

Food-associated gastrointestinal disease

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The ingestion of food is frequently associated with specific adverse gastrointestinal symptoms, including emesis, diarrhea, abdominal cramping, and gastrointestinal bleeding. This brief review discusses a variety of food-induced gastrointestinal diseases and will highlight the recent information pertaining to the pathophysiology, clinical presentation, diagnostic approach, and treatment of these disorders. Reactions resulting from immediate hypersensitivity and cell-mediated processes will be reviewed in detail, as well as other proposed pathophysiologic mechanisms. The clinical presentation and diagnostic approach to several food-induced gastrointestinal diseases will be individually examined. In addition, the treatment, especially the proper use of nutritionally balanced restriction diets and hypoallergenic formulas, will be discussed.

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Current Opinion in Pediatrics 1996, 8:471–475

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ISSN 1040–8703

The ingestion of specific foods has been implicated in a variety of immediate and delayed gastrointestinal diseases [1]. Whether this association is ultimately confirmed requires a comprehensive medical history and a careful diagnostic approach. Approximately 5% to 6% of the population is thought to have experienced some type of adverse food reaction. These adverse food reactions, which are primarily in the pediatric population, are defined as any abnormal reaction following the ingestion of food and can be divided into two major categories [1]. First, food allergy or hypersensitivity includes all immunologically mediated adverse reactions to foods (*eg*, IgE-mediated or cell-mediated reactions). Second, food intolerances are nonimmunologically mediated reactions to foods (*eg*, mucosal enzyme deficiencies such as lactose intolerance, direct toxin or chemical effect of food). Although the gastrointestinal system is frequently involved in adverse food reactions, the exact prevalence of these reactions is unknown.

This review of published scientific investigations from the past year explores a variety of clinical gastrointestinal diseases and syndromes that are thought to be secondary to the ingestion of a specific food(s). These reactions include IgE-mediated food allergy, food intolerances, and gastrointestinal syndromes with undefined pathogenic mechanisms. The pathophysiology, clinical features, diagnostic methods, and current treatment of these food-associated gastrointestinal diseases are highlighted.

Pathophysiology

The gastrointestinal tract, especially the specialized gut-associated lymphoid tissue, is a major immunologic organ of the human body that apparently plays an active role in the suppression of adverse reactions to foods and in the induction of oral tolerance [2]. A failure in the normal digestive process may underlie food-associated gastrointestinal diseases [3]. For example, a breakdown in normally efficient small bowel digestive processes may help toxins and antigens from food penetrate the intestinal surface and enter the systemic circulation. Moreover, partial digestion of food may reveal new antigenic epitopes and small molecular weight peptides with potent pharmacologic properties. Specific and nonspecific molecular and cellular factors are thought to be actively involved in maintaining the integrity of the gastrointestinal immune system. Examples of these factors include specific antibodies, especially of the IgA isotype, antigen-reactive lymphocytes, phagocytic cells in the gut, and cytokines with immunoregulatory or inflammatory properties [2,3].

Investigators continue to hypothesize that food allergic diseases result from the breakdown of oral tolerance or from a failure in its induction [2]. Several factors need to be considered in this process including the genetic background and age of the host; the nature, dose, and route of exposure of the offending antigen; and the immunologic status of the host. The role of specific enteropathic cytokines in this process is unknown. It is commonly agreed that more investigations are needed to elucidate specific mechanisms involved in the induction of oral tolerance and to increase our understanding of gastrointestinal immunoregulation as it relates to health and disease.

Several pathophysiologic mechanisms have been proposed in food-associated gastrointestinal diseases [2]. First and foremost, immediate hypersensitivity or IgE-mediated reactions have been investigated in the greatest detail [4•,5]. Reactions resulting from antibody-dependent cytotoxicity (involving natural killer cells and T lymphocytes) as well as immune complexes have been proposed, but limited data are available to confirm these mechanisms. Finally, reactions resulting from cell-mediated delayed-type hypersensitivity processes to foods have been implicated in specific gastrointestinal diseases [6].

