

Pathophysiology, diagnosis and treatment of food protein-induced gastrointestinal diseases

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Purpose of review

Although our general understanding of food hypersensitivity has improved in recent years, gastrointestinal food protein-induced diseases still pose diagnostic and therapeutic dilemmas.

Recent findings

Food allergy in children and adults may involve any part of the gastrointestinal tract. Clinical presentations include protein-induced enterocolitis syndrome, enteropathy and proctocolitis, as well as eosinophilic gastroenteritis and related disorders. For many of these conditions, our understanding of the pathophysiology is incomplete. Manifestations are mostly non-IgE mediated, and skin prick testing and measurement of food-specific IgE antibody levels are of limited diagnostic value. Atopy patch testing may be of benefit in identifying food items associated with late-onset gastrointestinal reactions. A definitive diagnosis of gastrointestinal food allergy, however, still relies on formal food challenges. Depending on the clinical presentation, gastrointestinal biopsies may be required. In infancy, hypoallergenic formula or maternal elimination diets have been shown to effectively control the gastrointestinal manifestations of food allergies. Growth parameters and micronutrient levels need to be carefully monitored while on elimination diets for prolonged periods. In older children and adults with eosinophilic gastrointestinal disorders, the response to dietary restriction is variable. Corticosteroids may be required to control symptoms in those who failed to respond to hypoallergenic diets. In eosinophilic esophagitis, steroids can be administered topically in the form of swallowed aerosols. Leukotriene receptor antagonists and other novel therapies may be useful as steroid-sparing agents.

Summary

Early diagnosis and treatment of food protein-induced gastrointestinal diseases may prevent significant nutritional complications. Further research is needed to develop diagnostic tools for these mainly cell-mediated disorders.

Keywords

food allergy, eosinophilic gastroenteritis, esophagitis, enteropathy, enterocolitis, elimination diet

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Abbreviations

APT	atopy patch test
CMA	cow milk allergy
FPIES	food protein-induced enterocolitis syndrome
GER	gastroesophageal reflux
SPT	skin prick test
TGF β	transforming growth factor- β
Th	T-helper
TNF α	tumor necrosis factor- α

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Introduction

Food allergy in children commonly involves the gastrointestinal tract [1•,2•]. Unlike the acute manifestations of IgE-mediated food hypersensitivity, slowly evolving gastrointestinal allergic reactions may be difficult to recognize. In children, a delayed diagnosis of gastrointestinal food allergy may result in significant growth impairment, anemia, hypoproteinemia and other deficiency states. Early diagnosis and appropriate treatment are therefore crucial in preventing the nutritional complications of gastrointestinal food allergy.

The close proximity of luminal antigens to the gut-associated immune system may explain why food-allergic disorders frequently cause gastrointestinal manifestations. In sensitized children and adults, food proteins are able to elicit a diverse range of upper and lower gastrointestinal pathologies, including mucosal inflammation and infiltration, ulceration, small intestinal villous damage, as well as changes in intestinal permeability and motility. For the majority of food-induced gastrointestinal conditions our understanding is still evolving. Most patients with gastrointestinal food allergy do not have evidence of systemic IgE sensitization, and food-specific IgE antibodies and skin prick tests (SPTs) are often negative. These disorders are predominantly mediated by T-helper 2 (Th2) lymphocytes and eosinophils. Relatively little progress has been made in developing diagnostic tests for cell-mediated food-allergic responses [3]. It is important to understand that the presence of eosinophils in the gastrointestinal tract does not automatically signify food allergy. The differential diagnosis includes inflammatory bowel disease (e.g. ulcerative colitis) as well as several systemic conditions, such as parasitic infection, malignancies or drug reactions [2•]. Furthermore, the role of environmental, nondietary allergens in the pathogenesis of eosinophilic gastroenteropathies is currently under evaluation.

There are several well characterized food-allergic gastrointestinal diseases. These conditions need to be distinguished from nonimmunological intolerance reactions to dietary constituents. Examples are carbohydrate or fat malabsorption – conditions that may present with abdominal pain and diarrhea following ingestion of the offending food ingredient. Dietary factors may also directly influence gut motility, for example, long-chain triglycerides may delay gastric emptying, induce vomiting, or cause biliary tract spasm. Furthermore, food-borne toxins can cause vomiting or diarrhea. It is important to consider these nonimmunologic reactions in the differential diagnosis of true food protein hypersensitivity. The following summary will review the current understanding of the pathophysiology, diagnosis and treatment of cell-mediated, slowly evolving gastrointestinal food-allergic disorders.

