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Summary and Recommendations: Classification of Gastrointestinal Manifestations Due to Immunologic Reactions to Foods in Infants and Young Children

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After individual presentations on various disorders of the gastrointestinal tract, issues of classification were discussed for consensus. As a beginning, the workshop participants agreed that the diagnosis of immunologic reactions to dietary products in the gastrointestinal tract in infants and young children is often made on the basis of one or more of the following criteria:

1. The history of an allergic (immunoglobulin [IgE]-mediated or non-IgE-mediated) or allergic-like hypersensitivity reactions to foods ingested or following exposure.
2. The exclusion of other anatomic, functional, or infectious reasons for such reactions.
3. The proven or presumed relationship to ingestion of a specific dietary product or food based on repeated hypersensitivity reactions, clinically, after either challenge or inadvertent re-exposure.
4. The finding of either positive immediate-reacting, IgE-mediated epicutaneous skin test reactions to commercial or fresh foods or in vitro identification of circulating IgE anti-food antibodies in proven or presumed IgE-mediated reactions.
5. The failure to respond to conventional therapies of gastrointestinal conditions of an anatomical, functional, or infectious nature.
6. The positive clinical response to avoidance of specific food or other dietary exposures, over time.
7. The positive clinical response to the use of medications, usually used to treat acute allergic or allergic-like conditions (e.g., epinephrine) by injection, to treat anaphylaxis or anaphylactoid reactions or allergic inflammation (e.g., corticosteroids).
8. The similarities of clinical manifestations of the reaction as well as other characteristics to clinical syndromes, either proven or presumed to be caused by immunologic mechanisms.
9. The lack of other explanations for this clinical allergic-like reaction.

In group discussions, it became clear that most attendees agreed that it is difficult to classify all the known or presumed types of immunologic gastrointestinal reactions to foods and other dietary products in infants and young children under a single unifying concept. From a mechanistic point of view, most reactions are presumed to be immunologic in nature, rather than proved to be so. The only clear-cut mechanism involves IgE anti-food antibodies and mast cell activation. The finding of eosinophils in a gastrointestinal biopsy is suggestive of a hypersensitivity reaction but does not in itself constitute a diagnosis of an immunologic reaction. Eosinophilic infiltrates detected in a tissue biopsy of the

gastrointestinal tract may be due to systemic disease unrelated to a specific dietary-induced hypersensitivity-like clinical reaction or may play a passive role rather than an active role in such a clinical reaction. A response or absence of response to a medication or other therapies does not in itself constitute a diagnosis of these conditions, because these same therapies are often used to treat other gastrointestinal diseases and conditions unrelated to diet or immunologic reactions. The clinical syndromes presumed to involve immune-mediated gastrointestinal reactions are often based on clinical and/or laboratory and biopsy criteria, which overlap with other gastrointestinal disorders unrelated to diet or a proven immunologic mechanism.

Regardless of the immunologic mechanism involved, symptoms of gastrointestinal hypersensitivity are very similar, but generally vary in time of onset, severity, and persistence. The consensus conference reviewed the terminology applied to disorders of infants and children associated with immune responses to foods. After extensive discussions, the group agreed on the terminology and classification approach presented in [Table 1](#). Each clinicopathologic entry is discussed in the following sections, along with the features that distinguish it from the others.

TABLE 1. *Classification of gastrointestinal hypersensitivities to food and other dietary products*

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Immunoglobulin E-Mediated Disorders

Immediate gastrointestinal hypersensitivity is defined as an IgE-mediated gastrointestinal reaction that often accompanies allergic manifestations in other target organs (e.g., skin, lungs) and results in a variety of symptoms (1) ([Table 2](#)). A variety of evidence supports this definition. In early studies of IgE-mediated food hypersensitivity, radiographic changes were associated with food-allergic reactions. Rowe gave four food-allergic patients barium mixtures containing specific food allergens. He then studied them radiographically, observing gastric retention, hypermotility of the intestine, and colonic spasm (2). In fluoroscopic studies by Fries and Zeiger of 12 food-allergic children, the outcome of barium meals with and without food allergens were compared (3). The most prominent findings included gastric hypotonia and retention of the allergen test meal, prominent pylorospasm, and subsequent increased or decreased

peristaltic activity of the intestines. “Immediate” allergic reactions in the stomachs of six food-allergic patients were also observed by gastroscopy (4). A small amount of the appropriate food allergen was placed on the gastric mucosa and then revisualized 30 minutes later. The mucosa then appeared markedly hyperemic and edematous with patches of thick gray mucus and scattered petechiae. Similar more recent studies have confirmed these earlier observations (5). In addition, biopsy samples obtained before and after challenges were found to have significant decreases in stainable mast cells and tissue histamine after positive food challenges consistent with IgE-dependent mast cell activation. Positive skin test or radioallergosorbent test (RAST) results to responsible food allergens are present in virtually all cases (<95%).

