

Eosinophilic Esophagitis, Gastroenteritis, and Colitis

James P. Franciosi, Jonathan E. Markowitz, and Chris A. Liacouras

KEY CONCEPTS

- Food allergens play a strong role in the pathogenesis of eosinophilic esophagitis (EoE).
- Elimination or elemental diets are highly effective treatments for EoE.
- EoE is distinct from eosinophilic gastroenteritis (EoG).
- It is essential to distinguish EoG from inflammatory bowel disease.

Primary disorders involving an accumulation of eosinophils in the gastrointestinal tract include eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis. The goal of this chapter is to provide an overview of these conditions.

Eosinophilic esophagitis

Introduction

Our understanding of eosinophilic esophagitis (EoE) has evolved over the past 30 years from isolated case reports of patients with prominent esophageal eosinophilia (often misclassified as gastroesophageal reflux) to a well-defined clinical disorder. This disease has been given several names including EoE, allergic esophagitis, primary EoE, and idiopathic EoE.

Definition

EoE is a distinct disease defined by a clinico-pathologic diagnosis involving a localized eosinophilic inflammation of the esophagus. Since symptoms are similar to gastroesophageal reflux, esophageal endoscopic biopsies are required to establish the diagnosis. EoE is defined as the presence of 15 or more eosinophils in the most severely involved high-powered field (HPF) (400×) isolated to the esophagus and associated with characteristic clinical symptoms, which do not respond to acid blockade. Other recognized causes of esophageal eosinophilia should be excluded prior to making the diagnosis (Table 15.1).

Table 15.1 Differential diagnosis of esophageal eosinophilia

-
- Gastroesophageal reflux
 - Inflammatory bowel disease
 - Food allergy
 - Eosinophilic gastroenteritis
 - Celiac disease
 - Parasitic infection
 - Connective tissue disease
 - Drug allergy
 - Hypereosinophilic syndrome
 - Autoimmune enteropathy
 - Candida esophagitis
 - Viral esophagitis (herpes or cucumber mosaic virus (CMV))
 - Churg–Strauss syndrome
-

Incidence and prevalence

In 2003, the incidence and prevalence of EoE in children 0–19 years of age were reported to be 1 and 4.3 per 10,000 children, respectively [1]. Other studies have suggested a rising prevalence of EoE in the last 10 years [2]. In adults, the prevalence of esophageal eosinophilia has been reported to be as high as 4.8% in a random sample of the Swedish population who electively underwent esophageal endoscopy with biopsy without any clinical indication [3]. These studies lack exclusion of patients with gastroesophageal reflux, did not have uniform treatment of patients with acid blockade medications prior to establishing the diagnosis of EoE and did not follow the definition of EoE as defined above. Further studies are needed to investigate the prevalence of EoE using current definitions.

Etiology

The exact etiology of EoE is unknown; however, EoE is believed to be a mixed IgE and non-IgE mediated allergic response to food antigens, with non-IgE cell-mediated responses predominating [4]. The identified esophageal eosinophilia is thought to represent only part of a complex cellular and molecular cascade of interactions between Th2 cells, mast cells, cytokines such as IL-5 and IL-13, endogenous chemokines such as eotaxin-1 and eotaxin-3, and eosinophils [5].

While several studies have documented resolution of EoE with the strict avoidance of food antigens, in 1995, Kelly *et al.* published a sentinel paper on EoE [6]. Kelly studied 10 patients with symptoms of chronic gastroesophageal reflux who failed medical and surgical therapy (six patients had ongoing symptoms and esophageal eosinophilia despite undergoing a fundoplication). Because the suspected etiology was an abnormal immunologic response to specific unidentifiable food antigens, patients were placed on a strict diet consisting of an amino-acid-based formula for a median of 17 weeks. Symptomatic improvement was seen within an average of 3 weeks after the introduction of the elemental diet (resolution in eight patients, improvement in two). All 10 patients demonstrated a significant histologic improvement in their esophageal eosinophilia. Subsequently, all patients reverted to previous symptoms upon reintroduction of foods. Open food challenges were then conducted with a return of symptoms with challenges to milk (seven patients), soy (four patients), wheat (two patients), peanut (two patients), and egg (one patient) [6].

Several authors have suggested that aeroallergens may play a role in the development of EoE. Mishra and Rothenberg used a mouse model to show that the inhalation of *Aspergillus* may cause EoE [7]. They found that the allergen-challenged mice developed elevated levels of esophageal eosinophils and features of epithelial cell hyperplasia that mimic EoE. In addition, Spergel reported a case of a 21-year-old female with EoE, asthma, and allergic rhinoconjunctivitis who became symptomatic from her EoE during pollen seasons followed by resolution during winter months [8].

Clinical features

Although the current reports suggest that patients with EoE are predominantly young Caucasian males, EoE can occur at any age or race and in either sex. Those affected typically present with one or more of the following symptoms: vomiting, regurgitation, nausea, epigastric or chest pain, dysphagia, water brash, globus, or decreased appetite [9]. Less common symptoms include growth failure, hematemesis, and esophageal dysmotility. Symptoms can be frequent and severe in some patients while extremely intermittent and mild in others (Table 15.2). The majority of children experience vomiting, chronic nausea, or regurgitation while older children and adolescents develop heartburn, epigastric

Table 15.2 Clinical symptoms of eosinophilic esophagitis

-
- Vomiting
 - Regurgitation
 - Dysphagia
 - Nausea
 - Epigastric pain
 - Chest pain
 - Esophageal food impaction
 - Irritability/feeding difficulties
 - Night time cough
-

Other complications that can occur with EoE include failure to thrive, malnutrition, feeding intolerance, esophageal strictures, hiatal hernia, small caliber esophagus, and esophageal perforation. Esophageal fungal or viral superinfection may also occur. Any patient who is being considered for surgical correction of gastroesophageal reflux (fundoplication) should first be evaluated endoscopically for EoE to prevent unnecessary surgery [10].

pain, or episodes of dysphagia. Up to 50% of patients manifest additional allergy related symptoms such as asthma, eczema, or rhinitis. Furthermore, up to 50% of patients have one or more parents with history of allergy. EoE should be strongly considered in those patients who have severe or refractory symptoms of gastroesophageal reflux, especially those who are refractory to medication.

Diagnosis

Children with chronic refractory symptoms of gastroesophageal reflux disease (GERD) or dysphagia should undergo evaluation for EoE. While laboratory and radiological assessment may be appropriate in most cases, all patients should undergo an upper endoscopy with biopsy. The diagnosis of EoE is made when there is an isolated severe histologic esophagitis, unresponsive to aggressive acid blockade, associated with symptoms similar to those seen in GERD or dysphagia.

Upper endoscopy should be performed to directly visualize the esophagus and to obtain tissue samples for pathologic investigation. EoE is best defined as the presence of at least 15 eosinophils per HPF isolated strictly to the esophagus. In 1999, Ruchelli evaluated 102 patients presenting with GERD symptoms who also were found to have at least one esophageal eosinophil without any other gastrointestinal (GI) abnormalities [11]. Patients were subsequently treated with acid blockade. It was demonstrated that the treatment response could be classified into three categories. Patients who improved and had a lasting response had on average 1.1 eosinophils per HPF, patients who relapsed upon completion of therapy had 6.4 eosinophils per HPF, and patients who remained symptomatic despite therapy had on average 24.5 eosinophils per HPF.

