

GASTROINTESTINAL SYNDROMES IN FOOD ALLERGY

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ABSTRACT

Gastrointestinal (GI) clinical syndromes can be categorised by immunopathophysiology into disorders with an acute onset after ingestion, mediated by food-specific IgE antibody (e.g. oral allergy syndrome (OAS)), those that are chronic in nature and sometimes associated with IgE (e.g. eosinophilic gastroenteropathies) and those that are T-cell-mediated (e.g. food protein-induced disorders). OAS is usually associated with allergic rhinoconjunctivitis and allergy to pollen, especially to birch, grass, ragweed and mugwort. Symptoms of OAS are confined to the oral cavity. The diagnosis of this disorder is primarily clinical. *Eosinophilic disorders* can occur at any age and should be considered in the differential diagnosis of patients presenting with chronic GI symptoms such as abdominal pain, nausea, vomiting, diarrhoea, failure to thrive and GI bleeding. GI mucosal biopsies are mandatory for the definitive diagnosis of these disorders. Food allergy may play a causative role in some patients and must be sought for. Treatment options include dietary elimination, elemental diet, corticosteroid therapy (oral or topical) and anti IL-5. *Food protein-induced disorders* present well-characterised immunological responses (T-cell-mediated reactions) to dietary protein, cow's milk and soya protein in particular. They present in infancy or early childhood and usually resolve by age 1-3 years. Dietary elimination and elemental feeds (extensively hydrolysed (eHF) or amino-acid formula) are the only treatment available for these disorders.

Food allergy can manifest as cutaneous, respiratory, systemic (anaphylaxis) or gastrointestinal (GI) symptoms. The GI manifestations are listed in Table I. Discussion of all the GI manifestations of food allergy are beyond the scope of this review. Instead, the article focuses on some of the well-recognised clinical syndromes in food allergy: oral allergy syndrome (IgE-mediated), the eosinophilic gastroenteropathies (mixed IgE/non-IgE-mediated), oesophagitis in particular and the food protein-induced disorders (T-cell mediated).

PATHOGENESIS OF FOOD ALLERGY

The GI barrier

The GI tract is a very specialised organ, rich in lymphoid tissue containing macrophages, immunoglobulins, mast cells, intraepithelial lymphocytes, and helper and suppressor T cells at the subepithelial level (*gut-associated lymphoid tissue (GALT)*). This well-organised system of cells and their products acts as the mucosal barrier, guarding the body against intrusive antigens.¹

There are also *nonspecific factors* that aid in protecting the GI tract from antigenic intrusions, which start at the moment of food intake. The digestion and breakdown of proteins start in the oral cavity, and continue in the stomach with the help of hydrochloric acid and pepsin, and in the small bowel in the presence of pancreatic proteases. In addition to the enzymatic breakdown of protein, other factors help in reducing the antigenic stimulation of the intestinal mucosa; these include the inherent GI motility, GI secretions (water, electrolytes, mucus and defensins), the epithelial barrier, the microvillous membrane and, at the level of enterocytes, the lysosomes.¹

The *intestinal mucosa is the gatekeeper*, preventing the penetration of macromolecules that could be potentially harmful. The intestinal surface is directly exposed to an environment rich in antigenic load and unique in the sense that its main role is that of suppression rather than active immune response.²

INTRODUCTION

The estimated prevalence of food allergy is 2-8% in the paediatric population and approximately 2% in adults. A few foods account for 90% of allergic reactions – cows' milk protein, egg, peanut, soya and wheat are the most common causative foods in infants and young children; peanuts, tree nuts, fish and shellfish are the most common in older children and adults.

The development of food allergy requires an immunological reaction directed to a food antigen. This reaction may involve immunoglobulin E (IgE) or T lymphocytes (T cells) or some components of both IgE and T cells (mixed IgE/non-IgE reaction).

Table I. Food Allergy: GI manifestations

IgE	IgE+Cellular	Cellular
		
• <i>Non-specific symptoms:</i>	• <i>Eosinophilic Gastroenteropathies</i>	• <i>Food Protein-Induced Disorders</i>
-abdominal pain / colic -nausea, vomiting -diarrhoea, constipation	-oesophagitis -gastroenteritis -proctocolitis	-proctocolitis -enterocolitis -enteropathy
• <i>Oral Allergy Syndrome</i>		• <i>Celiac Disease</i>

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Immunological reactions

As previously started, two types of immunological reactions have been described in the development of GI allergies: IgE-mediated and T-cell-mediated (also known as non-IgE-mediated) reactions. Certain GI disorders may involve elements of both these mechanisms.

