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Eosinophilic Gastrointestinal Disorders



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INTRODUCTION

The eosinophilic gastroenteropathies are an interesting, yet somewhat poorly defined set of disorders that by definition include the infiltration of at least one layer of the gastrointestinal (GI) tract with eosinophils. First reported over 50 years ago, the clinical spectrum of these disorders was defined solely by various case reports. As these reports became more frequent, various aspects of the disease became better described and stratified. Additional insight into the role of the eosinophil in health and disease has allowed further description of these disorders with respect to the underlying defect that drives the inflammatory response in those afflicted (Table 1). Perhaps, most important to the definition has been the understanding of the heterogeneity of the sites affected within the gastrointestinal tract. Within the broad classification of these disorders lie at least three clinical entities that are defined in large part by the presence of abnormal num-

bers of eosinophils in various GI sites: eosinophilic proctocolitis (EP), eosinophilic gastroenteritis (EG), and eosinophilic esophagitis (EE) (Table 2).

EOSINOPHILIC PROCTOCOLITIS (EP)

Eosinophilic Proctocolitis, also known as allergic proctocolitis or milk-protein proctocolitis, has been recognized as one of the most common etiologies of rectal bleeding in infants (1). This disorder is characterized by the onset of rectal bleeding, generally in children less than six months of age.

Epidemiology/Etiology

The GI tract plays a major role in the development of oral tolerance to foods. Through the process of endocytosis by the enterocyte, food antigens are generally degraded into non-antigenic proteins (2). 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 (3). 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,

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Table 1
Causes of Tissue Eosinophilia

Gastrointestinal

- Eosinophilic esophagitis
- Gastroesophageal reflux
- Eosinophilic gastroenteritis
- Eosinophilic colitis
- Crohn's disease
- Menetrier's disease

Infectious

- Parasitic disease
- Scarlet fever
- Erythema multiforme

Autoimmune/Immunologic

- Chronic granulomatous disease
- Vasculitis
- Hyper IgE syndrome
- Idiopathic hypereosinophilic syndrome
- Polyarteritis nodosa

Hematologic

- Leukemia
- Post-splenectomy
- Hodgkin's disease

Allergy

- Food allergy
- Environmental allergy
- Asthma

Dermatologic

- Pemphigus
- Dermatitis herpetiformis

Other

- Poisons (Black widow spider bite)
- Sarcoid
- Oral gold therapy
- Post-irradiation

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 (4,5). Soy protein allergy is felt to be less common than cow's milk allergy, with reported prevalence of approximately 0.5%. Soy protein intolerance becomes more prominent in individuals who have developed milk protein allergy, as there is significant cross-reactivity between these proteins, with prevalence from 15% to 50% or more in milk protein sensitized individuals (6). 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.

Maternal breast milk represents a different challenge to the immune system. Up to 50% of the cases of EP 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 (7). More recently, the presence of cow's milk antigens in breast milk has been established (8). When a problem with antigen handling occurs, whether secondary to increased absorption through an immature GI tract, or because of 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 (9).

Clinical Features

Diarrhea, rectal bleeding and increased mucus production are the typical symptoms seen in patients who present with EP (10). In a well-appearing infant, rectal bleeding often 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

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 EP are derived from the proteins found in these foods.

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 and rarely appear ill. Other manifestations of GI tract inflammation, such as vomiting, abdominal distention, or weight loss almost never occur.

Differential Diagnosis

EP 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 the diagnosis of EP and should prompt evaluation for other causes of gastrointestinal bleeding. A complete blood count is useful, as the majority of infants with EP have normal hemoglobin. An elevated serum eosinophil count may be present. 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 & B should also be considered. While *C. difficile* may cause colitis, infants may be asymptotically colonized with this organism (11). 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 (12).

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(13). Histologic findings typically include increased eosinophils 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(14).

Treatment

In a well appearing patient with a history consistent with EP, it is acceptable to make an empiric change in the protein source of the formula. Because of the high degree of cross-reactivity between milk and soy protein

Table 2

Definitions of Eosinophilic Gastroenteritis, Eosinophilic Colitis and Eosinophilic Esophagitis

Eosinophilic Gastroenteritis

- Gastrointestinal eosinophilia in 2 or more locations of the gastrointestinal tract:

Esophagus	>15 per HPF
Stomach	>10 per HPF
Duodenum	>10 per HPF
Right Colon	>20 per HPF
Left Colon	>10 per HPF

Eosinophilic colitis

- Eosinophilia limited to the colon
- Exclude other causes (parasites, IBD, medications, systemic disorders)

Eosinophilic Esophagitis

- Clinico-pathologic diagnosis
- Isolated esophageal eosinophilia
- >15 eosinophils in the most densely involved 40× HPF
- Unresponsive to aggressive acid blockade
- Clinically:
 - GERD symptoms, dysphagia
 - Exclude other possible causes (GERD, infectious, medication)
 - Responds to the elimination of food

in sensitized individuals, a protein-hydrolysate formula is often the best choice (9). 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 four to six 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.