Since EoE has been described as a patchy disease, multiple esophageal biopsies should be obtained from the mid

and distal esophagus. In the past, early reports suggested that EoE patients developed proximal or mid-esophageal eosinophilia; however, recent information demonstrates that severe mucosal eosinophilia can occur in any portion (proximal, mid, distal) of the esophagus [12–14]. To make an accurate diagnosis, the remainder of the GI tract must be normal; thus, biopsies should be obtained from the gastric antrum and duodenum to rule out other diseases.

EoE has been associated with visual findings on endoscopy in 68% of patients: concentric ring formation (called “trachealization” or a “feline esophagus”), longitudinal linear furrows, and patches of small, white papules on the esophageal mucosal surface [15]. Most investigators believe that the esophageal rings and furrows are a response to full thickness esophageal tissue inflammation. The white papules appear to represent the formation of eosinophilic abscesses. However, the esophagus may be visually normal on endoscopy in over 30% of patients. Therefore, whenever the diagnosis of EoE is suspected, esophageal biopsies must be performed.

In 2000, Fox utilized high-resolution probe endosonography in patients with EoE in order to determine the extent of tissue involvement [16]. He compared eight patients with EoE to four control patients without esophagitis. He discovered that the esophageal tissue layers were thicker in EoE patients compared to controls (total wall thickness 2.8 versus 2.2 mm, $p < 0.01$; combined mucosal and sub-mucosal thickness 1.6 versus 1.1 mm, $p < 0.01$; muscularis propria thickness 1.3 versus 1.0 mm, $p < 0.05$). These findings suggested that EoE patients had more than just surface involvement of eosinophils.

While other non-invasive tests have been used in an attempt to diagnose EoE, upper endoscopy with biopsy is the only test that can precisely determine the diagnosis of EoE. The other non-invasive GI diagnostic tests include radiographic upper GI series (UGI), pH probe, and manometry. Although radiographs demonstrate anatomic abnormalities, they do not identify tissue eosinophilia. However, in patients suspected of having esophageal strictures, an UGI can provide important information. Patients with EoE usually have normal or borderline normal pH probes. Patients may have mild GERD secondary to abnormalities in esophageal motility due to tissue eosinophilic infiltration; however, there have been no specific manometric findings of EoE to date.

Allergy testing

Once EoE is suspected, patients should be encouraged to seek an allergy consultation. Serum peripheral eosinophilia or elevated IgE levels are not present in the majority of patients. Furthermore, these tests have been found to be unreliable due to the fact that they usually respond to environmental allergens as well as ingested or inhaled allergens. Serum RAST (radioallergosorbent test) testing for food specific IgE antibodies has a very limited role in EoE due to its low sensitivity. Use of a combination of peripheral

blood absolute eosinophil count (AEC), levels of eosinophil-derived neurotoxin (EDN), and eotaxin-3 as non-invasive biomarkers are under investigation; however, these tests do not currently appear to have the sensitivity or negative predictive value needed for widespread clinical practice [17].

A combination of skin prick testing (SPT) and atopy patch testing (APT) attempts to identify IgE and non-IgE based causative food allergens, respectively. In a study population of 146 pediatric patients, elimination diet based on foods identified by a combination of SPT and APT led to resolution of esophageal eosinophilia in 67% of patients, and histologic improvement in 82% of patients [4,18]. In EoE patients, SPT most frequently identifies positive reactions to egg, milk, and soy. Given the non-IgE mediated mechanism of most of the food reactions in EoE patients, APT may play an important role in the successful identification of causative food antigens. Presently, the lack of standardization of APT methodologies in addition to variability in technique and interpretation are likely explanations for the non-uniform results of APT. Interpretation is based on a no reaction, or 1 – 3+ scale depending on the degree of erythema, papules and/or vesicles. The most common foods identified by APT are corn, soy, and wheat [18].

Treatment

Acute management

Several treatment options are available to patients diagnosed with EoE. Currently, most investigators do not believe that esophageal acid exposure is the etiology of EoE; however, because of the severity of mucosal and submucosal disease seen in EoE, secondary acid reflux often occurs. Additionally, because there may be some histologic overlap between patients with EoE and those with GERD, it is important to exclude acid reflux as a cause of esophageal inflammation. In rare cases, acid reflux may cause significant esophageal eosinophilia. Therefore, patients suspected of having EoE should be prescribed a proton pump inhibitor so that GERD can be excluded. A case series by Ngo and colleagues have identified several patients with significant esophageal eosinophilia that resolved 1 month after taking a proton pump inhibitor medication [19]. A 4 to 6-week course of acid blockade and repeat endoscopy is important to confirm the diagnosis of EoE.

Adult gastroenterologists have reported the use of esophageal dilation for their patients who present acutely with esophageal strictures secondary to EoE. While esophageal dilation may relieve dysphagia and improve an esophageal stricture, many physicians describe esophageal tearing during endoscopy and dilation [20–23]. Higher rates of esophageal perforation after attempted esophageal endoscopic dilation have been reported in this setting [23,24]. Thus, while esophageal dilation has a role in alleviating severe esophageal strictures in patients with EoE, its results are generally temporary and the problem often recurs. Gastroenterologists should be extremely careful whenever

performing endoscopy or dilation as perforation is a distinct possibility. A diagnostic endoscopy should be performed and medical or dietary therapy instituted prior to performing dilation.

Systemic corticosteroids were the first medical treatment shown to be effective in improving both symptoms and esophageal histology in patients with EoE [25]. Patients were treated with oral solumedrol (average dose 1.5 mg/kg/day; maximum dose 48 mg/day) for 1 month. Symptoms were significantly improved in 19 of 20 patients by an average of 8 days. A repeat endoscopy with biopsy (4 weeks after the initiation of therapy) demonstrated almost complete normalization of esophageal histology. However, upon discontinuation of corticosteroids, 90% had recurrence of symptoms. Oral corticosteroids should be used whenever patients have severe dysphagia (with or without strictures) or other clinical symptoms that may be contributing to possible hospitalization because of a feeding disorder, poor weight gain, or dehydration. While systemic steroids work rapidly, their disadvantages include the fact that they cannot be used chronically, that they do not cure the disease, and that they often have serious side effects with a prolonged use (bone, growth, and mood abnormalities).

Instead of prescribing systemic steroids, topical corticosteroids can be utilized [26–29]. Medications, such as fluticasone propionate, can be sprayed into the pharynx and swallowed. Within a few weeks, both clinical symptoms and esophageal histology dramatically improve. In a study by Konikoff, the authors conducted a randomized, double-blind, placebo-control trial of swallowed fluticasone in patients with active EoE [30]. Thirty-six patients were randomly assigned to receive either 880 µg of fluticasone daily or placebo. Of these, 50% of the fluticasone-treated patients achieved complete histologic remission compared to 9% of patients who received placebo. In addition, resolution of clinical symptoms occurred more frequently with fluticasone than with placebo. The authors concluded that swallowed fluticasone was effective in inducing histologic remission and clinical symptoms in EoE in a significant number of patients.