The *IgE-mediated reaction* is also known as an immediate-onset allergic reaction (*type I*). In a type I reaction, the IgE antibodies bind to the mast cells in the GI tract, skin, and lungs, causing a release of mediators when they are exposed to determinate antigens.³ Circulating IgE also binds and activates basophils, eosinophils, and macrophages. The process involves initial sensitisation to the offending antigen; subsequent exposure results in binding to the cell surface of the IgE molecule triggering the release of histamine, prostaglandins, leukotrienes and cytokines.

A *type II reaction* has been reported only rarely in food allergy. Conditions associated with this type of immunological response (antibody-mediated) are autoimmune haemolytic anaemia and Goodpasture's syndrome.

A *type III reaction* involves the formation of immune complexes with IgG antibodies and activation of the complement cascade. The appearance of symptoms is not immediate and may occur 1-20 hours after the exposure.

A *type IV reaction*, also known as delayed-onset hypersensitivity reaction, is caused by T-cell lymphocyte activation (T-cell-mediated hypersensitivity). As a result of this sensitisation, interleukins (ILs) 4 and 5 are produced, causing an inflammatory response. Patients exhibiting a delayed hypersensitivity reaction have shown an imbalance in the production of IL-4 and interferon gamma.⁴

GI CLINICAL SYNDROMES

Oral allergy syndrome

Oral allergy syndrome (OAS) is a common problem in patients with allergic disease. In OAS, IgE antibody is involved but in a slightly different manner than in classic IgE-mediated food allergy. The patients are usually sensitised to an aeroallergen initially and it is these antibodies that cause OAS. The IgE antibodies to the aeroallergen crossreact with the proteins in fresh fruits and vegetables to cause symptoms. The age of onset of OAS is beyond infancy but often before schoolgoing age and it usually persists into adulthood.

Associations

There are a few well-described associations between aeroallergens and the fruits that elicit the OAS symptoms. The most studied is the association between *birch pollen sensitivity* and the symptoms after ingestion of apple, pear, cherries, apricots, hazelnuts, celery, carrots and occasionally other fruits and vegetables. Recently there has been advancement in recognising the crossreactive proteins in plants (Table II). Cross-reactive proteins are thought to be within homologous groups called pathogenesis-related proteins (PR). These are a group of proteins involved in plant defence and resistance to stress in their environment. For example the major birch allergen, Bet v 1, and the major apple allergen, Mal d 1, are similar in structure and have been shown to be crossreactive. Both proteins belong to the PR-10 family.⁶ Foods from different families of plants can contain similar PR proteins and thus cause the same symptoms. Prior to the identifica-

Table II. Common crossreactivities in oral allergy syndrome

Pollen	Fruit/vegetable
Birch	Apple, hazelnut, carrot, potato, kiwi, celery, cherry, pear, others
Mugwort (artemisia)	Celery, carrot, fennel, parsley, others
Ragweed	Melon, banana
Grass	Potato, tomato, watermelon, kiwi, peanuts?

From Bruijnzeel-Koomen *et al.*⁵

tion of these proteins the association between different families of plants was not well understood.

Another common association is between *ragweed pollen sensitivity* and symptoms caused by ingestion of different melons and bananas. There is also a description of *mugwort-celery-carrot-spice syndrome*. There are multiple other associations between aeroallergens and plant proteins with crossreactive antibodies. As plant proteins are characterised in more detail, it will be easier to identify the potential of the crossreactions. However, not all patients with crossreactive antibodies will actually experience symptoms. In addition, the crossreactive antibodies may not be between the dominant allergenic proteins within the plant. For example, a majority of patients who have OAS symptoms after ingestion of apples and are birch-pollen allergic will have crossreactive antibodies between Mal d 1 and Bet v 1. Certain patients will have specific IgE towards other homologous proteins in apple and birch that elicit the same symptoms.

Clinical manifestations

Symptoms of OAS are usually confined to the oral cavity. The most common complaint among patients is itching or tingling of the mouth after ingestion of fresh fruit or vegetables. Patients may also experience angio-oedema localised to the mouth. Some patients will develop abdominal cramping or discomfort after ingestion but rarely vomiting or diarrhoea. An important observation is that the patient does not experience any symptoms if the fruit or vegetable is cooked. Almost all patients will have associated allergic rhinitis or conjunctivitis as the IgE antibodies to an aeroallergen are crossreacting with the fruit or vegetable proteins.