EOSINOPHILIC GASTROENTERITIS (EG)

Eosinophilic Gastroenteritis is a general term that describes a constellation of symptoms attributable to

the GI tract, in combination with pathologic infiltration by eosinophils. Shaped in large part by case reports and series over the years, there are no strict diagnostic criteria for this disorder. Rather, a combination of gastrointestinal complaints with supportive histologic findings is sufficient to make the diagnosis. EG was originally described by Kaijser in 1937 (15). It is a disorder characterized by tissue eosinophilia that can affect different layers of the bowel wall, anywhere from mouth to anus. The gastric antrum and small bowel are frequently affected. In 1970, Klein classified EG into three categories: a mucosal, muscular and serosal form (16).

Epidemiology/Etiology

EG 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. Mucosal EG may affect any portion of the GI tract. The exact etiology of EG remains unknown, although it is now recognized as a result of both IgE and non-IgE mediated sensitivity (17). Specific foods have been implicated in the cause of EG (18). Speculation has also surrounded the role of non-IgE mediated immune dysfunction, specifically, the interplay between lymphocyte-produced cytokines and eosinophils. Interleukin (IL)-5 is a chemoattractant responsible for tissue eosinophilia (19). Desreumaux, et al found that among patients with EG, the levels of IL-3, IL-5, and granulocyte-macrophage colony stimulating factor (GM-CSF) were significantly increased as compared to control patients (20). 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. This mixed type of immune dysregulation in EG has implications in the way this disorder is diagnosed, as well as the way it is treated.

Clinical Features

The most common symptoms of EG include colicky abdominal pain, bloating, diarrhea, weight loss, dysphagia and vomiting (21). In addition, up to 50% have

a past or family history of atopy. Other features of severe disease include gastrointestinal bleeding, iron deficiency anemia, protein losing enteropathy (hypoalbuminemia) and growth failure (22). Approximately 75% of affected patients have an elevated blood eosinophilia. Males are more commonly affected than females. Rarely, ascites can occur (23).

Differential Diagnosis

EG should be considered in any aged patient who presents with a chronic history of vomiting, abdominal pain, diarrhea, anemia, hypoalbuminemia, or poor weight gain in combination with the presence of eosinophils in the GI tract. As identified in Table 1, other causes of eosinophilic infiltration of the GI tract include the other disorders of the eosinophilic gastroenteropathy spectrum (EP, EE), as well as parasitic infection, inflammatory bowel disease, neoplasm, chronic granulomatous disease, collagen vascular disease and the hypereosinophilic syndrome (24).

In an infant, EG may present in a manner similar to hypertrophic pyloric stenosis, with progressive vomiting, dehydration, electrolyte abnormalities, and thickening of the gastric outlet (25). 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 EG should be considered in the diagnosis before surgical intervention if possible. Uncommon presentations of EG include acute abdomen, colonic obstruction, serosal eosinophilic infiltration, abdominal distention, eosinophilic ascites, and bowel perforation (26–28).

Evaluation

When EG is suspected, there are a number of tests that may aid in the diagnosis, however no single test is pathognomonic. Before EG can be truly entertained as a diagnosis, the presence of eosinophils in the GI tract must be documented. This is most readily done with biopsies of either the upper GI tract through esophagogastroduodenoscopy or the lower GI tract through

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flexible sigmoidoscopy or colonoscopy. A history of atopy is supportive of the diagnosis, but is not a necessary feature. Blood evaluation may demonstrate an elevated peripheral eosinophil count or IgE level in approximately 70% of affected individuals (29). 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. 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 EG (30).

Evaluation of other causes of eosinophilia should be undertaken, including stool analysis for ova and parasites. Signs of intestinal obstruction warrant abdominal imaging. RAST testing, as well as skin testing for environmental antigens is rarely useful. Skin testing using both traditional prick tests and patch tests may increase the sensitivity for identifying foods responsible for EG by evaluating both IgE mediated and T-cell mediated sensitivities (31).