Manifestations	• Nausea, abdominal pain and vomiting within 1 to 2 hours • Diarrhea within 2 to 6 hours • Frequently associated with atopic disease • Food-specific IgE antibodies • Radiographic: gastric hypotonia and pyloruspasm
Age of onset	• Infancy, childhood
Proteins implicated	• Milk, egg, peanut, soy, cereal, fish
Pathology	• Immunoglobulin E-mediated
Treatment	• Protein elimination
Genetics	• Familial • Often associated with other atopic diseases
Natural history	• 80% of cases resolve after protein elimination diet (except in the case of peanut and fish allergy)

TABLE 2. *Immediate gastrointestinal hypersensitivity*

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It was agreed that symptoms due to immediate gastrointestinal hypersensitivity typically develop within minutes to 2 hours of consumption of the responsible food allergen. These consist of nausea, abdominal pain, colic, vomiting within 1 to 2 hours, and/or diarrhea within 2 to 6 hours. In young infants, immediate vomiting is not always a consistent finding, and some of these infants vomit intermittently and show failure to thrive. In children with atopic dermatitis and food allergy, the repeated ingestion of food allergen appears to induce a partial desensitization of gastrointestinal mast cells resulting in subclinical reactions. Frequently, these children have poor appetite, poor weight gain, and intermittent abdominal pain, but carbohydrate permeability studies, a measure of gut wall integrity, demonstrate abnormal permeability in such patients (6,7).

Oral allergy syndrome (OAS) is estimated to affect up to 40% of adults who have pollen allergy, especially to birch, ragweed, and mugwort pollens (8) (Table 3). It is reported as a form of IgE-mediated

contact allergy that is confined to the oropharynx, and rarely affects other target organs. This conference endorses this description. Local IgE-mediated mast cell activation provokes the rapid onset of pruritus, burning, tingling and swelling of the lips, tongue, palate and throat and, occasionally, a sensation of pruritus in the ears and/or tightness in the throat. Symptoms are recognized as usually short-lived and are most commonly associated with the ingestion of various fresh fruits and vegetables (9,10). Ragweed-allergic patients may experience OAS after contact with various fresh melons (e.g., watermelon, cantaloupe, honeydew) and bananas (10,11). Symptoms may be more prominent after the ragweed season, corresponding to the seasonal rise in ragweed-specific IgE levels. Birch pollen-allergic patients may have symptoms after the ingestion of raw potatoes, carrots, celery, apples, hazelnuts, and kiwi (10–13). Cross-reactivity between birch pollen and various fruits and vegetables is due to homology among various pathogenesis-related proteins important in the defense against plant diseases. Oral symptoms also have been described among several fruits in the *Prunoideae* subfamily, and appear to be due to a homologous 9-kDa protein found in these fruits (peach; [Pru p 1]), cherry, apricot, and plum) and Brazil nuts (Ber e 1) (14,15). Patients with OAS generally can ingest these foods in the cooked form without difficulty.

Oral manifestations	• Burning • Swelling • Itching • Erythema • Immediate onset of symptoms
Age of onset	• Beyond infancy • Typically less than 5 years
Proteins implicated	• Heat-labile fresh fruit and vegetable allergens • Pollen and latex cross-reactivity
Pathology	• Immunoglobulin E antibodies
Treatment	• Avoidance • Cooking
Genetics	• Familial • Frequent allergic rhinitis
Natural history	• Unknown

TABLE 3. Oral allergy syndrome

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Mixed IgE- and Non-IgE-Mediated Disorders📈

Allergic eosinophilic esophagitis, gastritis, and gastroenterocolitis are characterized by various infiltrations of the esophagus, stomach, and/or intestinal walls with eosinophils, an absence of vasculitis, and peripheral eosinophilia in approximately 50% of patients. The eosinophilic infiltrate may involve the mucosal, muscular, and/or serosal layers of the stomach or small intestine, and clinical symptoms correlate with the extent of eosinophilic infiltration of the bowel wall (16–19). Eosinophilic infiltration of the

muscular layer leads to thickening and rigidity-provoking symptoms of obstruction, whereas infiltration of the serosa results in ascites containing eosinophils. Although peripheral blood T cells from these patients have been shown to secrete excessive amounts of interleukin (IL)-4 and IL-5 compared with normal controls (20), the underlying immunopathogenesis of these disorders is poorly understood.

