeks, although normalization of gut histology may require months. If symptoms resolve on the elemental diet, foods must be systematically re-introduced in order to determine which foods are provoking symptoms. New foods must be ingested for 4–5 days before it can be considered 'safe', and occasionally in young children, foods previously tolerated may later provoke symptoms. Unlike other food hypersensitivity disorders, multiple food sensitivities appear common in this disorder. With strict food allergen elimination, at least some of the children 'outgrow' their reactivity over 2–3 years.

When specific foods cannot be implicated in the etiology, oral steroids are generally required to alleviate symptoms, although successful treatment is occasionally reported in uncontrolled trials with oral cromolyn [76] and oral budesonide [77]. Symptoms generally respond to oral steroids (1–2 mg/kg/day), but recurrent symptoms are not infrequent when steroids are discontinued. With recurrence, a regimen of low-dose prednisone or every other day prednisone may be successful in suppressing symptoms [27, 28].

Management

GI food allergy is most common in young infants, and fortunately most infants will 'outgrow' their sensitivity over the first few years of life. As with other forms of food-allergic reactions, appropriate treatment of GI food hypersensitivities requires identification of the responsible food allergens and strict elimination of that food from the diet. A number of well-characterized GI disorders have been delineated, but they must be distinguished from a variety of food intolerances which may present with similar symptoms.

Acknowledgments

Supported in part by grants AI 24439 from National Institute of Allergy and Infectious Disease, and RR00052 from the Division of Research Resources, National Institutes of Health.

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