Treatment

There is as much ambiguity in the treatment of EG as there is in its diagnosis. This is in large part because the entity of EG was defined mainly by case series, each of which employed their own mode of treatment. Because EG is a difficult disease to diagnose, randomized trials for its treatment are uncommon, leading to considerable debate as to which treatment is best. Food allergy is considered one of the underlying causes of EG, and elimination of pathogenic foods, as identified by any form of allergy testing, or by random removal of the most likely antigens, should be a first line treatment. Unfortunately, this approach results in improvement only in a limited number of patients. In severe cases, or when other treatment options have failed, the administration of a strict diet, utilizing an elemental formula, has been shown to be successful (32). In these cases, amino acid based formulas (Elecare at www.ross.com and Neocate at www.neocate.com) provided as the sole source of nutrition, have been reported to be effective in the resolution of clinical symptoms and tissue eosinophilia.

When the use of a restricted diet fails, corticosteroids are often employed due to their high likelihood of success in attaining remission. 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. 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 symptom control.

Orally administered cromolyn sodium has been used with some success, and recent reports have detailed the efficacy of other oral anti-inflammatory medications (33). Montelukast, a selective leukotriene receptor antagonist used to treat asthma, has been reported to successfully treat two patients with EG (34). Treatment of EG with inhibition of leukotriene D4, a potent chemotactic factor for eosinophils, relies on the theory that the inflammatory response in EG is perpetuated by the presence of the eosinophils already present in the mucosa causing an interruption in the chemotactic cascade breaking the inflammatory cycle.

Given the possibilities for treatment of EG, the combination of therapies incorporating the best chance of success with the smallest likelihood of side effects should be employed. When particular food antigens

Table 3
Foods that cause EE/EG in order of most likely (milk) to least likely (other vegetables)

- Milk
- Soy
- Wheat
- Eggs
- Nuts
- Shellfish
- Corn
- Rice
- Beef, Pork
- Chicken, Turkey
- Other fruits
- Other vegetables

that may be causing disease can be identified, elimination of those antigens should be employed as a first line therapy. When testing fails to identify potentially pathogenic foods, a systematic elimination of the most commonly involved foods can be employed (Table 3) (35). If this approach fails, total elimination diet with an amino acid-based formula should be considered. Trials of non-steroid anti-inflammatory medications such as Cromolyn, montelukast, and suptast, are a reasonable option, although some might prefer to wait for more detailed studies. When other treatments fail, corticosteroids remain a reliable treatment for EG, with attempts at limiting the total dose, or the number of treatment courses where possible.

EOSINOPHILIC ESOPHAGITIS (EE)

Introduction

Recently, eosinophilic esophagitis (EE) has come to the forefront in individuals previously suspected as having severe, chronic gastroesophageal reflux disease. EE is a disease of children and adults characterized by an isolated, severe eosinophilic infiltration of the esophagus manifested by gastroesophageal reflux like symptoms, such as regurgitation, epigastric and chest pain, vomiting, heartburn, feeding difficulties, and dysphagia unresponsive to acid suppression therapy.

History of Eosinophilic Esophagitis

In 1977, Dobbins reported one of the first cases of dysphagia associated with eosinophilic esophagitis (36). He described a case of a 51-year-old man, with asthma and environmental allergies, who presented with dysphagia and chest pain. An upper endoscopy demonstrated a severe eosinophilic esophagitis combined with increased eosinophils in the duodenum. In 1983, Matzinger reported dysphagia associated with a significant esophageal eosinophilia in an adolescent (37). Shortly thereafter, Lee (1985) reported on a series of 11 patients with documented eosinophilic esophagitis consisting of greater than 10 eosinophils per 40× high-powered microscopic field (HPF) (38). These patients were initially studied because all 11 presented with dysphagia, symptoms of gastroesophageal reflux, vomiting and strictures.

