Allergic disorders of the gastrointestinal tract

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Introduction

The patient with presumed food hypersensitivity continues to present a challenge for the clinician. In certain instances, it is clear that food protein antigens induce objective signs and symptoms, and that these can be reproduced by re-exposure to the offending antigen. Examples include IgE mediated anaphylactic reactions, and infantile cow’s milk protein induced colitis. However, gastrointestinal disorders characterized by predominantly eosinophilic inflammation in tissue may not be associated with known sensitization to specific, identifiable food antigens. There is considerable overlap in what is observed in food allergy and idiopathic eosinophilic gastroenteropathy, with eosinophilic inflammation of tissue occurring in either condition. The incidence of food allergy and other atopic disorders are increasing, raising questions about the effects of genetic versus environmental factors.

The goal of this presentation will be to provide an overview of current thinking about food hypersensitivity, eosinophilic gastroenteropathy and eosinophilic esophagitis. The clinical spectrum of presentation of allergic disease of the intestinal tract will be outlined, with an approach to diagnosis and management.

Definitions

Any adverse reaction to the ingestion of food can be termed intolerance or sensitivity. (Table 1). This definition does not imply any specific underlying mechanism, and therefore encompasses symptoms caused by immunologic or non-immunologic mechanisms. For example, chemicals in food such as caffeine or lactose intolerance may cause reproducible gastrointestinal symptoms, but are not mediated by immunologic reactions. On the other hand, true food allergy or food hypersensitivity is defined as a reproducible adverse reaction to a food protein antigen that is immune mediated (Figure 1). The classic example is IgE mediated anaphylaxis to food, where specific IgE antibodies can be measured, or demonstrated by skin-prick tests. Other immune mechanisms are possible, although less well characterized, and these probably represent the majority of food allergy that is seen by pediatric gastroenterologists.

The term eosinophilic gastroenteropathy will be defined as gastrointestinal disease characterized by increased eosinophils in tissue, but with no proven relation to demonstrable food protein allergy. The rationale for this is to try to distinguish idiopathic eosinophilic gastroenteropathy from specific food allergy that is likely to have different pathophysiology, treatment and natural history. This distinction is somewhat arbitrary, as both entities may be characterized by tissue eosinophilia, and what is considered idiopathic may respond to the elimination of food protein antigens even though our ability to document a defined immune mechanism may be lacking. This means that overlap exists between these disorders. Many patients with possible GI allergic or eosinophilic diseases are atopic individuals with a propensity towards Th-2 immunity and eosinophils in blood and tissue, and positive IgE testing by blood or skin-prick– it is important to remember that a causal relationship between food testing and disease is difficult to prove. Also, we do not have good data on the normal numbers of eosinophils in the gut of these individuals.

Table 1: How foods may induce GI symptoms

- Chemicals – MSG, caffeine, sulfites, nitrates other
- CHO Malabsorption: Disaccharidase deficiency – lactose intolerance, high fructose, sugar-free
- Fat malabsorption (rare in pediatrics)
- Irritable Bowel Syndrome – heightened gastro colic reflex, diarrhea, constipation
- Eating disorders
- Maunchausen by proxy
- Celiac Disease
- Type I Food Allergy
- Type IV Food Allergy
- FPIES
Prevalence, natural history of food allergy and the “Hygiene Hypothesis”

Food allergy is perceived by parents as being common. Difficulties in determining the prevalence and defining the pathophysiology of food allergy stem from multiple studies where the definition of food allergy was not standardized, the lack of objective tests particularly for non-IgE mediated allergy, and the fact that many young children ‘outgrow’ their allergies with time. A prospective study (Bock) of 480 infants from birth to age three revealed 133 (28%) were suspected as having symptoms related to specific foods; however, this was confirmed by open or blinded challenges in only 37 (8%), mostly in the first year of life. Two-thirds of these were attributable to cow’s milk. The prevalence after age one declines to the adult level of approximately 2-3%. Strict avoidance of the antigen was the only effective method of treatment, although more recent evidence supports the efficacy of desensitization protocols. However, these are labor intense and difficult to administer outside of research protocols. For IgE-mediated cow’s milk and peanut allergy, it is clear that patients who persist with higher levels of food-specific IgE are more likely to retain their allergy. Similarly, studies by Hill and duPont demonstrated that infants and young children with severe, non-IgE mediated multiple food protein intolerance requiring treatment amino-acid based formula tend to have more persistent allergies than those with single and less severe sensitivity.