Using jejunal biopsy specimens before and after food challenges, a group of Japanese investigators reported that activated CD4+ lymphocytes in the lamina propria of the small intestinal mucosa appear to contribute significantly to mucosal damage in patients with food-sensitive enteropathy as compared with small intestinal biopsy specimens from control patients [6]. Another investigation examined lymphoid cell subset distribution in the duodenal cryosections of 4-week-old piglets fed heat-treated versus ethanol-treated soybean proteins [7]. The authors concluded that atrophy in the duodenal villi in the piglets receiving heat-treated soybean proteins may, in part, be related to significant increases in CD4+ and CD8+ T lymphocyte subsets in the lamina propria and duodenal mucosa.

Clinical features and diagnosis

Food allergy and IgE-mediated food reactions

A recent review of anaphylactic reactions following food ingestion emphasized that gastrointestinal symptoms were second only to cutaneous findings in patients experiencing allergic reactions to foods [8•]. Typically, these gastrointestinal symptoms occur immediately or within the first hour following food ingestion and include nausea, vomiting, abdominal pain, and cramping. One report from Turkey within the past year confirmed previous data regarding the epidemiology of IgE-mediated cow milk allergy. The authors determined that the incidence of this disease was approximately 2% in the first year of life and affected infants frequently become tolerant by their second birthday [4•].

The proper diagnostic evaluation of gastrointestinal symptoms secondary to food allergy should include a thorough medical history supplemented by skin tests or radioallergosorbent tests to the suspected food [9], a nutritionally balanced exclusion diet [10], and most importantly, confirmatory-blinded food challenges [8•,9,10]. Although a recent report [11] advocated testing of IgE in the stool as a simple and economical means of identifying patients with food allergy, confirmatory investigations defining its usefulness are lacking [1].

Food-induced enterocolitis syndrome

This is an uncommon systemic reaction to specific food ingestion [8•], and the precise mechanism for this disorder remains unclear. Affected patients present by 6 months of age. Symptoms typically appear 4 to 6 hours following ingestion of the food and include projectile emesis, diarrhea, dehydration, and a "septic" appearance. Diagnostic tests to determine specific IgE to the offending foods, which are usually cow milk and soy proteins, are usually negative. The diagnosis can be confirmed with a food challenge and when positive, gastrointestinal symptoms and listlessness appear several hours following an oral feeding of at least 0.6 g protein/kg of the suspected food. In addition, a rise in the peripheral circulating leukocyte count accompanies the clinical symptoms. Tolerance to the protein is usually documented by the patient's second birthday.

Food-sensitive enteropathy

Patients with this disorder typically have an atopic background [3] and usually present with diarrhea, emesis, malabsorption, or failure to thrive. The most commonly implicated foods include cow milk, soy, chicken, rice, fish, and eggs. Biopsy of the small intestine has the following characteristics: villous atrophy with hyperplasia of crypts, patches of thinned mucosa, and an elevation of the intraepithelial lymphocyte count [10]. There is a rapid clinical improvement when the offending protein is eliminated from the patient's diet. In some patients, a food challenge may be needed to confirm the diagnosis. These reactions typically resolve by 1 year of age [3]. Although cell-mediated and humoral mechanisms have been proposed for these reactions, a recent review concluded that the evidence for T cell-mediated immunity in food-sensitive enteropathies is largely circumstantial [12•].

Food-sensitive or allergic colitis

This reaction is the result of inflammatory changes in the rectum and colon following immune-mediated reactions to ingested foreign proteins, which are usually cow milk and soy proteins. Patients appear well-nourished and typically present before 1 year of age with rectal bleeding with or without diarrhea [3,10,13••]. Although no single laboratory test is sensitive or specific enough to confirm the diagnosis of allergic colitis, the finding of either peripheral eosinophilia or eosinophils in the stool stained

with Wright's stain is suggestive of this disorder. The definitive diagnostic evaluation is an endoscopic biopsy revealing eosinophils in the lamina propria of an otherwise normal-appearing intestinal mucosa [13••]. Typically, greater than 60 eosinophils per 10 high-power fields are observed in the lamina propria. Complete relief of symptoms is observed on a diet restricting the offending protein, and in some cases a food challenge may be needed to confirm the diagnosis. Most affected patients will become tolerant to the offending protein by 2 years of age [10]. It is believed that eosinophils are directly responsible for much of the tissue injury in this disease, but the specific factors that influence the recruitment, activation, and degranulation of eosinophils in allergic colitis have not been elucidated [13••].