Diagnosis

The diagnosis of OAS is based almost entirely on the patient's *history*. A history of allergy to aeroallergens and typical symptoms after eating fresh fruit or vegetables is enough to make the diagnosis of OAS. The OAS reaction is usually immediate and can occur as soon as the fruit or vegetable is placed into the mouth. A thorough history should be obtained to ensure that the patient has no signs of a more serious IgE-mediated food allergy. Patients should be questioned about what foods were ingested around the same time; excluding those foods as the cause of the reaction would be appropriate. This may include skin-prick testing, specific IgE antibody testing and food challenge.

Skin-prick testing with fruits and vegetables for the diagnosis of OAS is not straightforward. Commercial extracts of most fruits and vegetables are available. During the processing of the extract, however, it is thought that proteins are altered and therefore less

reactive with skin-prick testing. If the initial skin-prick tests are negative with a suggestive clinical history, it is recommended that skin-prick testing be done with the fresh fruit or vegetable in question by the prick-prick method (Fig. 1). This procedure is done by pricking the fruit with the lancet, and then using the same lancet immediately for the skin prick. This transfers protein from the fresh fruit onto the lancet. Eating cooked fruit does not elicit symptoms, and the fact that there are no symptoms beyond the oropharynx suggests that the allergenic proteins are easily altered by heat and digestion. Commercial extracts are not as good as fresh fruit for skin-prick testing.⁷

Treatment

Most patients with OAS will avoid the fruit that provoke their symptoms. However, if the patient strongly desires the offending food and can tolerate the symptoms, it is safe to continue eating it because there is no risk of any systemic reactions. An alternative approach would be to consume the vegetable or fruit in a cooked form (usually tolerated). It would be inappropriate for a person to take an antihistamine prior to eating the food in case they have symptoms beyond the OAS (i.e. systemic symptoms). Patients who experience systemic symptoms do not have OAS and should be treated as if they have classic IgE-mediated food allergy with strict avoidance of the food. There has been one randomised prospective study that demonstrated that allergen immunotherapy with birch pollen ameliorated symptoms of OAS caused by apple ingestion.⁸ Patients with severe symptoms benefited the most from immunotherapy. Although the immunological response to immunotherapy is not understood completely, it seems intuitive that causing tolerance to birch protein would also cause tolerance to homologous proteins in the fruits and vegetables.



Fig. 1. Prick-prick skin test with fresh apple.

Eosinophilic gastroenteropathies

The eosinophilic gastroenteropathies comprise a group of disorders characterised by dense eosinophilic infiltration of at least one layer of the GI tract. Within the broad definition of these disorders lie at least three clinical entities that are defined largely by the presence of abnormal numbers of eosinophils in various GI sites: eosinophilic oesophagitis (EE), eosinophilic proctocolitis (EP) and eosinophilic gastroenteritis (EG). EP and EG are relatively uncommon.

EE is a disease that is being recognised with increasing frequency. It affects children and adults, being more common in males than females. The disease is characterised by isolated infiltration of the oesophagus by eosinophils (Fig. 2).

Aetiology/pathogenesis

The immunopathogenesis of EE involves an allergic response to environmental and food allergens^{9,10} and the pro-inflammatory cytokines IL-5 and IL-13.^{9,10} Both IgE and T cells appear to be involved. Foods play a role in 90% of cases and those most commonly implicated in EE include cow's milk, egg, soya, wheat, peanuts and maize.^{9,10}

Clinical presentations

The presentation of EE in *children* is similar to that of gastroesophageal reflux disease (GERD) (Table III). Typical symptoms include nausea, vomiting, regurgitation, epigastric pain and poor appetite. Young children may demonstrate food refusal, whereas adolescents often experience dysphagia. *Adults* present with similar symptoms, but dysphagia occurs much more commonly and can be associated with oesophageal strictures. Uncommon symptoms include growth failure and haematemesis. The clinical features of EE may evolve over years. Symptoms such as abdominal pain and heartburn occur regularly, but vomiting and dysphagia may occur sporadically or infrequently. Although the use of acid suppression medication may improve the patient's symptoms, it does not abolish the symptoms or alter the abnormal oesophageal histology. Approximately 50% of affected children also exhibit manifestations of other allergic disorders, including bronchospasm, allergic rhinitis, and eczema.¹⁰ Frequently, there is a strong family history of food allergies or other allergic disorders¹⁰ (more common in children than adults).