The advantage of using topical steroids is that their side effects are less than that seen with systemic steroids. The disadvantages include not treating the disease fully (the disease generally recurs when the treatment is discontinued) and the development of possible side effects such as epistaxis, dry mouth, and esophageal candidiasis. When using topical, swallowed corticosteroids, the initial dose varies from 110 to 880 µg, twice daily, depending on patient's age and size. Patients do not eat, drink, or rinse their mouth for 20–30 minutes after using this medication. Other atopic diseases should be controlled as rhinitis and environmental allergies may be linked to EoE. The patient should undergo endoscopy after 2–3 months of therapy. If improved, fluticasone can be weaned empirically. The medication can be discontinued as tolerated; however in many patients the disease

recurs. Recently, the use of a swallowed viscous budesonide solution has been reported with some effectiveness [31].

Several other medications have also been utilized. Cromolyn sodium has been used as a therapy for EoE in a small number of patients. However, cromolyn sodium did not demonstrate any histologic or clinical improvement in a series of 14 patients [32]. Leukotriene receptor antagonists have also been utilized to treat EoE [24]. Initial doses of 10–100 mg per day were prescribed with reports of symptomatic improvement; however, on repeat biopsy, there was no significant change in the patient's esophageal eosinophilia. While the advantage of using a leukotriene receptor antagonist is that it has minimal side effects and it may alleviate the patient's clinical symptoms, there have been no reports documenting improvement in the patient's histology. Additionally, the patient's clinical symptoms recur when the medication is discontinued.

Dietary therapy has been reported to be extremely effective for pediatric patients with EoE [6,7]. While there has been no definitive evidence that EoE is a food allergy, the removal of food antigens has been clearly demonstrated to successfully treat both the clinical symptoms and the underlying histopathology in well over 95% of patients with EoE. The elimination of causative foods can follow several therapeutic regimens. First, specific food elimination can be based on allergy testing and clinical history [18,33]. Second, the most likely causative foods can be removed regardless of history. Recently, a study utilized the removal of six foods (milk, eggs, wheat, soy, nuts, shellfish), without the aid of allergy testing, and demonstrated resolution of symptoms in over two-thirds of patients [8]. When comparing these studies, similar outcomes occur. In both studies, food elimination successfully improved symptoms in approximately 75% of patients. Moreover, although esophageal histology also significantly improved, in most patients it did not normalize.

While every attempt should be made to identify and eliminate potential food allergens through food elimination, a significant number of patients remain symptomatic and continue to have abnormal esophageal histology. In these cases, the administration of a strict diet utilizing an amino-acid-based formula is often necessary. As established by Kelly and Liacouras, the use of an elemental diet in children is greater than 95% successful in resolving both the clinical symptoms and histologic abnormalities of EoE [6,7]. Although the strict use of an amino acid-based formula (typically provided by nasogastric tube feeding) may be difficult for patients (and parents) to comprehend, its benefits outweigh the risks of other treatments. Once the esophagus is healed, foods are reintroduced systematically. Since the clinical symptoms are often erratic, endoscopy with biopsy should be performed in order to determine the improvement in esophageal histology.

In our experience of over 164 compliant patients, who were treated with an amino acid-based diet, 97% of patients

Table 15.3 EoE food introduction following an elemental diet

A	B	C	D
Vegetables (non-legume)	Other fruits	Peas	Milk
Carrots, squash	Apple, banana,	White potato	Corn
sweet potato,	kiwi, pineapple,	Grains	Peanut
spinach, broccoli,	mango,	Rice, oat, barley,	Wheat
lettuce	watermelon,	rye	Beef
Fruit	honeydew,	Meat*	Soy
Grapes, pear	cantaloupe,	Lamb, chicken,	Egg
peaches, plum,	papaya, guava,	turkey, pork	
apricot, cherries	avocado	Fish/shellfish	
orange,	Legumes	Tree nuts	
grapefruit, lemon,	lima beans,	Almond, walnut,	
lime, cherries,	chickpeas, white/	hazelnut, brazil	
strawberries,	black/red beans,	nut, pecan	
blueberries	string beans		

*Progress from well cooked to rarer.

had a clinical and histologic improvement in their EoE [32]. In those that required an elemental diet, over 84% had specific food antigens identified and were able to discontinue the elemental diet after approximately 6 months using a graded food reintroduction protocol (Table 15.3). Dietary restriction using a combination of patch and skin prick testing alone without the need for an elemental diet was successful in over 50% of 130 children. Elimination of the responsible foods usually does not lead to immediate resolution of symptoms. Rather, improvement of symptoms occurs approximately 1–3 weeks after the removal of the causative antigen. Also, in patients with EoE, symptoms do not always occur immediately after food reintroduction and may return after several days to weeks. In some cases, the responsible food antigens must be identified using a systematic approach: foods are eliminated for 6–8 weeks and repeat endoscopy is performed. New foods are typically introduced every 7 days and repeat biopsies are performed based on clinical symptoms or after 5–8 new foods are introduced. Nutritional support is also an important component in the management of EoE patients. Foods considered to be the most antigenic for EoE include milk, eggs, soy, corn, wheat, and beef.

Finally, other medications are being developed that target specific chemokines and other inflammatory mediators involved in eosinophil proliferation, recruitment, and activation. Medications such as anti-interleukin-5 (anti-IL-5), very late activating antigen, and monoclonal eotaxin antibody may benefit those patients who have severe EoE. Recently, Stein studied the use of anti-IL-5 in four patients identified with EoE [34]. These patients had long-standing dysphagia and esophageal strictures. After receiving

monthly intravenous infusions of anti-IL-5 for 3 consecutive months, clinical symptoms and repeated upper endoscopy were evaluated. Anti-IL-5 therapy was associated with marked decreases of peripheral blood and esophageal eosinophilia along with improved clinical symptoms and significant resolution of dysphagia.

Long-term management

The focus of long-term management of EoE should be to provide symptom relief along with histologic healing. At this point, topical corticosteroids and dietary restriction have both been shown to be successful in the long-term treatment of EoE. Several reports have demonstrated esophageal healing and symptom resolution with dietary therapy ranging from the removal of a few foods to the use of a total elemental diet strictly using an amino acid-based formula.

Unlike infantile milk-protein allergy, the majority of patients with EoE require long-term, indefinite food antigen removal. In our series of 231 patients, only a few patients appeared to “outgrow” their food allergy; however, recent evidence suggests that an increasing number of patients may develop “tolerance” if the food antigens are removed for a prolonged period of time (years) [35].

With regard to medical therapy, because of the possibility of secondary gastroesophageal reflux due to chronic esophageal inflammation, acid blockade is effective in improving patient’s symptoms. Recent adult literature suggests that proton pump inhibitor therapy may be associated with a significantly increased risk of hip fractures if used for more than 1 year [36]. Further research into the safety of long-term proton pump inhibition therapy in adults and children is needed, and the risk–benefit ratio of any medication should always be evaluated in the individual patient clinical context. Topical, swallowed fluticasone has been shown to be an effective treatment for EoE [28,30]. Unfortunately, when therapy is discontinued, EoE almost always recurs. While the long-term use of topical steroids appears reasonably safe, several side effects have been reported which include esophageal candidiasis, epistaxis, and dry mouth. In addition, long-term effects on growth, bone health, and esophageal fibrosis are currently not known. Finally, in the future, biologic therapy utilizing monoclonal antibodies such as anti-IL-5 shows promising results for both initial and maintenance therapy for patients with moderate to severe EoE. These agents are currently undergoing clinical trials [34].