Allergic eosinophilic esophagitis, it is agreed, is seen most frequently during infancy through adolescence, and involves chronic esophagitis with or without reflux, as demonstrated by a 24-hour pH probe study dysphagia, intermittent emesis, food refusal, abdominal pain, irritability, sleep disturbance, failure to respond to conventional reflux medication, and, occasionally, esophageal strictures (Table 4). Total serum IgE is normal or slightly elevated, and peripheral eosinophilia is uncommon. Esophageal biopsy reveals infiltration of the mucosa and submucosa with eosinophils, papillary elongation, and basal zone hyperplasia. Older patients frequently are reactive to several foods, presumably on a non-IgE-mediated basis, because skin test and/or RAST results are frequently negative.

Manifestations	• Chronic reflux esophagitis or gastroesophageal reflux • Emesis • Food refusal • Failure to thrive • Abdominal pain • Dysphagia • Irritability • Sleep disturbance • Failure to respond to conventional reflux treatment • Normal to slightly elevated serum IgE • Peripheral eosinophilia uncommon
Age at onset	• Infant to adolescent
Proteins implicated	• Cow's milk, wheat, soy, peanut, egg • Often multiple antigens • Poor correlation to skin tests
Pathology	• Eosinophilic, PMN infiltration of mucosa, submucosa, and esophagus • Papillary elongation • Basal zone hyperplasia
Treatment	• Protein elimination • Good response to hydrolyzed protein formula in infants • Excellent response to L-amino acid formula • Excellent acute response to steroids • Efficacy of long-term antigen restriction is under investigation
Genetics	• Unknown
Natural history	• Some cases persist in more than 1 year • Cow's milk: 80% of cases resolve in less than 1 year

IgE, immunoglobulin E; PMN, polymorphonuclear neutrophil.

TABLE 4. *Allergic eosinophilic esophagitis* IgE, immunoglobulin E; PMN, polymorphonuclear neutrophil.

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Young infants often respond to extensively hydrolyzed infant formulas, but older patients typically require amino acid-derived formulas for resolution of symptoms (21). Symptoms also respond to systemic steroids (e.g., 2 mg/kg per day) but generally return when steroids are tapered. Symptoms due to one or

two foods (e.g., milk) frequently resolve in 1 to 2 years. One study of children less than 1 year of age with gastroesophageal reflux found that 40% of infants studied had cow's milk hypersensitivity and a characteristic phasic pattern on 24-hour pH probe studies (22).

Allergic eosinophilic gastritis, it is agreed, is more common between infancy and adolescence, with symptoms including postprandial vomiting, abdominal pain, anorexia, early satiety, hematemesis, failure to thrive, gastric outlet obstruction (rarely, pyloric stenosis [23]), and gastric bleeding (Table 5).

Approximately half these patients have atopic features, elevated serum IgE levels, and peripheral eosinophilia. Gastric biopsy reveals marked infiltration of the mucosa and submucosa with eosinophils, especially in the gastric antrum. Treatment and outcome are similar to that seen in allergic eosinophilic esophagitis, except that long-term outcome is more guarded in older patients.

Manifestations	• Vomiting • Abdominal pain • Anorexia • Early satiety • Hematemesis • Failure to thrive • Gastric outlet obstruction • Gastric bleeding • 50% of cases atopic • Elevated immunoglobulin E • 50% of cases with peripheral eosinophilia • Radiographic: antral obstruction, thickened folds • Gastroesophageal reflux • Failure to respond to H₂-blockers • Responds to protein elimination
Age at onset	• Neonate to adolescent
Proteins implicated	• Cow's milk, egg, corn, cod, soy • Often single antigen • Less than 50% skin test specificity
Pathology	• Marked eosinophilic infiltration of gastric mucosa, submucosa, especially in the gastric antrum
Treatment	• Protein elimination • Excellent response to hydrolyzed protein formula in patients less than 2 years of age • Excellent response to L-lysine acid formula • Excellent response to low-dose, often long-term steroids
Genetics	• Atopic predisposition possible
Natural history	• Guarded outcome in older patients

TABLE 5. *Allergic eosinophilic gastritis*

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Allergic eosinophilic gastroenterocolitis, it is agreed, may occur at any age, with symptoms similar to esophagitis and/or gastritis (Table 6). Weight loss or failure to thrive is a hallmark of this disorder. Up to 70% of patients with this allergic eosinophilic disorder are atopic, and food-induced IgE-mediated reactions have been implicated in a subset of patients. Hypogammaglobulinemia and generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy, often in the presence of minimal gastrointestinal symptoms such as occasional vomiting and diarrhea (24).