Recently, interest has grown over the apparent increase in food allergy and atopic disorders in industrialized nations compared with children of similar genetic background in the developing countries. The hypothesis basically contends that through evolution, the human immune system has developed in relation to a specific microbial environment, and is dependant on “priming” from the environment to develop normal responses. These responses include development of tolerance when appropriate (eg no sensitization to foods or normal commensal organisms) and immune response to pathogens. Factors which promote a higher exposure to microbes such as the presence of older siblings, large family size, exposure to farm animals, increase in fecal-oral infections, higher population exposure to mycobacterium, and life in less developed nations all reduce the incidence of atopic disorders. Likewise, there is evidence that the timing, type and magnitude of bacterial flora in the GI tract may protect infants in less developed areas, and promote allergy in the developed world. These observations lend support for the growing interest in probiotic therapy and other novel treatment approaches for food allergy (below).

Type I Immediate (IgE Mediated) Hypersensitivity Reactions to Food

Immediate hypersensitivity reactions to foods are most common in young children, with 50% of these reactions occurring in the first year of life. The majority are due to cow’s milk and soy protein from infant formulas. Other foods begin to predominate in older children, including egg, fish, peanut and wheat, and along with milk and soy account for over 90% of food allergy in children. It is commonly thought that these patients frequently are allergic to multiple foods. However, double-blind food challenges demonstrate that over 80% of these children respond to only one or two foods. Exposures may occur inadvertently due to improper labeling, changes in product composition with time, and contamination of foods by processing techniques. Symptoms referable to the gastrointestinal tract typically
begin within minutes of the ingestion and include nausea, vomiting, abdominal pain and diarrhea, often with oral symptoms, skin manifestations, wheezing or airway edema. The experience with **fatal and near fatal anaphylactic reactions** to foods in children and adolescents has been well characterized. Most patients have a history of significant asthma, and common foods include tree nuts, peanut, egg, and milk. Early administration of epinephrine after symptom onset is associated with improved survival. Families, caregivers and patients with a history of anaphylaxis to food, require education on diet, the use of epinephrine, and observation in a hospital setting after a significant reaction.

**Exercise induced anaphylaxis** to specific foods has been reported in children, where the ingestion of antigen by itself does not cause symptoms; however, the combination of ingestion followed by exercise leads to anaphylaxis. **Oral allergy syndrome (OAS)** is a clinical syndrome where fresh foods, often fresh fruits, provoke local symptoms of itching of the mouth and pharynx, and typically do not progress to more severe reactions. **Chronic urticaria** can be caused by foods, however only a fraction of children with urticaria have proven allergy. **Atopic dermatitis (AD)** is a chronic pruritic skin condition found in atopic individuals with a characteristic distribution varying with age. Patients with AD often have a history of adverse reactions to food. In several studies, double blind food challenges were used to determine the 30-40% prevalence of food allergy with AD.

**Investigation and Management of Immediate Hypersensitivity Reactions**

The rapid onset of these symptoms after food ingestion correlates highly with positive skin prick or IgE-RAST tests to the offending antigen, making confirmation of immediate hypersensitivity straightforward. Caution must be used however, since skin prick and RAST tests do not always predict clinically relevant reactions in blinded food challenges. If the clinical history is equivocal then double blind food challenges in a controlled environment are needed to prove or disprove a reaction. Consultation with a dietitian is recommended and groups such as The Food Allergy Network can provide support and educational materials for families. The newer IgE CAPRAST FEIA tests provide a result in KIU/L, allowing IgE levels to be compared to other patients who have undergone challenges in the past. For common foods, specific antibody levels help predict whether an individual patient can be safely challenged.