Eosinophilic gastroenteritis (gastroenterocolitis)

Introduction

Eosinophilic gastroenteritis or gastroenterocolitis (EoG) is a general term that describes a constellation of symptoms and a pathologic infiltration of the GI tract by eosinophils. EoG was originally described by Kaijser in 1937 [37]. It is

a disorder characterized by tissue eosinophilia that can affect different layers of the bowel wall, anywhere from the mouth to the anus. In 1970, Klein classified EoG into three categories: mucosal, muscular, and serosal [38].

Definition

There are no strict diagnostic criteria for EoG, and its definition has been largely shaped by multiple case reports and case series. A combination of GI complaints with supportive histologic findings is sufficient to make the diagnosis of EoG and investigate the differential diagnosis (Table 15.4).

Prevalence

Currently, the prevalence of EoG is not known. Our clinical experience is that EoG occurs less frequently than inflammatory bowel disease in children (7 per 100,000 children) [39].

Table 15.4 Differential diagnosis of eosinophilic gastroenteritis

Celiac disease	
Chronic granulomatous disease	Infectious
	<i>Ancylostoma caninum</i> (hookworm)
	<i>Anisakis</i>
Connective tissue diseases/vasculitis	<i>Ascaris</i>
Systemic lupus erythematosus	EBV
Scleroderma	<i>Enterobius vermicularis</i> (pinworm)
Dermatomyositis	<i>Eustoma rotundatum</i>
Polymyositis	<i>Giardia lamblia</i>
Churg–Strauss syndrome	<i>Helicobacter pylori</i>
Polyarteritis nodosa	Schistosomiasis trichus
Others	Stercoalis
	Strongyloides
Food allergies	Toxocara canis
	Trichinella spiralis
Hypereosinophilic syndrome	Others
	Inflammatory bowel disease*
	Inflammatory fibroid polyp
	Malignancy
	Medications
	Azathioprine
	Carbamazepine
	Clofazimine
	Enalapril
	Gemfibrozil
	Gold
	Others [40,41]

Note this list is not exhaustive – case reports of other etiologies have been reported.

*In our experience, inflammatory bowel disease (often in young children) can initially manifest histologically as eosinophilia.

Etiology

The exact etiology of EoG remains unknown, although it is now recognized to occur as a result of both IgE- and non-IgE-mediated sensitivity [42]. The association between IgE-mediated inflammatory response (typical allergy) and EoG is supported by the increased likelihood of other allergic disorders such as atopic disease, food allergies, and seasonal allergies [43,44]. Specific foods have been implicated in the cause of EoG [45,46]. In contrast, the role of non-IgE-mediated immune dysfunction, in particular the interplay between lymphocyte-produced cytokines and eosinophils, has also received attention. IL-5 is a chemoattractant responsible for tissue eosinophilia [47]. Desreumaux *et al.* found that among patients with EoG, the levels of IL-3, IL-5, and granulocyte–macrophage colony stimulating factor (GM-CSF) were significantly increased as compared to control patients [48]. Once recruited to the tissue, eosinophils may further recruit similar cells through their own production of IL-3 and IL-5, as well as production of leukotrienes [49]. This mixed type of immune dysregulation in EoG has implications in the way this disorder is diagnosed, as well as in the way it is treated [50].

Clinical features

EoG affects patients of all ages, with a slight male predominance. Most commonly, eosinophils infiltrate only the mucosa, leading to symptoms associated with malabsorption, such as growth failure, weight loss, diarrhea, and hypoalbuminemia. Additional symptoms of EoG include colicky abdominal pain, bloating, dysphagia, and vomiting [51–53]. Other features of severe disease include GI bleeding, iron deficiency anemia, protein losing enteropathy (hypoalbuminemia), and growth failure [51]. Approximately 75% of affected patients have an elevated blood eosinophil levels [51]. Rarely, ascites can occur [54,55]. In addition, up to 50% of patients have a past or family history of atopy [56].

In an infant, EoG may present in a manner similar to hypertrophic pyloric stenosis, with progressive vomiting, dehydration, electrolyte abnormalities, and thickening of the gastric outlet [57,58]. When an infant presents with this constellation of symptoms, in addition to atopic symptoms such as eczema and reactive airway disease, an elevated eosinophil count, or a strong family history of atopic disease, then EoG should be considered before surgical intervention.

Uncommon presentations of EoG include an acute abdomen (even mimicking acute appendicitis), isolated ulceration, obstruction, or mass lesions [59–63]. There also have been reports of serosal infiltration with eosinophils, with associated abdominal distention, eosinophilic ascites, and bowel perforation [55,61,64–67].

Diagnosis

EoG should be considered in any patient with a history of chronic symptoms including vomiting, abdominal pain,

diarrhea, anemia, hypoalbuminemia, or poor weight gain in combination with the presence of eosinophils in the GI tract. The number of eosinophils that are defined as abnormal depends on the location in the GI tract, and has geographic variability [68,69].

A number of tests may aid in the diagnosis of EoG, however no single test is pathognomonic and there are no standards for diagnosis. Eosinophils in the GI tract must be documented before EoG can be truly entertained as a diagnosis. This is most readily done with biopsies of the upper GI tract through esophagogastroduodenoscopy and the lower tract through colonoscopy with terminal ileal intubation. In our experience, inflammatory bowel disease is an important entity in the differential diagnosis, and eosinophilia can be the initial presentation especially in young children. Mucosal EoG may affect any portion of the GI tract. A review of the biopsy findings in 38 children with EoG revealed that all patients examined had mucosal eosinophilia of the gastric antrum [56]. Seventy-nine percent of the patients also demonstrated eosinophilia of the proximal small intestine, with 60% having esophageal involvement, and 52% having involvement of the gastric corpus. Those with colonic involvement tended to be under 6 months of age and were ultimately classified as having allergic colitis.

Radiographic contrast studies may demonstrate mucosal irregularities or edema, wall thickening, ulceration, or luminal narrowing. A lacy mucosal pattern of the gastric antrum known as *areae gastricae* is a unique finding that may be present in patients with EoG [70].

Evaluation of other causes of eosinophilia should be undertaken that include parasitic infection, inflammatory bowel disease, neoplasm, chronic granulomatous disease, collagen vascular disease, and the hypereosinophilic syndrome [71–75] (Table 15.4). Specifically, consultations with an allergist, gastroenterologist, infectious disease specialist, and rheumatologist should be obtained. Signs of intestinal obstruction warrant abdominal imaging and surgical consultation.