Approximately half of patients are believed to respond to allergen-elimination diets, but resolution of symptoms often requires 3 to 8 weeks after the elimination of responsible food allergens (frequently only a few foods). Biopsy of the esophagus and duodenum reveals infiltration of the mucosa and submucosa with eosinophils, and biopsy of the colon may reveal eosinophils and crypt abscesses.

Manifestations	• Abdominal pain • Anorexia • Early satiety • Failure to thrive • Gastric outlet obstruction • Gastric or colonic bleeding • $\pm$70% of cases atopic • Elevated immunoglobulin E • a Food-specific immunoglobulin E • 50% of cases with peripheral eosinophilia • Radiographic: antral obstruction, Menetrier's Disease, gastroesophageal reflux, bowel wall edema, vomiting, diarrhea, protein-losing enteropathy, decreased albumin
Age at onset	• Neonate to adolescent
Proteins implicated	• Cow's milk, egg, fish, soy, cereals • Less than 50% skin test specificity
Pathology	• Marked eosinophilic infiltration of mucosa and submucosa; gastric antrum, esophagus, and duodenum; and colon • Ascites evident if serosal
Treatment	• 50% of patients respond to dietary elimination of documented allergen • Excellent response to hydrolyzed protein formula in patients less than 2 years of age • Excellent response to L-amino acid formula • Responsive to steroids
Genetics	• Unknown
Natural history	• Disorder is typically prolonged

TABLE 6. Allergic eosinophilic gastroenterocolitis

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Similar to the other allergic eosinophilic disorders, allergic eosinophilic gastroenterocolitis responds to elemental diets or systemic steroids. The natural history of this disorder is typically prolonged.

Non-IgE-Mediated Disorders📌

By consensus, *dietary protein enterocolitis* is a disorder most frequently seen in the first several months of life in which infants show irritability, with protracted vomiting and diarrhea, not infrequently resulting in dehydration (25,26) (Table 7). Vomiting generally occurs 1 to 3 hours after feeding, and diarrhea 5 to 8 hours after feeding. Continued exposure to the food allergen may result in bloody diarrhea, anemia, abdominal distension, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein-based formulas but occasionally result from food proteins passed in maternal breast milk. A similar enterocolitis syndrome has been reported in older infants and children due to egg, wheat, rice, oat, peanut, nuts, chicken, turkey, and fish sensitivity (27). Hypotension occurs in approximately 15% of cases after allergen ingestion (27,28). In adults, shellfish (e.g., shrimp, crab, and lobster) sensitivity may

provoke a similar syndrome with severe nausea, abdominal cramps, and protracted vomiting. Stools often contain occult blood, polymorphonuclear neutrophils (PMNs) and eosinophils, and Charcot–Leyden crystals. Prick skin test responses to the suspected foods are negative. Jejunal biopsies classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. Increased numbers of IgM-and IgA-containing plasma cells are seen in the jejunal mucosa (29). Although the immunopathogenic mechanism of this syndrome remains to be elucidated, studies suggest that food antigen-induced secretion of tumor necrosis factor (TNF)-[alpha] from local mononuclear cells may be responsible for the diarrhea and hypotension (30).

Manifestations	• Diarrhea with bleeding • Anemia • Emesis • Abdominal distension • Failure to thrive • Hypotension • Fecal leukocytes • Normal immunoglobulin E • Food challenge: vomiting in 3 to 4 hours; diarrhea in 5 to 8 hours
Age at onset	• 1 day to 1 year
Implicated proteins	• Cow's milk, soy, rice, poultry, fish
Pathology	• Patchy villous injury and colitis • Food challenge with offending protein (PMNs): peripheral leukocytosis, fecal leukocytes/blood within 4 to 6 hours of challenge • Food challenge risk is high; can develop hypotension/shock
Treatment	• 80% or more of cases respond to hydrolyzed casein formula and symptoms clear in 3 to 10 days • Up to 20% of cases require L-lysine acid formula or temporary intravenous therapy
Genetics	• Unknown
Natural history	• In general: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months • Cow's milk: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months • Soy: illness is often more persistent

PMN, polymorphonuclear neutrophils.

TABLE 7. *Dietary protein enterocolitis*PMN, polymorphonuclear neutrophils.