In 1993, Attwood was the first to compare patients with eosinophilic esophagitis to those with gastroesophageal reflux disease (39). He studied 12 patients who presented with dysphagia and had more than 20 eosinophils per 40× HPF found by biopsy. These patients had an average of 56 eosinophils per HPF and their symptoms were unresponsive to acid blockade. Eleven had normal pH probe monitoring, seven had evidence of systemic allergy including rhinitis, asthma, and eczema, and only one had increased antral eosinophils. This group was compared to a group of 90 patients with gastroesophageal reflux disease documented by an abnormal pH probe. All of the patients diagnosed with reflux were responsive to acid blockade and only 43 had evidence of an esophageal eosinophilia with a mean number of 3.3 eosinophils per HPF. The patients with severe esophageal eosinophilia did not respond to acid blockade. Two years later, Vitellas (1995) reported a series of 13 male patients with an isolated eosinophilic esophagitis (40). Twelve patients demonstrated dysphagia and an increased peripheral eosinophilia while 10 had atopic symptoms and esophageal strictures requiring repeated dilatation. All but one patient responded to systemic corticosteroids and in these patients esophageal dilatation was no longer required.

Role of Esophageal Eosinophils

Eosinophils in the gastrointestinal tract have long been associated with intestinal inflammatory disorders such as eosinophilic gastroenteritis, inflammatory bowel disease, parasitic infections, and acid related disorders. In normal, healthy volunteers, eosinophils are commonly visualized in almost all portions of the gastrointestinal tract (except the esophagus), which often makes the diagnosis of a pathologic process, secondary to eosinophilia, difficult. In 1982, Winter suggested that esophageal intraepithelial eosinophils might be related to tissue injury secondary to gastroesophageal reflux. He postulated that these eosinophils could be used as a new diagnostic criterion for reflux esophagitis (41). He evaluated 46 patients, aged three months to 19 years who had recurrent vomiting, epigastric pain and other symptoms of gastroesophageal reflux disease including dysphagia, abdominal pain and regurgitation. Diagnostic testing was performed

with pH probes, manometry and upper endoscopy. These patients were compared to a group of nine asymptomatic control patients. The control group had normal pH probe results, normal esophageal manometry and no esophageal eosinophils by biopsy. In contrast, in the study group, 18 patients demonstrated esophageal eosinophils on biopsy with a mean of two eosinophils per HPF. The majority of these patients also had abnormal pH probes and other histologic features of gastroesophageal reflux including basal zone thickening and papillary lengthening. Winter concluded that the presence of intraepithelial eosinophils correlated with delayed esophageal acid clearance.

Etiology of EE

EE appears to be caused by an abnormal immunologic response to specific food antigens. In 1995, Kelly published the classic paper on EE (42). Because the suspected etiology was an abnormal immunologic response to specific unidentifiable food antigens, each patient was treated with a strict elimination diet, which included an amino acid based formula (Neocate®). Patients were also allowed clear liquids, corn and apples. Seventeen patients were initially offered a dietary elimination trial with 10 patients adhering to the protocol. The initial trial was determined by a history of anaphylaxis to specific foods and abnormal skin testing. These patients were subsequently 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 three weeks after the introduction of the elemental diet (resolution in eight patients, improvement in two). In addition, all 10 patients demonstrated a significant improvement in esophageal eosinophilia. Subsequently, all patients reverted to previous symptoms upon reintroduction of foods. Pre- and post-dietary trial evaluation demonstrated significant improvement in clinical symptoms; additionally, histologic resolution occurred (mean of 41 eosinophils per HPF to <1 per HPF). Open food challenges were then conducted with a demonstration of a return of symptoms with challenges to milk (7 patients), soy (4), wheat (2), peanut (2) and egg (1).

While an exact etiology was not determined, Kelly suggested an allergic or immunologic cause, sec-

ondary to a delayed hypersensitivity or a cell-mediated hypersensitivity response. For the next few years, an argument existed among pediatric gastroenterologists and pathologists regarding the etiology of a severe, isolated esophageal eosinophilia (43–45). The dispute centered upon small numbers of patients who were identified with EE (most likely due to the thought that esophageal eosinophilia was only considered to be diagnostic of reflux disease) and the lack of controlled trials demonstrating a response of a severe esophageal eosinophilia to the removal of foods. Spergel demonstrated that foods that cause EE are often not based on an immediate hypersensitivity reaction (31). By using a combination of traditional skin testing and a newer technique of “patch testing,” he established that a delayed cellular mediated allergic response might be responsible for many cases of EE. Other investigations suggest that CD8 lymphocytes are the predominant T cell within the squamous epithelium of patients diagnosed with EE (46). Finally, aeroallergens and infectious agents have also been considered as a potential cause of EE; however, only food antigens have thus far been implicated (47).