Laboratory evaluation

In contrast to EoE, peripheral eosinophilia or an elevated IgE level occurs in approximately 70% of affected individuals [76]. Allergic investigation is the same as for patients with EoE, however it is less often revealing. Infectious work-up should include stool ova and parasite testing on three separate stool samples, serum (and possibly tissue) EBV PCR, giardia antigen, and *Helicobacter pylori* testing [77–82]. Rheumatologic testing should be considered in the appropriate clinical context [83,84]. Measures of absorptive activity such as the D-xylose absorption test and lactose hydrogen breath testing may reveal evidence of malabsorption, reflecting small intestinal damage. Inflammatory bowel disease serologies may also be considered, but with the recognition that they have limited sensitivity especially

in younger children [85,86]. Negative anti-Saccharomyces cerevisiae (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) do not exclude the diagnosis of inflammatory bowel disease.

Treatment

Acute management

Since EoG is a rare and difficult disease to diagnose, randomized trials for its treatment are lacking and there is considerable debate as to which treatment is best.

Food allergy is considered one of the underlying causes of EoG, and its management is the same as described previously for EoE. In some cases, the administration of a strict diet, utilizing an elemental formula, has been shown to be successful [44,87,88]. Unfortunately, unlike EoE, elemental diets are not uniformly successful for patients with EoG.

When the use of a restricted diet fails, corticosteroids are often employed due to their high likelihood of success in attaining remission [52]. However, when weaned, the duration of remission is variable and can be short-lived, leading to the need for repeated courses or continuous low doses of steroids [89]. In addition, the chronic use of corticosteroids carries an increased likelihood of undesirable side effects, including cosmetic problems (cushingoid facies, hirsutism, acne), decreased bone density, impaired growth, and personality changes. A response to these side effects has been to look for substitutes that may act as steroid-sparing agents, while still allowing for control of symptoms. Budesonide (Entocort®) is a steroid formulation with less systemic toxicity that has been successful for some patients with EoG [90,91].

Orally administered cromolyn sodium has been used with some success [51,91–94], and recent reports have detailed the efficacy of other oral anti-inflammatory medications. Montelukast, a selective leukotriene receptor antagonist used to treat asthma, has been reported to be successful in the treatment of two patients with EoG [95–97]. Treatment of EoG with inhibition of leukotriene D₄, a potent chemotactic factor for eosinophils, relies on the theory that the inflammatory response in EoG is perpetuated by the presence of eosinophils already present in the mucosa. Suplatast tosilate and ketotifen have also been reported as treatments for EoG [98,99]. Anti-IL-5 therapy for EoG is also being investigated.

Long-term management

As with EoE, every attempt should be made to identify and restrict potential food allergens in a stepwise approach. Given the limited possibilities for treatment of EoG, the combination of therapies incorporating the best chance of success with the smallest likelihood of side effects should be employed.

When other treatments fail, corticosteroids remain a reliable treatment for EoG, with attempts at limiting the total dose, or the number of treatment courses where possible. Due to the diffused and inconsistent nature of symptoms

in this disease, serial endoscopy with biopsy is a useful and important modality for monitoring disease progression. Particularly in younger children, protean manifestations of inflammatory bowel disease should be considered with every endoscopy.

Eosinophilic proctocolitis

Introduction

Eosinophilic proctocolitis (EoP), also known as allergic proctocolitis or milk-protein proctocolitis, has been recognized as one of the most common etiologies of rectal bleeding in infants [56,100]. This disorder is characterized by the onset of rectal bleeding, generally in children less than 2 months of age.

Definition

EoP is strictly defined as an abnormal number of eosinophils confined to the colon. However, in clinical practice, endoscopy is usually not performed. The diagnosis is established when infants present with rectal bleeding that resolves when placed on a protein hydrolysate formula.

Prevalence

It is felt that up to 7.5% of the population in developed countries exhibit cow's milk allergy, although there is wide variation in the reported data [101–103]. Soy-protein allergy is felt to be less common than cow's milk allergy, with a reported prevalence of approximately 0.5% [103]. However, soy-protein intolerance becomes more prominent in individuals who have developed milk-protein-induced proctocolitis, with a prevalence from 15% to 50% or more in milk-protein-sensitized individuals [105].

Etiology

The GI tract plays a major role in the development of oral tolerance to foods. Through the process of endocytosis by the enterocytes, food antigens are generally degraded into non-antigenic proteins [106,107]. Although the GI tract serves as an efficient barrier to ingested food antigens, this barrier may not be mature for the first few months of life [108]. As a result, ingested antigens may have an increased propensity for being presented intact to the immune system. These intact antigens have the potential for stimulating the immune system, and driving an inappropriate response directed at the GI tract. Because the major component of the young infant's diet is milk or formula, it stands to reason that the inciting antigens in EoP are derived from the proteins found in them. Cow's milk and soy proteins are the foods most frequently implicated in EoP.

Commercially available infant formulas most commonly utilize cow's milk as the protein source. There are at least 25 known immunogenic proteins within cow's

milk, with the caseins and β -lactoglobulin serving as the most antigenic [104]. For this reason, substitution of a soy-protein-based formula for a milk-protein-based formula in patients with suspected milk-protein proctocolitis is often unsuccessful. However, because of the expense of protein hydrolysate formulas, practitioners may attempt to use soy formulas initially.

Maternal breast milk represents a different challenge to the immune system. Up to 50% of the cases of EoP occur in breast-fed infants; but, rather than developing an allergy to human milk protein, it is felt that the infants are manifesting allergy to antigens ingested by the mother and transferred via the breast milk. The transfer of maternal dietary protein via breast milk was first demonstrated in 1921 [109]. More recently, the presence of cow's milk antigens in breast milk has been established [110–112].

When a problem with antigen handling occurs, whether secondary to increased absorption through an immature GI tract or through a damaged epithelium secondary to gastroenteritis, sensitization of the immune system results. Once sensitized, the inflammatory response is perpetuated with continued exposure to the inciting antigen. This may explain the reported relationship between early exposures to cow's milk protein or viral gastroenteritis and the development of allergy [113–115].

Clinical manifestations

Diarrhea, rectal bleeding, and increased mucus production are the typical symptoms seen in patients who present with EoP [56,116]. There is a bimodal age distribution with the majority of patients presenting in infancy (mean age at diagnosis of 60 days) and the other group presenting in adolescence and early adulthood [117].

The typical infant with EoP is well appearing with no constitutional symptoms. Rectal bleeding begins gradually, initially appearing as small flecks of blood. Usually, increased stool frequency occurs accompanied by water loss or mucus streaks. The development of irritability or straining with stools is also common and can falsely lead to the initial diagnosis of anal fissuring. Atopic symptoms such as eczema and reactive airway disease may be associated. Continued exposure to the inciting antigen causes increased bleeding and may, on rare occasions, cause anemia or poor weight gain. Despite the progression of symptoms, the infants are generally well appearing. Other manifestations of GI tract inflammation such as vomiting, abdominal distention, or weight loss almost never occur (Table 15.5).