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Dietary protein proctitis, it is agreed, typically occurs in the first few months of life, with blood-streaked stools in otherwise healthy-looking infants (Table 8). Up to 60% of cases are seen in breast-fed infants (31–33), with the remainder largely in infants fed cow's milk– or soy protein–based formula. Blood loss is typically modest but occasionally produces anemia. Mild hypoalbuminemia and peripheral eosinophilia rarely occur. Bowel lesions generally are confined to the distal large bowel and endoscopy reveals linear erosions and mucosal edema. Biopsy reveals infiltration of eosinophils (>20 eosinophils; 140 × high-power field) and lymphoid nodular hyperplasia in approximately 20% of patients. In severe lesions with crypt destruction, PMNs are also prominent (34). Elimination of the responsible food allergen usually

results in resolution of gross bleeding within 72 hours, whereas complete resolution of occult bleeding may take a few weeks. Some children have been found to be sensitive to extensively hydrolyzed infant formulas (e.g., Alimentum, Ross Laboratories; Nutramigen, Mead Johnson, Evansville, IN, U.S.A.) the usual form of therapy in this disorder, and require the use of amino acid–derived formulas (e.g., EleCare, Ross Laboratories, Columbus, OH, U.S.A.; or Neocate, Scientific Hospital Supplies, Gaithersburg, MD, U.S.A.) for resolution of symptoms (35). Most patients are believed to “outgrow” their hypersensitivity in 1 year.

Manifestations	• Blood-streaked, soft-to-loose stools • Fecal leukocytes • Mild peripheral eosinophilia • Mild hypoalbuminemia • Low risk of anemia • Food challenge: symptoms in 6 to 72 hours
Age at onset	• 1 day to 6 months • Most cases manifest at 2 to 8 weeks
Proteins implicated	• 60% of reported infants exclusively breast fed • Cow's milk, egg, soy
Pathology	• Endoscopic: focal to diffuse colitis, linear erosions • Microscopic: eosinophilic colitis more than 20 eosinophils/40 per high-power field; 20% of cases with nodular lymphoid hyperplasia
Treatment	• Protein elimination • Symptoms generally clear in 72 hours in patients given extensively hydrolyzed formula • Resume or continue breast-feeding on maternal antigen-restricted diet
Genetics	• May be familial
Natural history	• Symptoms usually clear by 1 year

TABLE 8. *Dietary protein proctitis*

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Dietary protein enteropathy, it is agreed, often appears in the first several months of life with diarrhea (not infrequently steatorrhea) and poor weight gain (36). Symptoms include protracted diarrhea, vomiting in up to two thirds of patients, failure to thrive, abdominal distension, early satiety, and malabsorption. (Table 9). Anemia, edema, and hypoproteinemia are occasionally seen. Serum IgE, food-specific IgE, and peripheral eosinophil counts are not abnormal. Cow's milk sensitivity is the most frequent cause of this syndrome in young infants, but it also has been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. Biopsy reveals patchy villous atrophy with increased crypt length and intraepithelial lymphocytes with few eosinophils. In cow's milk–induced enteropathy, serum IgA and IgG antibodies to cow's milk proteins are elevated. Elimination of the responsible food allergen leads to clearing of symptoms in 3 to 21 days. Most patients are believed to outgrow their hypersensitivity in 2 to 3 years.

Manifestations	• Diarrhea • Malabsorption • Failure to thrive • Emesis • Abdominal distension • Early satiety • Anemia • Edema • Hypoproteinemia • Protein-losing enteropathy • Normal serum immunoglobulin E • No peripheral eosinophilia • No food-specific immunoglobulin E • No increase in atopy • Anti-endomysium antibody negative • Radiographic: small bowel edema • Food challenge: vomiting and/or diarrhea in 40 to 72 hours
Age at onset	• Dependent on age of exposure to antigen • Cow's milk and soy: up to 2 years
Proteins implicated	• Cow's milk, soy, cereal, egg, fish
Pathology	• Variable small bowel villus injury and increased crypt length; often patchy, sub-total intraepithelial lymphocytes; few eosinophils
Treatment	• Strict elimination of offending antigen • Symptoms clear in 3 to 21 days • Rechallenge and consider another biopsy at 1 to 2 years • Low risk of severe acute symptoms
Genetics	• Unknown
Natural history	• Most cases resolve in 2 to 3 years

TABLE 9. *Dietary protein enteropathy*

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Celiac disease, it is recognized, is well described. It is a dietary protein enteropathy characterized by a more extensive loss of absorptive villi and hyperplasia of the crypts leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distension, flatulence, and weight loss or failure to thrive (Table 10). Oral ulcers and other extraintestinal symptoms secondary to malabsorption are not uncommon. Patients with celiac disease are sensitive to gliadin, the alcohol-soluble portion of gluten found in wheat, rye, barley, and possibly oat. Celiac disease is associated with the HLA-DQ2 (and DQ8) haplotype, and approximately 90% of patients with celiac disease ingesting gliadin possess IgA anti-gliadin and anti-endomysium antibodies (37). In addition, celiac disease is associated with dermatitis herpetiformis, diabetes mellitus, thyroid disease, Down syndrome, and IgA deficiency. Histology typically reveals total villous atrophy and extensive cellular infiltrate. The prevalence of celiac disease has been reported in between 1 in 3700 and 1 in 300 people (38), and a recent study among normal blood donors in the United States revealed IgA anti-endomysium antibodies in 1 in 250 subjects (39). Recent studies suggest that the severity of celiac disease varies from a debilitating malabsorption syndrome to a “silent,” subclinical disorder. Chronic ingestion of gluten-containing grains in patients with celiac disease is associated with increased risk of malignancy, especially T-cell lymphoma (40).