Clinical Presentation and Diagnosis of EE

Eosinophilic esophagitis occurs in children and adults. The presentation of EE in children is similar to the symptoms associated with gastroesophageal reflux (Table 4). Males develop EE more frequently than females. The typical symptoms include nausea, vomiting, regurgitation, epigastric abdominal pain, and poor eating (48). Young children may demonstrate food refusal while adolescents often experience dysphagia. Adults present with similar symptoms; however, dysphagia occurs much more commonly and can be associated with esophageal strictures. Uncommon symptoms include growth failure, hematemesis, globus, and water brash. The clinical features of EE may evolve over years. Symptoms such as abdominal pain and heartburn occur regularly; however, patients with vomiting or dysphagia may display these symptoms sporadically complaining only once or twice a month. While the use of acid suppression medication often improves the patient’s symptoms, it does not eliminate

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Table 4
Diagnostic comparison between Eosinophilic Esophagitis and Reflux Esophagitis

	<i>Eosinophilic Esophagitis</i>	<i>Reflux</i>
Symptoms	Dysphagia > GERD	GERD > Dysphagia
Endoscopic findings	Furrows, rings, white	Erosions, ulcer plaques
Histologic findings	Usually >20 eos/HPF	Usually <5 eos/HPF
Esophageal strictures	Mid-esophagus	Distal esophagus
pH probe results	Usually normal	Abnormal
Acid blockade		
Symptoms	Minimally improved	Significantly improved
Histology	No significant change	Significantly improved

the symptoms nor change the abnormal esophageal histology. Approximately 50% of affected children also exhibit other allergic signs and symptoms including bronchospasm, allergic rhinitis and eczema. Frequently, there is a strong family history of food allergies or other allergic disorders.

While other non-invasive tests have attempted to diagnose EE, upper endoscopy with biopsy is the only test that can precisely determine the diagnosis of EE. The other non-invasive diagnostic tests have included the evaluation of serum IgE levels and quantitative peripheral eosinophils, radiographic upper gastrointestinal series (UGI), pH probe and manometry, RAST testing, and skin prick and patch testing. Serum IgE levels and serum eosinophils have been found to be unreliable due to the fact that these tests usually respond to environmental allergens as well as ingested or inhaled allergens. Although radiographs demonstrate anatomic abnormalities, such as esophageal strictures, they do not identify tissue eosinophils. Patients with EE usually have normal or borderline normal pH probes. Patients may have mild GERD secondary to abnormalities in esophageal motility due to tissue eosinophilic infiltration.

Eosinophilic esophagitis is a clinico-pathologic diagnosis. It is best defined as the presence of more than 15 eosinophils per HPF isolated strictly to the esophageal mucosa associated with typical clinical symptoms. In order to make the diagnosis of EE, other causes of esophageal eosinophilia must be excluded. In

1999, Ruchelli evaluated 102 patients presenting with GERD symptoms who also were found to have at least one esophageal eosinophil without any other GI abnormalities (49). After treatment with aggressive acid blockade, Ruchelli demonstrated that patients who improved averaged 1.1 eosinophils per HPF, patients who relapsed upon completion of therapy averaged 6.4 eosinophils per HPF, while patients who remained symptomatic averaged 24.5 eosinophils per HPF.

Visually, EE has been associated with several features including longitudinal linear furrows (Figure 1), concentric ring formation called “trachealization” or a “feline esophagus” (Figure 2), and patches of small, white papules on the esophageal surface (Figure 3). The white papules appear to represent the formation of eosinophilic abscesses. Histologically, EE is manifested by more than 15 eosinophils in the most severely affected HPF isolated to the esophagus. Typically, significant basal cell hyperplasia is present. In some cases, esophageal surface eosinophilic abscess formation can be appreciated (Figure 4). In 2000, Fox utilizing high-resolution probe endosonography in patients with EE demonstrated that the esophageal mucosa, submucosa and muscular layers were all affected (50).