Pathophysiological mechanisms

Several aspects are of particular importance in the pathophysiology of gastrointestinal food allergy: oral tolerance development and bacterial intestinal microflora, intestinal barrier function, transepithelial transport of food antigens, eosinophil recruitment in the gastrointestinal tract, and effect of food allergens on gastrointestinal motility.

Oral tolerance development and bacterial intestinal microflora

Complex interactions between the gastrointestinal immune system and environmental factors actively regulate the development of immune tolerance to dietary and microbial antigens [4]. After birth, human milk represents the first physiological exposure of the gastrointestinal tract of the newborn infant to food antigens [5]. Small amounts of intact food antigens, including β -lactoglobulin, egg, peanut and gliadin, are secreted by the mammary epithelium into breast milk [6–9]. The development of oral tolerance in response to low-dose food antigen exposure requires production of transforming growth factor- β (TGF β) by T lymphocytes [10•]. Several studies have demonstrated that reduced levels of TGF β are associated with food sensitization [10•,11•,12]. In a recent study by Perez-Machado *et al.* [10•], low numbers of TGF β -producing lymphocytes were found in the duodenal epithelium and the lamina propria of children with food allergies. In the same study, numbers of T-helper 3 (Th3) lymphocytes were also reduced. Th3 lymphocytes are closely involved in regulating oral tolerance development in response to stimulation by microbial antigens. Failure to generate Th3 cells, as a result of insufficient stimulation of innate immune responses by commensal intestinal microbes, may be a factor contributing to impaired development of oral tolerance [10•,13].

In breast-fed infants, lactobacilli and bifidobacteria predominate in the intestinal microflora [14]. Differences in the composition of the fecal microflora have been found between infants with and without atopic manifestations. Infants with atopic dermatitis had lower colonization rates of enterococci and lactobacilli, as compared with healthy infants [15]. Commensal gut bacteria interact with the gut-associated immune system via toll-like receptors. Microbial stimulation of the infant's immune system is thought to modulate early adaptive immune responses from a Th2 to a Th1-type cytokine profile [4,13,16•,17]. A recent Swedish study demonstrated differences in cytokine profiles relating to the interaction of different bacterial strains with specific toll-like receptors, TR-2 and TR-4 [16•]. The authors speculated that commensal bacterial strains exert a differential effect on the maturation of the neonatal immune system. The molecular mechanisms through which toll-like receptors are involved in the development of oral tolerance are still under investigation.

Intestinal mucosal barrier function

Intestinal mucosal barrier function is of major pathophysiological importance in food allergy. Impaired barrier function may increase the risk of sensitization to ingested food antigens. Conversely, increased permeability has been described in patients with food allergies [18,19•]. In the mature gut, macromolecules such as intact food antigens cannot easily cross the mucosal barrier. A recent study in premature and term infants showed that permeability is higher in premature than in term infants, and that barrier function improves within the first week of life [20]. This increased permeability may, in theory, be of clinical importance as it could increase the risk of sensitization to food antigens in the early neonatal period. The incidence of food-allergic disorders, however, does not appear to be increased in premature infants.

Several cytokines influence and regulate intestinal permeability. Tumor necrosis factor- α (TNF α), which is secreted by activated T lymphocytes, may increase intestinal permeability, whereas TGF β improves mucosal barrier function. In a mouse model of food allergies, impaired mucosal barrier function was partially reversed after administration of glucagon-like peptide-2 (GLP-2). This phenomenon is thought to be due to inhibition of transepithelial antigen uptake [21•].

Permeation of the intestinal epithelium occurs through both paracellular and transcellular routes. Paracellular transport involves tight junctions which are distributed around the apical membranes of enterocytes; these limit the transport of molecules greater than 500 Da across the epithelium. Proteins may also be absorbed into the enterocyte by endocytosis, which may be followed by intracellular degradation. Alternatively, intact protein

may be passaged across the cell and released from the basolateral surface as part of 'transcellular' transport. Dual sugar absorption studies are used to assess both aspects of mucosal transport. A low molecular weight sugar (rhamnose or mannitol) that is passively absorbed via the paracellular route provides indirect evidence of small intestinal villous integrity. Larger sugars such as lactulose, which are normally not absorbed across the epithelium via the paracellular route, are used to assess the 'leakiness' of the gut. Excretion of both sugars into urine is measured, and intestinal permeability expressed as the ratio of both sugars (e.g. lactose/rhamnose ratio). A study of 200 children with cow milk allergy (CMA) and 105 controls examined changes in intestinal permeability in relation to food allergy, using dual sugar absorption studies [18]. Intestinal permeability was significantly increased in children with CMA, as compared with normal controls. The diagnostic accuracy of the lactulose-mannitol permeability test was highest in infants aged between 6 and 12 months, whereas the sensitivity was low in children older than 3 years [18].