Manifestations	• Chronic diarrhea • Abdominal distension • Failure to thrive/growth failure • Complications of malabsorption • Abdominal pain • No increased IgG • No increased atopy • Associated diseases: dermatitis herpetiformis, diabetes mellitus, thyroid disease, Down Syndrome, IgA deficiency • IgA gamma endomysium antibodies • IgG/IgE antigliadin antibodies • "Silent" disease possible • Atypical manifestation with isolated symptoms possible • Radiographic: malabsorption pattern
Age of onset	• Dependent on timing of gluten introduction • Typically more than 6 months
Proteins implicated	• Wheat, rye, barley, possibly oats
Pathology	• Extensive villous atrophy • Elongated crypt length • Increased intraepithelial lymphocytes? • Increased $\gamma\delta$ T cells
Treatment	• Gluten elimination
Genetics	• HLA-DQ2 (and DQ8)-associated
Natural history	• Illness is life-long

TABLE 10. *Celiac disease*Ig, immunoglobulin.

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Histopathologic studies show that lymphocytes, predominantly of the CD8⁺ cytotoxic-suppressor phenotype, are prominent in the intraepithelial space, and [gamma]/[delta]-T cells are increased in the jejunal mucosa and the peripheral blood (41). Recent evidence suggests that celiac disease is associated with increased mucosal activity of tissue transglutaminase (tTGase) on specific protein-bound glutamine (42). Gliadin is one of the few substrates for tTGase, which deamidates specific glutamines within gliadin, creating epitopes that bind efficiently to DQ2 gut-derived T cells (43). tTGase has been shown to be the target of the anti-endomysium antibodies, and antibodies to tTGase may supplement anti-endomysium antibodies as a diagnostic tool. It is now believed that generation of unique gliadin epitopes by tTGase enzymatic modification leads to activation of DQ2 (and DQ8)-restricted T cells, a breakdown in tolerance, and initiation of an autoimmune process that generates inflammation in the gut. Elimination of gliadin from the diet results in downregulation of the T-cell–induced inflammatory process.

CONCLUSIONS📌

Immunologic reactions to foods in the gastrointestinal tract include a continuum of gastrointestinal symptoms. The best-fit method of classification of immunologic gastrointestinal reactions to foods and other dietary products in infants and children is one based on symptom complex and anatomical regions affected (mouth, esophagus, stomach, small intestine, large intestine, rectum), as was used in making the above classification. The characteristic or exclusionary criteria separating specific allergic or allergic-like hypersensitivity reactions from other forms of gastrointestinal disease at each anatomical level include characteristic symptoms and signs, usual age of onset, immune studies (skin test/in vitro test) or

biopsy findings, and a response or absence of response to food challenge, food exclusion, specific medications, or other therapies (see tables).

After reviewing the literature and personal experiences of many investigators, participants in the workshop were able to agree on a working classification system for gastrointestinal food allergies. This document is meant to provide a framework for communication and further study and should be viewed as a work in progress. In our attempt to generate this classification system for gastrointestinal allergies, the paucity of hard data in this area was very evident and brought home the need for further research. It is the hope of all participants at the 1998 consensus workshop that a second larger workshop can be held in the future to reassess the utility of the proposed classification system and to generate a more accurate synopsis based on additional years of directed research.