Diagnosis

EoP is primarily a clinical diagnosis, although several laboratory parameters and diagnostic procedures may be useful. Initial assessment should be directed at the overall health of the child. A toxic appearing infant is not consistent with

Table 15.5 Characteristics of eosinophilic proctocolitis

• Clinical symptoms
– Blood streaked stools
– Diarrhea
– Mild abdominal pain
– <3 months of age
– Usually normal weight gain
– Well appearing
– Eczema, atopy – rare
• Laboratory features
– Fecal leukocytes, eosinophils
– Mild peripheral eosinophilia
– Rarely
• Hypoalbuminemia
• Anemia
– Pin prick, RAST testing negative (usually not needed)

the diagnosis of EoP and should prompt evaluation for other causes of GI bleeding. Stool studies for bacterial pathogens, such as *Salmonella* and *Shigella*, should be performed in the setting of rectal bleeding. In particular, an assay for *Clostridium difficile* toxins A and B should also be considered. While *C. difficile* may cause colitis, infants may be asymptotically colonized with this organism [118,119]. A stool specimen may be analyzed for the presence of white blood cells, and specifically for eosinophils. The sensitivity of these tests is not well documented, and the absence of a positive finding on these tests does not exclude the diagnosis [120]. Eosinophils can also accumulate in the colon in other conditions such as pin and hookworm infections, drug reactions, vasculitis, and inflammatory bowel disease. Depending on the clinical situation, it may be important to exclude these diagnoses especially in older children.

Although not always necessary, flexible sigmoidoscopy may be useful to demonstrate the presence of colitis. Visually, one may find erythema, friability, or frank ulceration of the colonic mucosa. Alternatively, the mucosa may appear normal, or show evidence of lymphoid hyperplasia [121,122]. Histologic findings typically include increased eosinophils in focal aggregates within the lamina propria, with generally preserved crypt architecture. Findings may be patchy, so that care should be taken to examine many levels of each specimen if necessary [123,124].

Laboratory evaluation

A complete blood count is useful, as the majority of infants with EoP have a normal or borderline low hemoglobin. An elevated serum eosinophil count may be present. A stool smear for eosinophils (Wright stain) may also support the diagnosis. Stool cultures for ova and parasites, bacteria, and *Clostridium difficile* toxins should be obtained in the appropriate clinical setting.

Treatment

Acute management

In a well-appearing patient with a history consistent with EoP, it is acceptable to make an empiric formula change. Given the high degree of reactivity to both milk and soy protein in sensitized individuals, a protein hydrolysate formula is often the best choice [114]. However, in mild cases, soy formulas may be attempted initially given the expense of protein hydrolysate formulas. Resolution of symptoms begins almost immediately after the elimination of the problematic food. Although symptoms may linger for several days to weeks, continued improvement is the rule. If symptoms do not quickly improve or persist beyond 4–6 weeks, other antigens should be considered, as well as other potential causes of rectal bleeding. In breast-fed infants, dietary restriction of milk and soy-containing products for the mother may result in improvement; however, care should be taken to ensure that the mother maintains adequate protein and calcium intake from other sources.

Long-term management

EoP in infancy is generally benign and withdrawing the milk-protein trigger resolves the condition. Though gross blood in the stool usually disappears within 72 hours, occult blood loss may persist for longer [117]. The prognosis is excellent and the majority of patients are able to tolerate the introduction of the responsible milk protein by 1–3 years of age. Given the unlikely possibility of an allergic reaction following milk reintroduction, milk challenges should be performed in a physician's office at 1 year of age. If a reaction does occur, infants are typically rechallenged at 15 months of age and then referred to an allergist. The prognosis for older onset EoP is less favorable than the infant presentation and is typically chronic and relapsing.

References

- 1 Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–1.
- 2 Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006;91:1000–4.
- 3 Ronkainen J, Talley NJ, Aro P, *et al.* Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2006;56:615–20.
- 4 Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363–8.
- 5 Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003;125:1419–27.
- 6 Kelly KJ, Lazenby AJ, Rowe PC, *et al.* Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–12.

- 7 Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83–90.
- 8 Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796–7.
- 9 Liacouras CA, Markowitz JE. Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis. *Curr Gastroenterol Rep* 1999;1:253–8.
- 10 Liacouras CA. Failed Nissen fundoplication in two patients who had persistent vomiting and eosinophilic esophagitis. *J Pediatr Surg* 1997;32:1504–6.
- 11 Ruchelli E, Wenner W, Voytek T, et al. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15–18.
- 12 Steiner SJ, Gupta SK, Croffie JM, Fitzgerald JF. Correlation between number of eosinophils and reflux index on same day esophageal biopsy and 24 hour esophageal pH monitoring. *Am J Gastroenterol* 2004;99:801–5.
- 13 Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660–9.
- 14 Katzka DA. Eosinophilic esophagitis. *Curr Treat Options Gastroenterol* 2003;6:49–54.
- 15 Orenstein SR, Shalaby TM, Di Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422–30.
- 16 Fox VL, Nurko S, Teitelbaum JE, et al. High-resolution EUS in children with eosinophilic “allergic” esophagitis. *Gastrointest Endosc* 2003;57:30–6.
- 17 Konikoff MR, Blanchard C, Kirby C, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1328–36.
- 18 Spergel JM, Brown-Whitehorn T, Beausoleil JL, et al. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:509–11.
- 19 Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus – peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006;101:1666–70.
- 20 Straumann A, Rossi L, Simon HU, et al. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? *Gastrointest Endosc* 2003;57:407–12.
- 21 Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. *Clin Gastroenterol Hepatol* 2003;1:433–7.
- 22 Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc* 2003;58:516–22.
- 23 Lucendo AJ, De Rezende L. Endoscopic dilation in eosinophilic esophagitis: a treatment strategy associated with a high risk of perforation. *Endoscopy* 2007;39:376;author reply 7.
- 24 Eisenbach C, Merle U, Schirmacher P, et al. Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis. *Endoscopy* 2006;38:E43–4.
- 25 Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380–5.
- 26 Faubion Jr WA, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;27:90–3.
- 27 Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003;78:830–5.
- 28 Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;2:568–75.
- 29 Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* 2006;63:3–12.
- 30 Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–91.
- 31 Aceves SS, Dohil R, Newbury RO, Bastian JF. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005;116:705–6.
- 32 Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198–206.
- 33 Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–43.
- 34 Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312–19.
- 35 Liacouras CA. Eosinophilic esophagitis: treatment in 2005. *Curr Opin Gastroenterol* 2006;22:147–52.
- 36 Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947–53.
- 37 Kaijser R. Zur Kenntnis der allergischen Affektionen des imma Verdanungskanal von Standpunkt desma Chirurgen aus. *Arch Klin Chir* 1937;188:36–64.
- 38 Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine (Baltimore)* 1970;49:299–319.
- 39 Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;143:525–31.
- 40 Barak N, Hart J, Sitrin MD. Enalapril-induced eosinophilic gastroenteritis. *J Clin Gastroenterol* 2001;33:157–8.
- 41 Kakumitsu S, Shijo H, Akiyoshi N, et al. Eosinophilic enteritis observed during alpha-interferon therapy for chronic hepatitis C. *J Gastroenterol* 2000;35:548–51.