Treatment of EE

Several treatment options are available to patients diagnosed with EE. Currently, most investigators do not

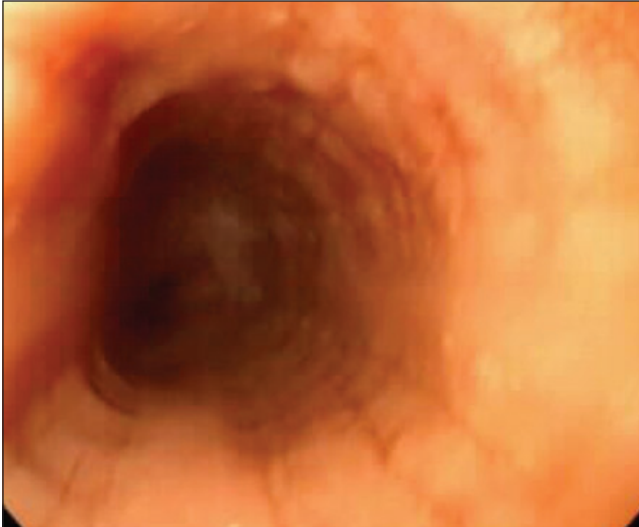


Figure 1. Endoscopic photograph of esophageal linear furrows.



Figure 2. Endoscopic photograph of esophageal rings, "trachealization."



Figure 3. Endoscopic photograph of esophageal white plaques denoting eosinophilic abscesses.

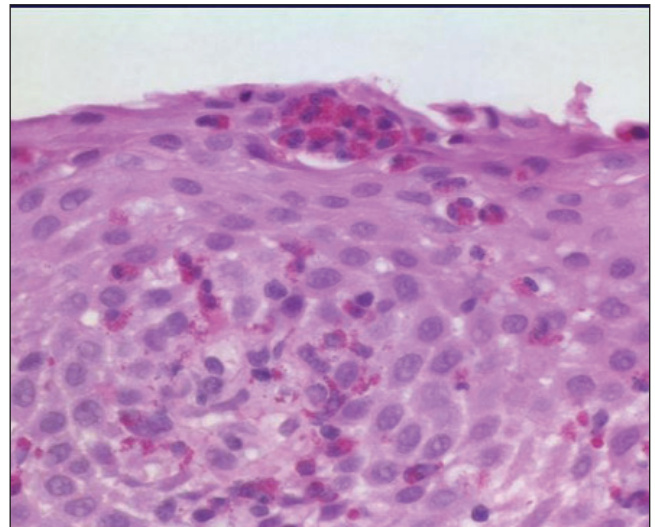


Figure 4. Histologic biopsy of distal esophagus. Numerous eosinophils as well as a surface eosinophilic abscess are present.

believe that esophageal acid exposure is the cause of EE; however, because of the severity of mucosal and submucosal disease seen in EE, secondary acid reflux often occurs. Additionally, because there may be some histologic overlap between patients with EE and those with GERD, it is important to exclude acid reflux as a cause of esophageal inflammation. Therefore, most investigators believe that the initial use of proton pump inhibitors is essential in any patient who has clinical symptoms of EE so that GERD can be excluded (51).

Adult gastroenterologists have reported the use of esophageal dilatation for their patients who present with esophageal strictures secondary to EE (52). While esophageal dilatation using rigid esophageal dilators

can relieve dysphagia, many of these physicians have described esophageal tearing during dilatation. In addition, there have been several reports of esophageal tearing simply with the introduction of the endoscope in patients with EE. Thus, gastroenterologists should be extremely careful whenever performing endoscopy or dilatation on a patient with EE as perforation is a distinct possibility.

Systemic corticosteroids were the first medical treatment shown to be effective in improving both symptoms and esophageal histology in patients with EE (53). Patients were treated with oral solumedrol (average dose 1.5 mg/kg/day; maximum dose 48 mg/day) for one month. Symptoms significantly improved in 19 of 20 patients in an average of eight days. A repeat endoscopy with biopsy, four weeks after the initiation of therapy, demonstrated almost complete normalization of esophageal histology. However, upon discontinuation of corticosteroids, 90% have 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 disadvantage includes 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 (46,54–57). 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. The advantage of using topical steroids is that their side effects are less than that seen with systemic steroids. The disadvantage includes not treating the disease fully (the disease generally recurs when the treatment is discontinued) and the development of possible side effects epistaxis, dry mouth and esophageal candidiasis. Recently, the use of a swallowed viscous solution containing budesonide has been reported with some effectiveness (58). When using topical, swallowed corticosteroids, the initial dose varies from 110–880 mcg, twice daily, depending on patient's age and size. Patients do not eat, drink, or rinse for 20–30 minutes after using the medication. Other atopic diseases should be controlled, as rhinitis and environmental allergies may be linked to EE. The patient should undergo endoscopy after two to three months of therapy. If improved, fluticasone can be weaned empirically. The medication can be discontinued as tolerated; however in many patients the disease recurs.