Eosinophilic gastroenteritis

This disease may affect any part of the intestinal tract [3,14–16], but the specific cause remains unknown. Although the presence of atopy (*eg*, to a dietary protein) appears to be an independent variable, its specific role remains controversial. Patients typically present with diarrhea, emesis, and a peripheral blood eosinophilia. One recent report highlighted eosinophilic gastroenteritis as a possible pathogenic factor in the development of pyloric stenosis in an infant presenting with emesis [15]. The hallmark diagnostic findings of eosinophilic gastroenteritis are radiologic findings including thickened edematous intestinal folds and intestinal biopsies demonstrating an eosinophilic infiltration. Corticosteroids have been demonstrated to be effective in the treatment of this disorder. As alluded to previously, a subset of infants with this disease have associated IgE-mediated food allergy and may respond to dietary elimination therapy [1].

Food intolerance

Lactase deficiency is a common example of a food intolerance [3]. Although this disease occurs in 50% to 90% of most populations, white, western Europeans are a common exception. An Italian investigation recently described four infants with rice intolerance with presenting features including shock, emesis, and diarrhea [17]. All affected patients had laboratory evidence of occult blood in the stool, but there was no evidence of an IgE-mediated allergy to rice or cow milk in any of the infants. Double-blind challenges with foods containing rice caused severe shock in three of the four infants and histologic alterations (ranging from infiltration with thickening of the mucosa to a marked shortening and fusion of the villi) were observed in the intestinal mucosa following the challenges. Some features of these reactions were similar to those described with the enterocolitis syndrome, but the reaction time following rice challenges was typically less than 1 hour.

To differentiate between cow milk intolerance and gastroesophageal reflux in infants presenting with persis-

tent vomiting, a recent investigation compared a test of small bowel permeability with a more invasive approach incorporating intestinal endoscopy and biopsy, as well as 24-hour pH probe monitoring [18•]. The data revealed that a simple noninvasive urine test of intestinal permeability (cellobiose:mannose ratio) was 95% accurate in identifying cow milk intolerance in the infants studied and may provide a more economical approach to this clinical problem.

Psychological intolerance to foods

Many healthy people complain of food-induced symptoms including nausea, bloating, abdominal pain, constipation, and diarrhea without any evidence of an immunologic reaction [3]. An improper diagnosis of food allergy may result in an inappropriate restriction diet. Most patients with irritable bowel syndrome experience symptoms that likely arise from abnormal motility and sensations in the gut; however, there may be a subset of these patients who do have food allergy as a cause of their symptoms [19]. These patients are usually atopic, and diarrhea is a major feature of their illness.

Treatment

Food-restriction diets

Dietary manipulations are the mainstay of therapy for all of the food-induced gastrointestinal diseases [10,20•]. For example, eliminating the offending food from the diet is the major form of therapy in the following diseases: cow milk allergy [4•], allergic colitis [13••], cow milk or soy enterocolitis syndrome [8•], food-sensitive enteropathy [3], and the food intolerances [3]. It is very important, however, to avoid giving inappropriate dietary advice and recommendations when dealing with these diseases. Nutritional deficiencies, such as electrolyte disturbances [21], continue to be reported after the prolonged or improper use of restriction diets. Therefore, the nutritionist should be actively involved in the design and overall management of this dietary treatment.

Hypoallergenic formulas

Limited or extensive *in vitro* enzymatic hydrolysis of cow milk proteins (*eg*, casein or whey), followed by heat treatment and ultrafiltration have traditionally been used in the manufacture of hypoallergenic infant formulas. Research from the Netherlands has demonstrated that many of these protein hydrolysate formulas retain some antigenicity that may be problematic in a subset of patients who are extremely allergic to cow milk proteins [22•]. More recently, amino acid-derived infant formulas, which should be less antigenic than the hydrolysate formulas, have been developed for clinical use [23•]. Hill *et al.* [23•] recently published information regarding the use of this type of formula in patients with either food allergy or food intolerance. These authors concluded that this nutritionally complete, amino acid-derived infant formula was safe and effec-

tive in the treatment of both groups of infants. Likewise, Isolauri *et al.* [24•] confirmed that this formula was an effective form of treatment for infants with cow milk allergy. This newer infant formula should be very useful in the treatment of patients who cannot tolerate the more traditional hypoallergenic formulas. For infants who are breast-fed, the maternal diet may need to be restricted to the offending food antigen, but this strategy is usually not effective. Investigators have expressed reticence in discontinuing breast-feeding unless the patient becomes anemic or hypoalbuminemic [25].