Transepithelial transport of food antigens

The intact mucosal intestinal barrier prevents direct exposure of luminal antigens to mast cells in the lamina propria. Several recent studies have demonstrated novel pathways that enhance active antigen uptake across the epithelial barrier [22,23•,24]. This mechanism is important in explaining the manifestations of immediate-type IgE-mediated food allergy. Animal studies in sensitized rats have demonstrated that the active transepithelial transport of food proteins across the intestinal epithelium is facilitated by rapid transcytosis, occurring within minutes of intestinal antigen exposure (phase I) [23•,24]. This mechanism is IgE-dependent and mast cell-independent. It is followed by a second phase (phase II) of increased antigen transport, with onset within 30 min of antigen exposure. This late-phase response is mediated by increased paracellular transport via tight junctions and appears to be mast cell-dependent [25]. The phase I response is associated with expression of low-affinity IgE receptor (CD23) on enterocytes [22], in response to increased local expression of IL-4 [24]. The process of endocytosis is controlled by specific CD23-splice forms that are internalized after binding to antigen/IgE complexes [23•]. Binding of allergens to CD23 may protect from lysosomal protein degradation and allow transport of intact antigen across the epithelial barrier [23•].

Eosinophil recruitment in the gastrointestinal tract

Much of our understanding on eosinophil recruitment in the gastrointestinal tract is based on studies in eosinophilic esophagitis. Several studies have demonstrated that this condition is a localized Th2-mediated disorder. Peripheral blood lymphocyte subsets and cytokine

profiles do not reflect the Th2-type immune profile in these patients [26]. Studies in mice demonstrated that IL-5, a major Th2 cytokine, is critical for eosinophil trafficking to the esophagus [27•]. This response appears to be specific for the esophagus as eosinophil numbers are not increased in stomach or duodenum [26]. Eotaxin-1 is another important mediator for eosinophil recruitment in the esophagus and lower gastrointestinal tract [27•,28,29]. IL-13 is produced and released by human eosinophils [30]. Recently, elevated IL-13 levels have been shown to be associated with airway eosinophilia and eosinophilic esophagitis by an IL-5, eotaxin and STAT6-dependent pathway [31•].

The role of inhalant antigens in eosinophilic gastroenteropathies has been proposed, following the observation by Mishra *et al.* [32] demonstrating eosinophilic esophagitis in animals in response to intranasal allergen challenge. This study suggested that inhalant allergens are able to elicit eosinophilic inflammation in the gastrointestinal tract. In a similar mouse model, repeated intratracheal administration of IL-13 or aeroallergens was associated with eosinophilic esophagitis – a process highlighting the link between pulmonary and esophageal eosinophilic inflammation [2•,31•]. These observations might explain the findings of a recent Swedish study involving nine adults with birch pollen allergy [33•]. In these patients, numbers of duodenal eosinophils and mucosal IgE-positive cells were increased during the pollen season, supporting the hypothesis of immunological interaction between the airways and the gut.

Effect of food allergens on intestinal motility

The understanding of allergic motility disorders is slowly evolving. Due to the difficulties in studying gastrointestinal motility, relatively few studies on this topic are available. Gastroesophageal reflux (GER) and constipation in infancy may, in part, be due to the motility effects of food allergen-induced mediators. More than 40% of infants with GER have been shown to suffer from CMA [34]. Electrophysiological studies have demonstrated gastric dysrhythmias in infants with CMA, presenting with GER or vomiting [35]. Experimental studies in sensitized animals have provided evidence of acute motility effects of food allergens on gastric, small intestinal and colonic motility [36,37]. The exact mechanisms by which food antigens elicit gastrointestinal motility disturbances are unclear. Release of mast cell and eosinophil mediators may affect mucosal plexus networks or may stimulate the release of motility-active gut hormones, such as motilin or vasoactive intestinal peptide. There is also indirect evidence that eosinophilic mucosal infiltration may cause neuronal axonal damage and contribute to gastrointestinal motility disturbances [38,39].