- 42 Spergel JM, Pawlowski NA. Food allergy. Mechanisms, diagnosis, and management in children. *Pediatr Clin North Am* 2002;49:73–96, vi.
- 43 Park HS, Kim HS, Jang HJ. Eosinophilic gastroenteritis associated with food allergy and bronchial asthma. *J Korean Med Sci* 1995;10:216–19.
- 44 Justinich C, Katz A, Gurbindo C, *et al*. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996;23:81–5.
- 45 Leinbach GE, Rubin CE. Eosinophilic gastroenteritis: a simple reaction to food allergens? *Gastroenterology* 1970;59:874–89.
- 46 Caldwell JH, Sharma HM, Hurtubise PE, Colwell DL. Eosinophilic gastroenteritis in extreme allergy. Immunopathological comparison with nonallergic gastrointestinal disease. *Gastroenterology* 1979;77:560–4.
- 47 Kelso A. Cytokines: structure, function and synthesis. *Curr Opin Immunol* 1989;2:215–25.
- 48 Desreumaux P, Bloget F, Seguy D, *et al*. Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. *Gastroenterology* 1996;110:768–74.
- 49 Takafuji S, Bischoff SC, De Weck AL, Dahinden CA. IL-3 and IL-5 prime normal human eosinophils to produce leukotriene C4 in response to soluble agonists. *J Immunol* 1991;147:3855–61.
- 50 Kweon MN, Kiyono H. Eosinophilic gastroenteritis: a problem of the mucosal immune system? *Curr Allergy Asthma Rep* 2003;3:79–85.
- 51 Kelly KJ. Eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr* 2000;30:S28–35.
- 52 Whittington PF, Whittington GL. Eosinophilic gastroenteropathy in childhood. *J Pediatr Gastroenterol Nutr* 1988;7:379–85.
- 53 Khan S. Eosinophilic gastroenteritis. *Best Pract Res Clin Gastroenterol* 2005;19:177–98.
- 54 Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990;31:54–8.
- 55 Santos J, Junquera F, de Torres I, *et al*. Eosinophilic gastroenteritis presenting as ascites and splenomegaly. *Eur J Gastroenterol Hepatol* 1995;7:675–8.
- 56 Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;10:75–86.
- 57 Aquino A, Domini M, Rossi C, *et al*. Pyloric stenosis due to eosinophilic gastroenteritis: presentation of two cases in mono-ovular twins. *Eur J Pediatr* 1999;158:172–3.
- 58 Khan S, Orenstein SR. Eosinophilic gastroenteritis masquerading as pyloric stenosis. *Clin Pediatr (Phila)* 2000;39:55–7.
- 59 Redondo-Cerezo E, Cabello MJ, Gonzalez Y, *et al*. Eosinophilic gastroenteritis: our recent experience: one-year experience of atypical onset of an uncommon disease. *Scand J Gastroenterol* 2001;36:1358–60.
- 60 Shweiki E, West JC, Klena JW, *et al*. Eosinophilic gastroenteritis presenting as an obstructing cecal mass – a case report and review of the literature. *Am J Gastroenterol* 1999;94:3644–5.
- 61 Huang FC, Ko SE, Huang SC, Lee SY. Eosinophilic gastroenteritis with perforation mimicking intussusception. *J Pediatr Gastroenterol Nutr* 2001;33:613–15.
- 62 Siahianidou T, Mandyla H, Dimitriadis D, *et al*. Eosinophilic gastroenteritis complicated with perforation and intussusception in a neonate. *J Pediatr Gastroenterol Nutr* 2001;32:335–7.
- 63 Markowitz JE, Russo P, Liacouras CA. Solitary duodenal ulcer: a new presentation of eosinophilic gastroenteritis. *Gastrointest Endosc* 2000;52:673–6.
- 64 Deslandres C, Russo P, Gould P, Hardy P. Perforated duodenal ulcer in a pediatric patient with eosinophilic gastroenteritis. *Can J Gastroenterol* 1997;11:208–12.
- 65 Wang CS, Hsueh S, Shih LY, Chen MF. Repeated bowel resections for eosinophilic gastroenteritis with obstruction and perforation. Case report. *Acta Chir Scand* 1990;156:333–6.
- 66 Hoefer RA, Ziegler MM, Koop CE, Schnaufer L. Surgical manifestations of eosinophilic gastroenteritis in the pediatric patient. *J Pediatr Surg* 1977;12:955–62.
- 67 Lerza P. A further case of eosinophilic gastroenteritis with ascites. *Eur J Gastroenterol Hepatol* 1996;8:407.
- 68 Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 1996;9:110–14.
- 69 Pascal RR, Gramlich TL, Parker KM, Gansler TS. Geographic variations in eosinophil concentration in normal colonic mucosa. *Mod Pathol* 1997;10:363–5.
- 70 Teele RL, Katz AJ, Goldman H, Kettell RM. Radiographic features of eosinophilic gastroenteritis (allergic gastroenteropathy) of childhood. *Am J Roentgenol* 1979;132:575–80.
- 71 DeSchryver-Kecskemeti K, Clouse RE. A previously unrecognized subgroup of “eosinophilic gastroenteritis”. Association with connective tissue diseases. *Am J Surg Pathol* 1984;8:171–80.
- 72 Dubucquoi S, Janin A, Klein O, *et al*. Activated eosinophils and interleukin 5 expression in early recurrence of Crohn’s disease. *Gut* 1995;37:242–6.
- 73 Levy AM, Yamazaki K, Van Keulen VP, *et al*. Increased eosinophil infiltration and degranulation in colonic tissue from patients with collagenous colitis. *Am J Gastroenterol* 2001;96:1522–8.
- 74 Griscom NT, Kirkpatrick Jr JA, Girdany BR, *et al*. Gastric antral narrowing in chronic granulomatous disease of childhood. *Pediatrics* 1974;54:456–60.
- 75 Harris BH, Boles Jr ET. Intestinal lesions in chronic granulomatous disease of childhood. *J Pediatr Surg* 1973;8:955–6.
- 76 Caldwell JH, Tennenbaum JI, Bronstein HA. Serum IgE in eosinophilic gastroenteritis. Response to intestinal challenge in two cases. *N Engl J Med* 1975;292:1388–90.
- 77 Tsiouris P, Galeas T, Moussia M, *et al*. Two cases of eosinophilic gastroenteritis and malabsorption due to *Enterobius vermicularis*. *Dig Dis Sci* 2005;50:2389–92.
- 78 Chira O, Badea R, Dumitrascu D, *et al*. Eosinophilic ascites in a patient with toxocara canis infection. A case report. *Rom J Gastroenterol* 2005;14:397–400.