Several other medications have also been attempted. Some investigators have used cromolyn sodium as an adjunct to therapy for EE. However, no studies have been conducted to prove its effectiveness (59). Leukotriene receptor antagonists have also been utilized to treat EE (60). Initial doses of 10 to 100 mgs per day have been 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 EE in a large number of studies (61,62). While there has not been any definitive evidence that EE 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 the majority of patients with EE. The elimination of causative foods can follow several therapeutic regimens. First of all, specific food elimination can be based on allergy testing and clinical history. In the past, skin prick and RAST testing have proven unreliable; however, the introduction of atopy patch testing used in combination with IgE skin prick testing, has significantly increased the ability to identify potential food allergens (63). Recently, a study from Chicago utilized the removal of the six most likely foods (dairy, eggs, wheat, soy, nuts, shellfish), without the aid of allergy testing, and demonstrated similar efficacy (64).

While every attempt should be made to identify and eliminate potential food allergens through a careful history and the use of allergy testing, it still may be difficult to determine the responsible allergic foods. 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 improving both clinical symptoms and histology in patients with EE (42,59). Reversal of symptoms typically occurs

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within 10 days with histologic improvement in four weeks. 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 many other treatments. Once the esophagus is healed, if allergy testing has not determined the causative foods, foods are reintroduced systematically. Because the clinical symptoms are often erratic, endoscopy with biopsy should be used to document an improvement in esophageal histology.

Finally, there have been reports of the development of other medications that will target specific chemokines and other inflammatory mediators that are involved in the activation of the eosinophil. Medications such as anti-interleukin-5, very late activating antigen, and monoclonal eotaxin antibody may benefit those patients who have severe EE (65).

CONCLUSION

Eosinophilic disorders of the gastrointestinal tract are becoming increasingly recognized. While EG is rare and difficult to diagnose, EP and EE are much more common and are easily diagnosed by endoscopic biopsy. Argument still exists regarding the etiology and best treatment for EE. Future research should focus on clarifying the prevalence and natural history (e.g., the potential development of strictures) and optimizing the diagnostic approach and treatment options of all gastrointestinal eosinophilic disorders. ■

References

- 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.
- Heyman M, Grasset E, Ducroc R, et al. Antigen absorption by the jejunal epithelium of children with cow's milk allergy. *Pediatr Res*, 1988;24:197-202.
- Kerner JA Jr. Formula allergy and intolerance. *Gastroenterol Clin North Am*, 1995; 24:1-25.
- Host A, Halcken 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.
- Strobel S. Epidemiology of food sensitivity in childhood—with special reference to cow's milk allergy in infancy. *Monogr Allergy*, 1993;31:119-30.
- Eastham EJ. Soy protein allergy. In: R H, ed. *Allergology, Immunology, Gastroenterology*. New York: Raven Press, 1989:223-236.
- Shannon WR. Demonstration of food proteins in human breast milk by anaphylactic experiments in guinea pig. *Am J Dis Child*, 1921;22:223-225.
- Axelsson I, Jakobsson I, Lindberg T, et al. Bovine beta-lactoglobulin in the human milk. A longitudinal study during the whole lactation period. *Acta Paediatr Scand*, 1986;75: 702-707.
- Juvonen P, Mansson M, Jakobsson I. Does early diet have an effect on subsequent macromolecular absorption and serum IgE? *J Pediatr Gastroenterol Nutr*, 1994;18:344-349.
- Katz AJ, Twarog FJ, Zeiger RS, et al. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol*, 1984;74:72-78.
- Donta ST, Myers MG. Clostridium difficile toxin in asymptomatic neonates. *J Pediatrics*, 1982;100:431-434.
- Hirano K, Shimojo N, Katsuki T, et al. Eosinophils in stool smear in normal and milk-allergic infants. *Alerugi*, 1997;46:594-601.
- Anveden-Hertzberg L, Finkel Y, Sandstedt B, et al. Proctocolitis in exclusively breast-fed infants. *Eur J Pediatr*, 1996;155:464-467.
- Machida HM, Catto Smith AG, Gall DG, et al. Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr*, 1994;19:22-26.
- Kajiser R. Zur Kenntnis der allergischen Affektionen des imma Verdanungskanal von Standpunkt desma Chirurgen aus. *Arch Klin Chir*, 1937;188:36-64.
- Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. *Medicine (Baltimore)*, 1970;49:299-319.
- Spergel JM, Pawlowski NA. Food allergy. Mechanisms, diagnosis, and management in children. *Pediatr Clin North Am*, 2002;49:73-96.
- Leinbach GE, Rubin CE. Eosinophilic gastroenteritis: a simple reaction to food allergens? *Gastroenterology*, 1970;59:874-889.
- Kelso A. Cytokines: structure, function and synthesis. *Curr Opin Immunol*, 1989;2:215-225.
- Desreumaux P, Bloget F, Seguy D, et al. Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. *Gastroenterology*, 1996;110:768-774.
- Kelly KJ. Eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr*, 2000;30 Suppl:S28-S35.
- Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut*, 1990;31:54-58.
- Santos J, Junquera F, de Torres I, et al. Eosinophilic gastroenteritis presenting as ascites and splenomegaly. *Eur J Gastroenterol Hepatol*, 1995;7:675-678.
- DeSchryver-Kecskemeti K, Clouse RE. A previously unrecognized subgroup of "eosinophilic gastroenteritis." Association with connective tissue diseases. *Am J Surg Pathol*, 1984;8:171-180.
- 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;158:172-173.
- Khan S, Orenstein SR. Eosinophilic gastroenteritis masquerading as pyloric stenosis. *Clin Pediatr (Phila)*, 2000;39:55-57.
- Shweiki E, West JC, Klana JW, et al. Eosinophilic gastroenteritis presenting as an obstructing cecal mass—a case report and review of the literature. *Am J Gastroenterol*, 1999;94:3644-3645.
- Huang FC, Ko SF, Huang SC, et al. Eosinophilic gastroenteritis with perforation mimicking intussusception. *J Pediatr Gastroenterol Nutr*, 2001;33:613-615.
- Caldwell JH, Tennenbaum JI, Bronstein HA. Serum IgE in eosinophilic gastroenteritis. Response to intestinal challenge in two cases. *NEJM*, 1975;292:1388-1390.
- Teele RL, Katz AJ, Goldman H, et al. Radiographic features of eosinophilic gastroenteritis (allergic gastroenteropathy) of childhood. *Am J Roentgenol*, 1979;132:575-580.
- Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in