Corticosteroids

In certain clinical situations, food-induced gastrointestinal diseases can be effectively managed with systemic corticosteroids. For example, this has been an effective therapy for eosinophilic gastroenteritis [14].

Cromolyn sodium

The use of cromolyn sodium to treat patients with food allergy has been actively debated in the past [26•]. Strobel [1] recently reviewed this issue and concluded that there continues to be a lack of adequate prospective investigations examining the use of this medication in the management of IgE-mediated food allergy. Rarely has this medication been demonstrated to be beneficial in the treatment of adverse food reactions.

Education of patient and family

In addition to dietary measures, the overall education of the family, patient, and school regarding the food-associated gastrointestinal disease cannot be overemphasized [27]. This education process should focus on the recognition of the specific reaction, the identification of commonly used words for the offending foods, preventing accidental ingestions of the foods, and anticipatory guidance measures for treating a reaction if it does occur.

Conclusions

The role of food ingestion in the development of certain gastrointestinal diseases is addressed in this review. There have been no major breakthroughs related to the development of oral tolerance to foods and the gut-associated immune system. More investigations are needed in this area to provide new insights into the pathophysiology of these reactions. Updated clinical data are provided for several food-associated gastrointestinal diseases, including food allergy, the enterocolitis syndrome, food-sensitive enteropathy, allergic colitis, and eosinophilic gastroenteritis. In addition, appropriate diagnostic approaches for these diseases are reviewed. The treatment of these diseases, especially the proper use of nutritionally balanced restriction diets and hypoallergenic formulas, is discussed. This includes updated information concerning the use of an amino acid-based infant formula in certain

patients with adverse reactions to foods. Hopefully, active basic and clinical investigation will continue in this area in the near future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
 - Of outstanding interest
1. Strobel S: **IgE-mediated (and food-induced) intestinal disease.** *Clin Exp Allergy* 1995, **25**:3–6.
 2. Strobel S: **Mechanisms of tolerance and sensitization in the intestine and other organs of the body.** *Allergy* 1995, **50**:18–25.
 3. Ferguson A: **The gastrointestinal tract.** *Allergy* 1995, **50**:33–38.
 4. Altintas D, Guner S, Evliyaoglu N, Yuksel B, Atici A, Serbest M: **A prospective study of cow's milk allergy in Turkish infants.** *Acta Paediatr* 1995, **84**:1320–1321.
 - This investigation provides useful data further confirming the incidence of cow milk allergy in infancy.
 5. Joral A, Villas F, Garmendia J, Villareal O: **Adverse reactions to food in adults.** *J Invest Allergy Clin Immunol* 1995, **5**:47–49.
 6. Nagata S, Yamashiro Y, Ohtsuka Y, Shioya T, Oguchi S, Shimizu T, Maeda M: **Quantitative analysis an immunohistochemical studies on small intestinal mucosa of food-sensitive enteropathy.** *J Pediatr Gastroenterol Nutr* 1995, **20**:44–48.
 7. Dreau D, Lalles JP, Toullec R, Salmon H: **B and T lymphocytes are enhanced in the gut of piglets fed heat-treated soybean proteins.** *Vet Immunol Immunopathol* 1995, **47**:69–79.
 8. James JM, Burks AW: **Systemic reactions: foods.** *Immunol Clin North Am* 1995, **15**:477–487.
 - This review article provides detailed information pertaining to food-induced anaphylaxis. The involvement of the gastrointestinal system in these reactions is discussed.
 9. Lessof MH: **The diagnosis of food intolerance.** *Clin Exp Allergy* 1995, **25**:14–15.
 10. Walker-Smith JA: **Diagnostic criteria for gastrointestinal food allergy in childhood.** *Clin Exp Allergy* 1995, **25**:20–22.
 11. Andre F, Andre C, Colin L, Cavagna S: **IgE in stools as indicator of food sensitization.** *Allergy* 1995, **50**:328–333.
 12. MacDonald TT: **Evidence for cell-mediated hypersensitivity as an important pathogenic mechanism in food intolerance.** *Clin Exp Allergy* 1995, **25**:13–16.
 - The author discusses the available data related to cell-mediated reactions in adverse food reactions. This has been an active area of investigation for the past few years.
 13. Odze RD, Wershil BK, Leichtner AM, Antonioli DA: **Allergic colitis in infants.** *J Pediatr* 1995, **126**:163–170.
 - This is an excellent review of allergic colitis. The authors thoroughly discuss the clinical presentation and diagnosis of this disease and elaborate on the potential role of the eosinophil in the pathogenesis of this food-associated gastrointestinal disease.
 14. Matsushita M, Hajiro K, Morita Y, Takakuwa H, Suzuki T: **Eosinophilic gastroenteritis involving the entire digestive tract.** *Am J Gastroenterol* 1995, **90**:1868–1870.
 15. Blakenberg FG, Parker BR, Sibley E, Kerner JA: **Evolving asymmetric hypertrophic pyloric stenosis associated with histologic evidence of eosinophilic gastroenteritis.** *Pediatr Radiol* 1995, **25**:310–311.
 16. Kay MH, Wylie R, Steffen RM: **The endoscopic appearance of eosinophilic gastroenteritis in infancy.** *Am J Gastroenterol* 1995, **90**:1361–1362.
 17. Cavataio F, Carroccio A, Montalto G, Iacono G: **Isolated rice intolerance: clinical and immunologic characteristics in four infants.** *J Pediatr* 1996, **128**:558–560.
 18. Staiano A, Troncone R, Simeone D, Mayer M, Finelli E, Cella A, Auricchio S: **Differentiation of cow's milk intolerance and gastro-oesophageal reflux.** *Arch Dis Child* 1995, **73**:439–442.
 - This article proposes a clinical screening test to help in the differentiation between food malabsorption and other adverse reactions to foods.