- 79 Van Laethem JL, Jacobs F, Braude P, *et al.* Toxocara canis infection presenting as eosinophilic ascites and gastroenteritis. *Dig Dis Sci* 1994;39:1370–2.
- 80 Papadopoulos AA, Tzathas C, Polymeros D, Ladas SD. Symptomatic eosinophilic gastritis cured with *Helicobacter pylori* eradication. *Gut* 2005;54:1822.
- 81 Montalto M, Miele L, Marcheggiano A, *et al.* Anisakis infestation: a case of acute abdomen mimicking Crohn's disease and eosinophilic gastroenteritis. *Dig Liver Dis* 2005;37:62–4.
- 82 Koga M, Fujiwara M, Hotta N, *et al.* Eosinophilic gastroenteritis associated with Epstein–Barr virus infection in a young boy. *J Pediatr Gastroenterol Nutr* 2001;33:610–12.
- 83 Sunkureddi PR, Baethge BA. Eosinophilic gastroenteritis associated with systemic lupus erythematosus. *J Clin Gastroenterol* 2005;39:838–9.
- 84 Schwake L, Stremmel W, Sergi C. Eosinophilic enterocolitis in a patient with rheumatoid arthritis. *J Clin Gastroenterol* 2002;34:487–8.
- 85 Reese GE, Constantinides VA, Simillis C, *et al.* Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006;101:2410–22.
- 86 Mamula P, Telega GW, Markowitz JE, *et al.* Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002;97:2005–10.
- 87 Vandenplas Y, Quenon M, Renders F, *et al.* Milk-sensitive eosinophilic gastroenteritis in a 10-day-old boy. *Eur J Pediatr* 1990;149:244–5.
- 88 Chehade M, Magid MS, Mofidi S, *et al.* Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr* 2006;42:516–21.
- 89 Chen MJ, Chu CH, Lin SC, *et al.* Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol* 2003;9:2813–16.
- 90 Siewert E, Lammert F, Koppitz P, *et al.* Eosinophilic gastroenteritis with severe protein-losing enteropathy: successful treatment with budesonide. *Dig Liver Dis* 2006;38:55–9.
- 91 Tan AC, Kruiemel JW, Naber TH. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. *Eur J Gastroenterol Hepatol* 2001;13:425–7.
- 92 Van Dellen RG, Lewis JC. Oral administration of cromolyn in a patient with protein-losing enteropathy, food allergy, and eosinophilic gastroenteritis. *Mayo Clin Proc* 1994;69:441–4.
- 93 Moots RJ, Prouse P, Gumpel JM. Near fatal eosinophilic gastroenteritis responding to oral sodium chromoglycate. *Gut* 1988;29:1282–5.
- 94 Di Gioacchino M, Pizzicannella G, Fini N, *et al.* Sodium cromoglycate in the treatment of eosinophilic gastroenteritis. *Allergy* 1990;45:161–6.
- 95 Schwartz DA, Pardi DS, Murray JA. Use of montelukast as steroid-sparing agent for recurrent eosinophilic gastroenteritis. *Dig Dis Sci* 2001;46:1787–90.
- 96 Neustrom MR, Friesen C. Treatment of eosinophilic gastroenteritis with montelukast. *J Allergy Clin Immunol* 1999;104:506.
- 97 Urek MC, Kujundzic M, Banic M, *et al.* Leukotriene receptor antagonists as potential steroid sparing agents in a patient with serosal eosinophilic gastroenteritis. *Gut* 2006;55:1363–4.
- 98 Shirai T, Hashimoto D, Suzuki K, *et al.* Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J Allergy Clin Immunol* 2001;107:924–5.
- 99 Katsinelos P, Pilpilidis I, Xiarchos P, *et al.* Oral administration of ketotifen in a patient with eosinophilic colitis and severe osteoporosis. *Am J Gastroenterol* 2002;97:1072–4.
- 100 Jenkins HR, Pincott JR, Soothill JF, *et al.* Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984;59:326–9.
- 101 Gerrard JW, MacKenzie JW, Goluboff N, *et al.* Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand Suppl* 1973;234:1–21.
- 102 Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45:587–96.
- 103 Strobel S. Epidemiology of food sensitivity in childhood – with special reference to cow's milk allergy in infancy. *Monogr Allergy* 1993;31:119–30.
- 104 Simpser E. Gastrointestinal allergy. In: Altschuler SM, Liacouras CA (eds.) *Clinical Pediatric Gastroenterology*. Philadelphia, PA: Churchill Livingstone, 1998:113–18.
- 105 Eastham EJ. Soy protein allergy. In: Hamburger RN (ed.) *Allergology, Immunology, and Gastroenterology*. New York: Raven Press, 1989:223–36.
- 106 Heyman M, Grasset E, Ducroc R, Desjeux JF. Antigen absorption by the jejunal epithelium of children with cow's milk allergy. *Pediatr Res* 1988;24:197–202.
- 107 Husby S, Host A, Teisner B, Svehag SE. Infants and children with cow milk allergy/intolerance. Investigation of the uptake of cow milk protein and activation of the complement system. *Allergy* 1990;45:547–51.
- 108 Kerner Jr JA. Formula allergy and intolerance. *Gastroenterol Clin North Am* 1995;24:1–25.
- 109 Shannon WR. Demonstration of food proteins in human breast milk by anaphylactic experiments in guinea pig. *Am J Dis Child* 1921;22:223–5.
- 110 Makinen-Kiljunen S, Palosuo T. A sensitive enzyme-linked immunosorbent assay for determination of bovine beta-lactoglobulin in infant feeding formulas and in human milk. *Allergy* 1992;47:347–52.
- 111 Axelsson I, Jakobsson I, Lindberg T, Benediktsson B. Bovine beta-lactoglobulin in the human milk. A longitudinal study during the whole lactation period. *Acta Paediatr Scand* 1986;75:702–7.
- 112 Pittschieler K. Cow's milk protein-induced colitis in the breast-fed infant. *J Pediatr Gastroenterol Nutr* 1990;10:548–9.

- 113 Vandenplas Y, Hauser B, Van den Borre C, *et al.* Effect of a whey hydrolysate prophylaxis of atopic disease. *Ann Allergy* 1992;68:419–24.
- 114 Juvonen P, Mansson M, Jakobsson I. Does early diet have an effect on subsequent macromolecular absorption and serum IgE? *J Pediatr Gastroenterol Nutr* 1994;18:344–9.
- 115 Kaczmarek M, Kurzatowska B. The contribution of some environmental factors to the development of cow's milk and gluten intolerance in children. *Rocz Akad Med Białymst* 1988;33–34:151–65.
- 116 Katz AJ, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984;74:72–8.
- 117 Hill SM, Milla PJ. Colitis caused by food allergy in infants. *Arch Dis Child* 1990;65:132–3.
- 118 Donta ST, Myers MG. *Clostridium difficile* toxin in asymptomatic neonates. *J Pediatr* 1982;100:431–4.
- 119 Cooperstock MS, Steffen E, Yolken R, Onderdonk A. *Clostridium difficile* in normal infants and sudden infant death syndrome: an association with infant formula feeding. *Pediatrics* 1982;70:91–5.
- 120 Hirano K, Shimojo N, Katsuki T, *et al.* Eosinophils in stool smear in normal and milk-allergic infants. *Arerugi* 1997;46:594–601.
- 121 Anveden-Hertzberg L, Finkel Y, Sandstedt B, Karpe B. Proctocolitis in exclusively breast-fed infants. *Eur J Pediatr* 1996;155:464–7.
- 122 Odze RD, Bines J, Leichtner AM, *et al.* Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. *Hum Pathol* 1993;24:668–74.
- 123 Machida HM, Catto Smith AG, Gall DG, *et al.* Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr* 1994;19:22–6.
- 124 Goldman H. Allergic disorders. In: Ming S-C, Goldman H (eds.) *Pathology of the Gastrointestinal Tract*. Philadelphia, PA: WB Saunders, 1992:171–87.