Clinical presentation

Celiac disease and cow milk-sensitive enteropathy were the first gastrointestinal conditions to be clinically recognized as food-induced disorders. Since then, the clinical spectrum of food-allergic disorders has expanded [40,41]. Several conditions, including GER, constipation and infantile colic have been shown to be associated with hypersensitivity to cow milk and other food proteins [1•,42–44]. Although several studies have demonstrated an association between food allergy and these conditions in early childhood, the strength of this association is as yet unclear.

Eosinophilic gastroenteritis

Gastrointestinal tissue eosinophilia is the diagnostic hallmark of eosinophilic gastroenteropathies [2•,45]. Except for the esophagus, the gastrointestinal tract normally contains mucosal eosinophils. When there are excessive numbers of eosinophils, their distribution may be used to define mucosal, muscular and serosal eosinophilic gastroenteritis. Furthermore, eosinophilic gastroenteritis can be divided according to its anatomical involvement into eosinophilic esophagitis, gastritis, enteritis or colitis.

The clinical presentations of eosinophilic gastroenteritis in children and adults are often fairly nonspecific, including vomiting, diarrhea, abdominal pain and poor weight gain. However, there is an increasing number of case reports on children and adults with atypical presentations of eosinophilic gastroenteritis; these include subacute bowel obstruction [46,47], neonatal intussusception [48], gastric outlet obstruction [49], duodenal strictures [50], acute appendicitis [51], and pancreatobiliary tract disease [52–55]. Functional intestinal pseudo-obstruction may occur in patients with eosinophilic infiltration of the colonic lamina propria and myenteric plexus [39].

Eosinophilic esophagitis

Eosinophilic esophagitis is considered to be a form of eosinophil gastroenteritis [56]. Since its first description in 1977, eosinophilic esophagitis has evolved from a rare to a relatively common condition [2•,57]. Eosinophilic esophagitis occurs in children [58,59,60•] and young adults [61,62], with an overrepresentation of male patients. Dysphagia for solids is the most characteristic symptom of eosinophilic esophagitis [59,60,63,64]. This may be associated with vomiting, chest or abdominal pain and weight loss. Eosinophilic esophagitis shares several clinical features with GER disease. Treatment with antireflux medications or fundoplication, however, is usually ineffective. Although its etiology is not entirely clear, there is evidence that food antigens are of etiological importance. As previously mentioned,

the role of inhaled antigens has also been explored [65,66].

Endoscopic biopsy is the cornerstone in the investigation for eosinophilic esophagitis. Eosinophils are usually absent from the esophagus. Small numbers of eosinophils may be found in the lower esophagus of patients with reflux esophagitis. More recently, eosinophilic esophagitis has been described as a separate clinical entity. Large numbers of eosinophils (>20 per high-power field) are considered diagnostic of eosinophilic esophagitis [59•]. Grasp biopsies should be taken from the upper and lower esophagus, as well as specimens from stomach and duodenum. The tissue eosinophilia involves the entire esophagus and, unlike in reflux esophagitis, is not limited to the lower esophagus. Typically, there is no associated eosinophilia in the stomach or duodenum [26]. Endoscopically, the esophageal mucosa appears thickened and displays characteristic longitudinal furrows [61]. The mucosa is friable and prone to abrasion, even with minimal trauma [67]. Strictures and mucosal rings may occur as a complication of eosinophilic esophagitis; these usually respond well to endoscopic dilatation [64].

Pediatric patients with eosinophilic esophagitis frequently have evidence of food hypersensitivity [68•]. In 26 patients with eosinophilic esophagitis, cow milk and egg were identified as allergens by SPTs, and wheat by atopy patch tests (APT). In 18/24 patients, dietary restriction of the identified allergen resulted in resolution of symptoms, and six patients had a partial response. This was associated with a significant drop in the number of mucosal eosinophils (55.8 to 8.4 per high-power field) [68•]. Based on these observations, SPT and APT may be helpful in directing elimination diets in patients with eosinophilic esophagitis.