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TABLE 1

IgE		Non-IgE	
Immediate gastrointestinal hypersensitivity			
Oral allergy syndrome			
		Allergic eosinophilic esophagitis	
		Allergic eosinophilic gastritis	
		Allergic eosinophilic gastroenterocolitis	
		Dietary protein enterocolitis	
		Dietary protein proctitis	
		Dietary protein enteropathy	
		Celiac disease	

TABLE 1. *Classification of gastrointestinal hypersensitivities to food and other dietary products*
From: Sampson: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement.January 2000.S87-S94

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TABLE 2

Manifestations	• Nausea, abdominal pain and vomiting within 1 to 2 hours • Diarrhea within 2 to 6 hours • Frequently associated with atopic disease • Food-specific IgE antibodies • Radiographic: gastric hypotonia and pylorospasm
Age of onset	• Infancy, childhood
Proteins implicated	• Milk, egg, peanut, soy, cereal, fish
Pathology	• Immunoglobulin E-mediated
Treatment	• Protein elimination
Genetics	• Familial • Often associated with other atopic diseases
Natural history	• 80% of cases resolve after protein elimination diet (except in the case of peanut and fish allergy)

TABLE 2. *Immediate gastrointestinal hypersensitivity*

From: Sampson: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement.January 2000.S87-S94

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TABLE 3

Oral manifestations	• Burning • Swelling • Itching • Erythema • Immediate onset of symptoms
Age of onset	• Beyond infancy • Typically less than 5 years
Proteins implicated	• Heat-labile fresh fruit and vegetable allergens • Pollen and latex cross-reactivity
Pathology	• Immunoglobulin E antibodies
Treatment	• Avoidance • Cooking
Genetics	• Familial • Frequent allergic rhinitis
Natural history	• Unknown

TABLE 3. *Oral allergy syndrome*

From: Sampson: J Pediatr Gastroenterol Nutr, Volume 30(1) Supplement. January 2000.S87-S94

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TABLE 4

Manifestations	• Chronic reflux esophagitis or gastroesophageal reflux • Emesis • Food refusal • Failure to thrive • Abdominal pain • Dysphagia • Irritability • Sleep disturbance • Failure to respond to conventional reflux treatment • Normal to slightly elevated serum IgE • Peripheral eosinophilia uncommon
Age at onset	• Infant to adolescent
Proteins implicated	• Cow's milk, wheat, soy, peanut, egg • Often multiple antigens • Poor correlation to skin tests
Pathology	• Eosinophilic, PMN infiltration of mucosa, submucosa, and esophagus • Papillary elongation • Basal zone hyperplasia

Treatment	• Protein elimination • Good response to hydrolyzed protein formula in infants • Excellent response to L-amino acid formula • Excellent acute response to steroids • Efficacy of long-term antigen restriction is under investigation
Genetics	• Unknown
Natural history	• Some cases persist in more than 1 year • Cow's milk: 80% of cases resolve in less than 1 year

IgE, immunoglobulin E; PMN, polymorphonuclear neutrophil.

TABLE 4. *Allergic eosinophilic esophagitis* IgE, immunoglobulin E; PMN, polymorphonuclear neutrophil.

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TABLE 5

Manifestations

- Vomiting
- Abdominal pain
- Anorexia
- Early satiety
- Hematemesis
- Failure to thrive
- Gastric outlet obstruction
- Gastric bleeding
- 50% of cases atopic
- Elevated immunoglobulin E
- 50% of cases with peripheral eosinophilia
- Radiographic: antral obstruction, thickened folds
- Gastroesophageal reflux
- Failure to respond to H-2 blockers
- Responds to protein elimination

Age at onset

- Neonate to adolescent

Proteins implicated

- Cow's milk, egg, corn, cod, soy
- Often single antigen
- Less than 50% skin test specificity

Pathology

- Marked eosinophilic infiltration of gastric mucosa, submucosa, especially

of gastric mucosa, submucosa, especially in the gastric antrum

Treatment

- Protein elimination
- Excellent response to hydrolyzed protein formula in patients less than 2 years of age
- Excellent response to L-amino acid formula
- Excellent response to low-dose, often long-term steroids

Genetics

- Atopic predisposition possible

Natural history

- Guarded outcome in older patients
-

TABLE 5. *Allergic eosinophilic gastritis*

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TABLE 6

Manifestations	• Abdominal pain • Anorexia • Early satiety • Failure to thrive • Gastric outlet obstruction • Gastric or colonic bleeding • $\pm 70\%$ of cases atopic • Elevated immunoglobulin E • $\pm$ Food-specific immunoglobulin E • 50% of cases with peripheral eosinophilia • Radiographic: antral obstruction, Menetrier's Disease, gastroesophageal reflux, bowel wall edema, vomiting, diarrhea, protein-losing enteropathy, decreased albumin
Age at onset	• Neonate to adolescent
Proteins implicated	• Cow's milk, egg, fish, soy, cereals • Less than 50% skin test specificity
Pathology	• Marked eosinophilic infiltration of mucosa and submucosa; gastric antrum, esophagus, and duodenum; and colon • Ascites evident if serosal

	• Ascites evident if serosal
Treatment	• 50% of patients respond to dietary elimination of documented allergen • Excellent response to hydrolyzed protein formula in patients less than 2 years of age • Excellent response to L-amino acid formula • Responsive to steroids
Genetics	• Unknown
Natural history	• Disorder is typically prolonged