Diagnosis

Evaluation of patients with suspected EE should include a radiographic upper GI series to rule out

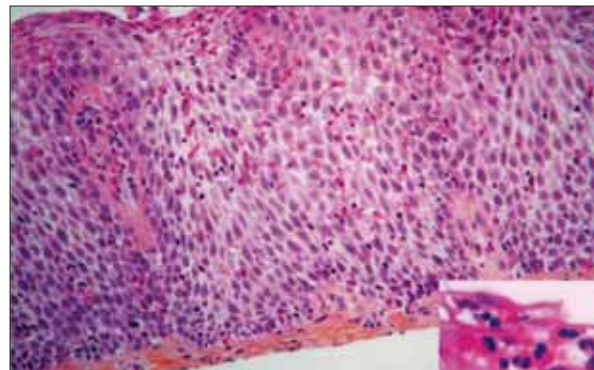


Fig. 2. Eosinophilic oesophagitis: histology. Dense eosinophil infiltration of oesophagus with (>20 per HPF). Similar appearance in upper and lower oesophagus.

Table III. Comparison between eosinophilic oesophagitis and reflux oesophagitis

	Eosinophilic oesophagitis	Reflux oesophagitis
Symptoms	Nausea, vomiting, epigastric pain, dysphagia	Nausea, dysphagia, vomiting, epigastric pain
Endoscopy	Oesophageal furrows, rings	Oesophageal erythema, ulceration
Histology	Usually >20 eosinophils per HPF	Usually <5 eosinophils per HPF
Oesophageal strictures	Midoesophageal strictures	Distal oesophageal strictures
pH study	Normal, except for increased frequency of episodes	Usually abnormal
Allergic history	Increased incidence of asthma, rhinitis, eczema	Not increased
Family history	Increased incidence of asthma, rhinitis, eczema	Not contributory
Dietary therapy	Effective	Not effective
Antireflux therapy		
– Symptoms	Minimally improved	Significantly improved
– Histology	No change in histology	Significantly improved
Fundoplication	Not effective	Effective in severe cases
Corticosteroid	Effective; however, disease recurs when discontinued	Unknown

HPF – high-power field.

anatomical abnormalities, a 24-hour pH probe, and an upper endoscopy with biopsy. In a patient with normal anatomy, the presence of an isolated, severe oesophageal eosinophilia, obtained while the patient is receiving adequate gastric acid blockade with a proton pump inhibitor, strongly suggests the diagnosis of EE. GERD is excluded with the performance of a 24-hour pH probe. The pH probe should be completed while the patient is off all acid-suppressing medications. Patients with severely abnormal pH study findings should undergo further evaluation for GERD.

Typical *endoscopic findings* of EE include white pinpoint exudates, linear furrows and a ringed oesophagus (Fig. 3). However, endoscopic findings may be unremarkable. Diagnosis is confirmed by the presence of 20 or more eosinophils per high power field in the oesophagus.^{11–13} Patients with EE should also be tested for associated food allergies.

Skin prick testing, Immunocap RAST and the atopy patch test (APT) can identify potentially causative foods.¹⁴ The APT (Fig. 4) is a particularly useful tool in the diagnostic work-up of children with food-allergy-related GI symptoms.¹⁴ The diagnostic accuracy of APT with fresh food is higher than with commercial food extract.¹⁵ The diagnosis of EE is confirmed on repeat endoscopy with biopsy after treatment.

Treatment

The available treatment options for EE include dietary manipulation, topical and systemic corticosteroids, humanised monoclonal antibodies against IL-5 and possibly montelukast (based on few anecdotal case reports).

Dietary *manipulation* remains the mainstay of treatment of EE. There are three different dietary approaches to the management of this disorder: (i) the elemental diet (amino acid formula), (ii) the removal of food based on allergy testing, and (iii) removal of foods that most commonly cause EE. In paediatric studies, the *elemental diet* has the highest (>95%) success rate (defined as resolution of symptoms and normalisation of biopsies), whereas the test-based elimination diet (>75%) and the six-food elimination diet (>70%) had lower success rates.¹⁰ There are no organised dietary trials in adults.

A few studies have reported improvement in symptoms of EE in adults and children after treatment with

oral corticosteroids.^{16,17} Of note, 90% of these patients experience a recurrence of symptoms on discontinuation of these agents. Potential adverse effects of systemic steroid in the long term limits their use. Recent reports claim that *swallowing inhaled corticosteroids* (ICS) may also be effective in the treatment of EE.¹⁸ However, the adverse effects of swallowed ICS includ-



Fig. 3a. Eosinophilic oesophagitis: demonstrates rings and furrows on endoscopy.



Fig. 3b. Eosinophilic oesophagitis: demonstrates pinpoint white exudates (eosinophils) on endoscopy.



Fig. 4. Atopy patch test.

ing oesophageal candidiasis and growth suppression, may also limit long-term use of this of this agent for the treatment of EE.