Corticosteroids provide an alternative to the dietary treatment of eosinophilic esophagitis. In 21 adults, treatment with topical corticosteroids for 6 weeks resulted in resolution of obstructive dysphagia symptoms [69]. In another study of 11 children with eosinophilic esophagitis, topically applied steroid aerosols (swallowed fluticasone) also resulted in resolution of symptoms [70•]. This was associated with a significant reduction in mucosal eosinophils, as well as CD3+ and CD8+ lymphocytes. Steroids are predominantly used in patients who have not responded to dietary elimination or who find it difficult to adhere to the often complex dietary regimens. A small open-label study has provided preliminary evidence that the leukotriene receptor antagonist, Montelukast, may improve symptom control [71•]. Montelukast has been shown to reduce the need for systemic corticosteroid treatment in patients with recurrent eosinophilic gastroenteritis [72].

Food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome (FPIES) is characterized by severe gastrointestinal allergic inflammation in the small intestine and colon of young infants with food allergies [73••]. FPIES usually presents with profuse diarrhea, vomiting, dehydration and failure to thrive [74]. Acute dehydration may lead to episodes of circulatory collapse and shock in about 20% of patients [73••]. Patients may present with significant intestinal bleeding and develop anaemia. Sensitization to multiple food proteins is common. Cow milk and soy are considered the main causative allergens. Other solid foods, including vegetables, cereals and poultry meats should also be considered as allergens in infants and young children with FPIES [73••]. FPIES does not appear to occur in breast-fed infants and seems to require direct dietary exposure of the offending food antigen. This is reflected in the age of onset, which was 1 month for cow milk and soy, and 5.5 months for solid food-induced FPIES [73••]. As for most cell-mediated food-allergic disorders, the pathological mechanisms causing FPIES are poorly understood. A study in infants with challenge-proven FPIES examined the role of $TGF\beta 1$, type 1 and 2 TGF receptor, and $TNF\alpha$ in duodenal biopsy specimens [11••]. In that study, duodenal villous atrophy was associated with increased tissue staining for $TNF\alpha$, whereas expression of duodenal $TGF\beta$ was reduced in patients with FPIES.

Food protein-induced enteropathy

Most infants and young children suffering from food protein-induced enteropathy will present with chronic diarrhea and failure to thrive. Like FPIES, this condition is closely associated with hypersensitivity to cow milk and soy protein. Although predominantly a disorder of infants, residual symptoms of cow milk-sensitive enteropathy may persist to school age [75]. Allergic inflammation in the small intestine causes mucosal damage with distortion of the villous architecture. This often leads to malabsorption of nutrients and osmotic diarrhea, and failure to thrive may develop as a consequence. Clinical and histological features share similarities with celiac disease – a condition that needs to be considered as the main differential diagnosis.

Earlier studies in cow milk-sensitive enteropathy demonstrated that the mucosal damage is mediated by eosinophils, in the presence of vascular cell adhesion molecule-1 [76]. IL-5 plays an important part in the activation of duodenal eosinophils in food allergic patients [77]. In adults with SPT-negative and serum IgE-negative food allergy, symptoms of food hypersensitivity correlated with duodenal IgE-bearing cells, as well as activated eosinophils and T lymphocytes [78••]. Milk-specific lymphocytes were identified in duodenal

biopsies of 60% of pediatric patients with allergic eosinophilic gastroenteritis or food protein-induced enteropathy [79••]. Gastrointestinal lymphocytes of patients with food allergies usually showed a Th2 cytokine profile, but lacked Th3 cytokines which are important for the development of oral tolerance. In a retrospective study of 121 children with multiple food allergies [80•], duodenal biopsies often revealed subtle histological abnormalities. A particular immunological pattern of increased IgG1, decreased IgG2/4 and low-normal IgA was commonly observed. Peripheral CD4+ and CD19+ lymphocytes were increased, while CD8+ and natural killer cells were reduced in these patients [80•].

Food protein-induced proctocolitis

This condition is the most common cause of low-grade rectal bleeding in young infants [81]. Symptoms usually develop between 3 and 6 weeks of age, but earlier presentations have been described [82]. Infantile proctocolitis occurs in both breast and formula-fed infants. The clinical presentation is often limited to low-grade diarrhea, containing small amounts of fresh blood. As blood loss is usually minimal, clinically significant anemia is relatively uncommon. Endoscopic biopsies typically demonstrate an eosinophilic proctocolitis. Numbers of intraepithelial lymphocytes, predominantly CD8+ cells, are also increased [83]. Eosinophils were present in stool smears in over 80% of infants [81]. The differential diagnosis of allergic proctocolitis in infants includes bacterial gastroenteritis, anal fissures, juvenile polyps or other nonallergic forms of colitis, such as chronic granulomatous disease [84] or inflammatory bowel disease [85].