**Non-IgE Mediated Food Allergy**

The clinical spectrum of non-IgE allergy is quite varied, and the presenting features often parallel the site of involvement, as it does for idiopathic EGE (Table 1). Avoidance of the food will resolve symptoms and histologic findings; re-challenge will reproduce the injury. Celiac disease is the classic T-cell mediated disease induced by immune reaction to gluten in wheat barley and rye. It is unique among non-IgE food allergy; patient require one or both genetic HLA markers (DQ2 or 8) and serum markers (IgA tissue transglutaminase, gliadin, reticulin or endomysial antibodies are often positive – they do not cause the disease).

**Table 2: Clinical presentation of formula protein allergy**

<table>
<thead>
<tr>
<th>Failure to thrive</th>
<th>Eosinophilic colitis (hematochezia)</th>
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<td>Protein losing enteropathy, edema</td>
<td>Atopic dermatitis</td>
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<tr>
<td>Iron deficiency anemia</td>
<td>Infantile colic</td>
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<tr>
<td>Chronic diarrhea</td>
<td>Food protein-induced enterocolitis syndrome</td>
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**Food protein-induced enterocolitis** is a unique clinical syndrome where patients have a severe reaction to a food, often delayed 4-6 hours, without evidence of an IgE mechanism. Patients present with extreme lethargy, profuse vomiting with subsequent diarrhea, often with blood. Third space loss of fluid may lead to shock. Laboratory findings include leukocytosis with left shift, mimicking sepsis. Usually recovery is within 6-8 hours after fluid resuscitation. Careful history usually reveals the offending food. The mechanism may involve a non-IgE mediated mast cell reaction. **Eosinophilic colitis** in young infants is probably the most common manifestation of formula protein allergy. It is characterized by blood and mucous in the stool, with or without diarrhea, typically in otherwise healthy infants. It has been described in exclusively breast-fed infants presumably due to maternal dietary antigens transmitted through breast milk. Removal of milk or soy protein from infants or breast-feeding mothers usually leads to prompt resolution in symptoms, although microscopic or gross blood may persist for several weeks. Sigmoidoscopy may helpful if blood is not resolving to exclude other causes of bleeding and to document eosinophilic colitis by mucosal biopsy. Food allergy
can also cause a small bowel enteropathy leading to chronic inflammation with villous atrophy. Most patients present with diarrhea and failure to thrive, often characterized by peripheral blood eosinophilia, iron deficiency anemia and hypoalbuminemia from protein-losing enteropathy. Studies have shown that the villous atrophy is associated with increased numbers of eosinophils, but also increased intraepithelial lymphocytes and IgE containing cells in the lamina propria. Treatment by avoiding the offending protein leads to resolution of symptoms, and the return of normal villi. Rechallenge reproduces symptoms and villous atrophy.

**Allergic gastritis** is a common feature of both protein allergy and idiopathic EGE. Symptoms include pain and vomiting, especially if the gastric outlet is narrowed by mucosal or muscle wall involvement. Mucosal biopsies demonstrate eosinophilia with intraepithelial eosinophils. This condition may mimic hypertrophic pyloric stenosis in infants, however patients respond to removal of the offending protein from the diet.