19. Edwards AM: **Food-allergic disease.** *Clin Exp Allergy* 1995, **25**:16–19.
20. Carter C: **Dietary treatment of food allergy and intolerance.** *Clin Exp Allergy* 1995, **25**:34–42.

The author provides a very good discussion of the appropriate dietary approach to the patient with food allergy and intolerance.

21. De Vizia BD, Mansi A, Giangregorio A, Troncone R: **Hazards of oligoantigenic diet restrictions.** *Acta Paediatr* 1995, **84**:103–105.
22. Van Berensteyn ECH, Meijer RJGM, Schmidt DG: **Residual antigenicity of hypoallergenic infant formulas and the occurrence of milk-specific IgE antibodies in patients with clinical.** *J Allergy Clin Immunol* 1995, **96**:365–374.

This has been an area of concern for the past few years. The authors provide interesting data concerning the residual antigenicity of some hypoallergenic infant formulas and the potential for allergic reactions occurring in patients with severe food allergies (eg, cow milk allergy) receiving these products.

23. Hill DJ, Cameron DJS, Francis DEM, Gonzalez-Andaya AM, Hosking CS: **Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance.** *J Allergy Clin Immunol* 1995, **96**:386–394.

This clinical investigation provides very useful data confirming the safety of an amino acid-based infant formula in infants with confirmed food allergy or food

intolerance. Moreover, they demonstrated that this infant formula was nutritionally complete.

24. Isolauri E, Sutas Y, Makinen-Kiljunen SM, 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 Paediatr* 1995, **127**:550–557.

This well-designed clinical investigation confirmed that an amino acid-based infant formula was an effective form of treatment for infants with cow milk allergy. The authors concluded that this formula should be very useful in the treatment of patients who cannot tolerate the more traditional hypoallergenic formulas.

25. Machinda H: **Breast milk-induced colitis.** *J Paediatr Gastroenterol* 1995, **20**:480.

26. Edwards AM: **Oral sodium cromoglycate: its use in the management of food allergy.** *Clin Exp Allergy* 1995, **25**:31–33.

This review article provides an interesting summary of the data related to the use of oral sodium cromoglycate in the management of various types of adverse food reactions. The available data do not sufficiently resolve the controversies that have surrounded the use of this medication in food-associated gastrointestinal diseases.

27. Vickers D: **Management of anaphylactic reactions to food.** *Arch Dis Child* 1995, **73**:184–185.