TABLE 6. *Allergic eosinophilic gastroenterocolitis*

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TABLE 7

Manifestations	• Diarrhea with bleeding • Anemia • Emesis • Abdominal distension • Failure to thrive • Hypotension • Fecal leukocytes • Normal immunoglobulin E • Food challenge: vomiting in 3 to 4 hours; diarrhea in 5 to 8 hours
Age at onset	• 1 day to 1 year
Implicated proteins	• Cow's milk, soy, rice, poultry, fish
Pathology	• Patchy villous injury and colitis • Food challenge with offending protein (PMNs): peripheral leukocytosis, fecal leukocytes/blood within 4 to 6 hours of challenge • Food challenge risk is high; can develop hypotension/shock
Treatment	• 80% or more of cases respond to hydrolyzed casein formula and symptoms

hydrolyzed casein formula and symptoms clear in 3 to 10 days

- Up to 20% of cases require L-amino acid formula or temporary intravenous therapy

Genetics

- Unknown

Natural history

- In general: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months
- Cow's milk: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months
- Soy: illness is often more persistent

PMN, polymorphonuclear neutrophils.

TABLE 7. *Dietary protein enterocolitis* PMN, polymorphonuclear neutrophils.

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TABLE 8

Manifestations	• Blood-streaked, soft-to-loose stools • Fecal leukocytes • Mild peripheral eosinophilia • Mild hypoalbuminemia • Low risk of anemia • Food challenge: symptoms in 6 to 72 hours
Age at onset	• 1 day to 6 months • Most cases manifest at 2 to 8 weeks
Proteins implicated	• 60% of reported infants exclusively breast fed • Cow's milk, egg, soy
Pathology	• Endoscopic: focal to diffuse colitis, linear erosions • Microscopic: eosinophilic colitis more than 20 eosinophils/40 per high-power field; 20% of cases with nodular lymphoid hyperplasia
Treatment	• Protein elimination • Symptoms generally clear in 72 hours in patients given extensively hydrolyzed formula

in patients given extensively
hydrolyzed formula

- Resume or continue breast-feeding on maternal antigen-restricted diet

Genetics

- May be familial

Natural history

- Symptoms usually clear by 1 year
-

TABLE 8. *Dietary protein proctitis*

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TABLE 9

Manifestations	• Diarrhea • Malabsorption • Failure to thrive • Emesis • Abdominal distension • Early satiety • Anemia • Edema • Hypoproteinemia • Protein-losing enteropathy • Normal serum immunoglobulin E • No peripheral eosinophilia • No food-specific immunoglobulin E • No increase in atopy • Anti-endomysium antibody negative • Radiographic: small bowel edema • Food challenge: vomiting and/or diarrhea in 40 to 72 hours
Age at onset	• Dependent on age of exposure to antigen • Cow's milk and soy: up to 2 years
Proteins implicated	• Cow's milk, soy, cereal, egg, fish
Pathology	• Variable small bowel villus injury and

Pathology	• Variable small bowel villus injury and increased crypt length; often patchy, sub-total intraepithelial lymphocytes; few eosinophils
Treatment	• Strict elimination of offending antigen • Symptoms clear in 3 to 21 days • Rechallenge and consider another biopsy at 1 to 2 years • Low risk of severe acute symptoms
Genetics	• Unknown
Natural history	• Most cases resolve in 2 to 3 years

TABLE 9. *Dietary protein enteropathy*

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TABLE 10

Manifestations	• Chronic diarrhea • Abdominal distension • Failure to thrive/growth failure • Complications of malabsorption • Abdominal pain • No increased IgE • No increased atopy • Associated diseases: dermatitis herpetiformis, diabetes mellitus, thyroid disease, Down Syndrome, IgA deficiency • IgA gamma endomysium antibodies • IgG/IgE antigliadin antibodies • "Silent" disease possible • Atypical manifestation with isolated symptoms possible • Radiographic: malabsorption pattern
Age of onset	• Dependent on timing of gluten introduction • Typically more than 6 months
Proteins implicated	• Wheat, rye, barley, possibly oats
Pathology	• Extensive villous atrophy • Elongated crypt length • Increased intraepithelial lymphocytes?

	• Increased intraepithelial lymphocytes? • Increased γ/δ T cells
Treatment	• Gluten elimination
Genetics	• HLA-DQ2 (and DQ8)–associated
Natural history	• Illness is life-long

Ig, immunoglobulin.

TABLE 10. *Celiac disease* Ig, immunoglobulin.

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