**Eosinophilic esophagitis** is characterized by dysphagia (older children), pain and symptoms mimicking gastroesophageal reflux (infants/young children). pH probe studies show no acid reflux; esophageal biopsy reveals intense eosinophilia. Infants may also present with feeding aversion in the absence of other symptoms. Treatment with elemental formula has been shown to resolve symptoms and histologic findings in infants. Older children may not respond adequately to dietary therapy or may not accept this treatment; both systemic corticosteroids and inhaled and swallowed corticosteroids can be effective treatments. Studies (Hill, Cavataio) have confirmed that reflux symptoms can be indistinguishable from formula allergy in infants, and that infants referred for persistent symptoms despite anti-reflux therapy frequently have allergy. Furthermore, milk allergy has been shown to induce acid reflux on pH probe in a subgroup of infants, therefore even with a diagnosis of acid reflux, allergy may be playing a significant role. Allergy can cause irritability and infantile colic-like symptoms. By definition, colic is an idiopathic condition with increased crying behavior in infants, and therefore it is not allergy. However, since allergy can potentially lead to inflammation and pain, formula allergy is often considered. Studies of treatment of colic with protein hydrolysate formulas have been inconclusive. Two new studies address the role of allergy in colic. Extensively hydrolyzed whey protein and an amino-acid based formula reduced crying behavior significantly in a subgroup of infants with colic.

There are poorly controlled studies describing a variety of other problems potentially associated with food allergy including joint disease, migraine and developmental disorders such as autism. Causal relationships between food allergy and these disorders, although of interest, remain unproven. One report describes constipation associated with perianal fissures in infants and young children, with improvement on a milk free diet, however, a selection bias of patients may have existed, therefore further studies are needed to establish a link between these entities.

**Investigation and Management of Non-IgE Mediated food Allergy**

Classical tests of allergy (IgE CAPRAST and skin prick tests) will be negative, unless the patient has both IgE and non IgE mediated disease. Investigators have designed in vitro tests of cell-mediated immunity such as lymphocyte proliferation assays with food antigens, but results vary and to date there are no tests which have come into routine use. Patch testing the skin with food antigens to demonstrate delayed hypersensitivity after 48-72 hours deserves further study, however, local skin reactions may not be representative of reactions in the gastrointestinal tract. If commonly available ancillary testing is not helpful, then the diagnosis will rest on the resolution of symptoms and/or histologic findings on an elimination diet, with a return of symptoms on re-challenge. Unlike the rapid response characteristic of IgE mediated disease, a prolonged challenge may identify delayed reactions with predominantly gastrointestinal symptoms up to a week after exposure. In patients highly sensitized to foods, amino acid-based products are useful. Elemental diet can be used as a treatment or as a diagnostic tool to assess complex food allergies, by eliminating dietary protein antigens completely, then systematically re-challenging the patient with offending foods. Avoidance of specific allergens remains the mainstay of therapy. Pharmacologic therapy has not been effective in preventing manifestations of food allergy. Randomized trials of mast cell stabilizers such as oral Cromolyn and Ketotifen have not demonstrated efficacy in children with atopic dermatitis and food hypersensitivity, although trials in non-IgE-mediated allergy are lacking. Initial reports suggesting that allergic disease could be prevented by altering gut flora with probiotic therapy in infancy have not proved to be effective.

**Idiopathic Eosinophilic Gastroenteropathy**

Idiopathic eosinophilic gastroenteropathy is an inflammatory condition of the gastrointestinal tract characterized by eosinophilic inflammation in tissue. Frequently it is accompanied by peripheral blood eosinophilia. It should be a ‘diagnosis of exclusion’ and it therefore requires the clinician to eliminate known causes of peripheral blood and tissue eosinophilia, including unusual parasitic infections. Every effort should be made to exclude known
allergies by appropriate skin prick and IgE CAPRAST tests. Cow’s milk protein remains the most common food allergen, and often a milk protein free diet is tried first. Care must be taken to totally exclude a protein that has been implicated since continued inadvertent ingestion of the offending antigen(s) may perpetuate the disease. The problem is that eosinophils may be seen in early inflammatory bowel disease and other conditions, they may be a response to infection in an atopic host so it is difficult to determine in the beginning if this will be a chronic or self limited condition.