Diagnostic evaluation

The diagnosis of gastrointestinal food allergy is hampered by the fact that allergic disease is often not considered. This may cause significant diagnostic delay. Symptoms may occur up to 48 h after allergen exposure and may persist for several days after the last exposure to the food antigen. Vomiting and diarrhea may occur in patients with immediate-onset IgE food allergy. The majority of patients with slowly evolving gastrointestinal food allergy, however, do not display evidence of IgE sensitization. Measurement of food-specific IgE antibodies [86] and SPTs [87] are therefore often not helpful. A definitive diagnosis of gastrointestinal food allergy still relies on formal food challenges [88••]. Depending on the clinical presentation, upper or lower gastrointestinal biopsies are required to adequately define the disorder at the tissue level [89]. Skin testing has become an integral part in the evaluation of gastrointestinal food-induced disorders [68••,90•]. In particular, APT holds promise as a new diagnostic tool in cell-mediated food allergy [90•,91]. De Boissieu *et al.*

[90•] have recently demonstrated that APTs were helpful in diagnosing patients with gastrointestinal CMA. Manifestations included GER, diarrhea, constipation and infantile colic. In that series, the APT had a sensitivity of 79%, and specificity of 91%. The diagnostic accuracy of the APT needs to be tested prospectively as other series have found a much lower sensitivity in the diagnosis of food allergy [91].

Treatment and prognosis

Due to the difficulties in defining the cell-mediated responses involved in gastrointestinal food allergy [3], the diagnosis often involves a sequence of dietary elimination and formal re-challenge after a period of symptomatic improvement [88•,92•]. The response to hypoallergenic diets may be variable. Hypoallergenic diets in infants may involve extensively hydrolyzed or amino acid-based formula, or maternal elimination diets in breast-fed infants [92•]. Maternal elimination diets need to be supervised by an experienced dietitian, and growth parameters and micronutrient levels carefully monitored if extensive elimination diets are maintained for prolonged periods [92•,93]. Younger infants and children with eosinophilic gastroenteropathies appear to have a better response to elimination diets, whereas dietary treatment in older children and adults is less successful. This may, in part, be due to difficulties with adherence to restrictive elimination diets in older children and adults. Alternatively, other factors such as environmental swallowed or inhaled allergens may contribute to the persistence of allergic gastrointestinal inflammation.

Food protein-induced enterocolitis, enteropathy or proctocolitis presenting in infancy and early childhood, if managed appropriately, have an excellent prognosis. These conditions are often transient and may remit spontaneously within the first years of life. Even infants with the most complex multiple food protein intolerances usually achieve tolerance by 3 years of age [94]. In a study of patients with FPIES, the majority of young children became tolerant to the offending food items by 3 years [73•]. In that series, patients with FPIES due to soy hypersensitivity appeared to follow a more protracted disease course.

Our understanding of the treatment and prognosis of eosinophilic esophagitis and other eosinophilic gastroenteropathies is still evolving. Treatment of eosinophilic esophagitis may involve hypoallergenic diets (including amino acid-based formula), swallowed steroid aerosols, systemic steroids and other antiallergic compounds, such as mast cell stabilizers, leukotriene inhibitors, or novel humanized antibodies [2•]. The response to dietary elimination in eosinophilic gastroenteritis is variable, and steroid treatment may be needed in refractory cases

[2•]. Similar to chronic asthma, long-term treatment is often required as the condition may relapse as soon as diets or steroids are discontinued. Novel therapies, such as humanized anti-IL-5 (mepolizumab) may be a useful adjunct in the treatment of severe refractory eosinophilic gastroenteropathies and other hypereosinophilic disorders [95•].

Conclusion

Gastrointestinal food allergy presents with a diverse range of clinical manifestations. Early recognition and treatment may prevent the potentially severe nutritional complications associated with these disorders. Although skin testing and measurement of food-specific IgE antibodies provide useful clinical information, a definitive diagnosis of gastrointestinal food allergy usually involves endoscopic investigation and formal food challenges. Simple diagnostic tests for these cell-mediated disorders are urgently needed. The response to elimination diets in patients with eosinophilic gastroenteropathies is variable. Corticosteroids and novel steroid-sparing agents may be required in patients with refractory or relapsing eosinophilic gastrointestinal disorders.

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