Anti-IL-5 is a promising therapeutic intervention for EE – in a study involving 3 patients, anti-IL-5 therapy was associated with marked decreases in peripheral blood and oesophageal eosinophilia in patients with EE and improved clinical outcomes.¹⁹

Food protein-induced disorders

This group of GI disorders include food protein-induced proctocolitis, enterocolitis and enteropathy. They represent well-characterised immunological responses to dietary proteins. Although distinct in their clinical presentation (Table IV), these disorders are T-cell-mediated and do not involve IgE antibody-mediated mechanisms. They generally present in infancy or early childhood and must be differentiated from disorders with similar symptoms.

Proctocolitis

Proctocolitis, most commonly due to cow's milk protein allergy, is usually seen during the first 6 months of life. The infant presents with a history of mucousy, bloody stools (specks of blood mixed with the stools or a more significant presence of blood). Up to 60% of the cases occur in breastfed infants,²⁰ but it also occurs in formula-fed (cow's milk or soya) infants.

Although the *diagnosis* can be made on clinical grounds, a flexible sigmoidoscopy can be performed for confirmation. Endoscopy reveals patchy erythema-

tous lesions, oedema of the mucosa and friability. There may be associated lymphonodular hyperplasia, which could be limited to the rectum and sigmoid colon, but it can also involve the entire colon. Biopsies obtained from the mucosa of the rectum or colon demonstrate abnormally high numbers of eosinophils, infiltration of the mucosa and penetration as deep as the muscularis mucosa.^{21,22}

In cow's milk or soy formula-fed infants, substitution with an extensively hydrolysed formula (eHF) is usually the first line of treatment – this generally leads to cessation of obvious bleeding within 72 hours. However, a proportion of infants may not tolerate eHF – these infants should be switched to an amino-acid formula (symptoms resolve rapidly on this formula).^{23,24} Management in breast-fed infants is more difficult. Restriction of cow's milk, soy or egg from the mother's diet usually results in resolution of symptoms.²⁵ In cases where there is no response to maternal dietary manipulation, an eHF or amino-acid formula may be substituted.

Cow's milk protein proctitis/proctocolitis is a disease of infancy and will resolve after elimination of the offending protein(s). It usually resolves between the ages of 6 and 9 months or by 1-2 years of age.^{21,22} Offending foods can be reintroduced into the infant's diet thereafter.

Enterocolitis syndrome

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe manifestation of a food hypersensitivity.²⁶ It has been associated not only with cow's milk protein and soya but also to other foods including fish, poultry, rice, oat, barley, and vegetables.^{27,28} The offending vegetables include sweet potatoes, squash, string beans and peas. Symptoms may appear during the first month of life and can be seen in association with growth faltering. Symptoms occur with a median time of appearance of 2 hours after ingestion of the protein and include vomiting, diarrhoea, lethargy and dehydration. The severity of this reaction can lead to acidaemia, methaemoglobinaemia and shock.²⁹

Because there is a high percentage of patients with sensitivity to cow's milk and soya, switching directly to an eHF is recommended. For the rare patients who are sensitive to eHF, substitution with an amino acid formula is appropriate.³⁰ Strict avoidance of cow's milk and/or soya is essential. Follow-up challenges should be performed at 12-24 month intervals to determine tolerance. These challenges should be performed under physician supervision with emergency medications (including IV fluids) readily available because adverse reactions, including shock, can occur. The majority of infants will outgrow the allergy by 2-3 years, but in some it may persist into childhood.²⁶

Enteropathy

Protein food enteropathy presents in infancy with symptoms of diarrhoea, vomiting and failure to thrive. This disorder can ultimately result in protein-losing enteropathy, oedema, and GI blood loss. Hypersensitivity to cow's milk protein is the most common cause, although other proteins like soya, egg, fish and cereal grains have also been implicated in this

Table IV. Food protein-induced disorders (Non-IgE – mediated)

	Enterocolitis	Enteropathy	Proctitis
Age Onset:	Infant	Infant/Toddler	Newborn
Duration:	12-24 mo	?12-24 mo	9-12 mo
Characteristics:	Failure to thrive Shock Lethargy Vomit Diarrhoea	Malabsorption Villous atrophy Diarrhoea	Bloody stools No systemic sx Eosinophiliic
- Typically milk and soya induced but solid foods may also be the cause - Spectrum may include colic, constipation and occult G1 blood loss			

condition. *Diagnosis* is based on the combined findings from endoscopy/biopsy, allergen elimination, and challenge testing. Biopsy reveals variable small-bowel villus injury, increased crypt length, and intraepithelial lymphocytes. *Treatment* of this condition is strict avoidance of the offending food(s). Protein-induced enteropathy usually resolves within 1-2 years at which time rechallenge is warranted.

Declaration of conflict of interest

The author declares no conflict of interest.

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