Clinical Presentation of EGE

The presenting symptoms and signs of eosinophilic gastroenteropathy depend on the distribution of the involved areas of the gastrointestinal tract and to what extent the depth of the bowel wall is affected. **Mucosal disease** is the most common form of EGE typically presenting with abdominal pain, vomiting and/or diarrhea, and rectal bleeding. The diarrhea may arise from mucosal disease leading to malabsorption and growth delay, or may arise from colonic disease with blood and net fluid secretion. Protein-losing enteropathy with hypoalbuminemia is a common finding. Diagnosis is best made by multiple endoscopic biopsies at multiple sites, as eosinophilia may be patchy. Eosinophilic colitis may mimic early inflammatory bowel disease. Eosinophilic esophagitis presents with dysphagia, pain and even stricture formation. Rare manifestations include obstruction, perforation, hepatobiliary disease and pancreatitis. **Muscle layer disease (rare)** presents with obstruction, and may affect any area of the bowel. However, the classic site of involvement in childhood is at the gastric outlet, and may mimic hypertrophic pyloric stenosis or other causes of gastric outlet obstruction. **Serosal eosinophilic gastroenteropathy (very rare)**, and typically presents with abdominal pain and ascites. Diagnostic paracentesis will show marked eosinophilia.

Pathologic Findings

EGE is characterized by increased eosinophils in tissue, although there is no widely accepted criteria for the pathologic diagnosis. For mucosal biopsies, emphasis is placed on number of eosinophils per high power field (eg. >20/hpf) or if eosinophils constitute more than 25% of the inflammatory infiltrate. I agree with those authors who attach greater significance to intraepithelial eosinophils, with clustering and degranulation, as indicators of activity of disease. A pediatric autopsy series from Texas found mean mucosal eosinophil counts ranging from up to 50 in the ileum and cecum, decreasing more distally in the colon, with 5 in rectum, 15 in the duodenum and up to 5 in the antrum. Eosinophils are not seen in the normal esophagus; small numbers (<15 per hpf) primarily in the distal esophagus typically indicate acid reflux disease, greater than 15 to 20 indicate eosinophilic esophagitis, especially if also in the mid or proximal esophagus.

Management of Idiopathic Eosinophilic Gastroenteropathy (EGE)

Despite the fact that ‘idiopathic’ EGE responds poorly to dietary therapy, an attempt should be made to identify potential food allergens and to eliminate these proteins first. Our practice is to perform a CBC and differential, albumin, IgE levels. Specific IgE skin=prick tests or CAPRAST tests for common food antigens are performed along with any specific food which may be implicated in the development of symptoms. If duodenal villous atrophy is profound, serology for celiac disease is included. Patch testing for delayed hypersensitivity for foods is of interest with one research group reporting high rates of positive results that direct subsequent management, however this has not been replicated and many groups either do not perform these tests or do not use the results to inform therapy. If these tests are unrevealing, or if the patient has not responded to elimination of suspected foods, then a milk-protein-free diet is tried. We have also used more extensive elimination diets avoiding all of the major food antigens to investigate which foods may be implicated. Complete exclusion of intact food protein using exclusive elemental diet can be used to determine whether food antigens are implicated in disease.

Corticosteroids are the mainstay of pharmacologic therapy for idiopathic EGE. We start with prednisone or equivalent at 2mg/kg per day with tapering to low dose alternate day therapy within 6-8 weeks. Eosinophilic inflammation typically responds promptly to treatment with corticosteroids. Some patients will relapse when tapered, and may do well with a low dose alternate day regime. Agents which stabilize mast cells have been used; anecdotal evidence from case reports argue for and against its efficacy sodium cromoglycate. Ketotifen is a mast cell stabilizing agent that has effects on eosinophil migration and activation. Although it can be efficacious it is not marketed in the USA, but it can be obtained. Fluticasone and budesonide for asthma can be swallowed as topically active agents and have been used successfully to treat eosinophilic esophagitis. There is no established use for antihistamines, or leukotriene receptor antagonists (singular).