- eosinophilic esophagitis. *J Allergy Clin Immunol*, 2002; 109:363-368.
32. Vandenplas Y, Quenon M, Renders F, et al. Milk-sensitive eosinophilic gastroenteritis in a 10-day-old boy. *Eur J Pediatr*, 1990;149:244-245.
 33. 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; 69:441-444.
 34. Schwartz DA, Pardi DS, Murray JA. Use of montelukast as steroid-sparing agent for recurrent eosinophilic gastroenteritis. *Dig Dis Sci*, 2001;46:1787-1790.
 35. Bengtsson U, Hanson LA, Ahlstedt S. Survey of gastrointestinal reactions to foods in adults in relation to atopy, presence of mucus in the stools, swelling of joints and arthralgia in patients with gastrointestinal reactions to foods. *Clin Exp Allergy*, 1996;26:1387-1394.
 36. Dobbins JW, Sheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. *Gastroenterology*, 1977;72:1312-1316.
 37. Matzinger MA, Daneman A. Esophageal involvement in eosinophilic gastroenteritis. *Pediatr Radiol*, 1983;13:35-38.
 38. Lee RG. Marked eosinophilia in esophageal mucosal biopsies. *Am J Surg Pathol*, 1985; 9:475-479.
 39. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci*, 1993;38:109-116.
 40. Vitellas KM, Bennett WF, Bova JG, et al. Idiopathic eosinophilic esophagitis. *Radiology*, 1993;186:789-793.
 41. Winter HS, Madara JL, Stafford RJ, et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology*, 1982;83:818-823.
 42. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*, 1995;109:1503-1512.
 43. Sondheimer JM. What are the roles of eosinophils in esophagitis? *J Pediatr Gastroenterol Nutr*, 1998;27:118-119.
 44. Hassall E. Macroscopic versus microscopic diagnosis of reflux esophagitis: erosions or eosinophils? *J Pediatr Gastroenterol Nutr*, 1996; 22:321-325.
 45. Levine MS, Saul SH. Idiopathic eosinophilic esophagitis: how common is it? *Radiology*, 1993;186:631-632.
 46. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology*, 2002;122:1216-1225.
 47. Furuta GT. Eosinophilic esophagitis: an emerging clinicopathologic entity. *Curr Allergy Asthma Rep*, 2002;2:67-72.
 48. 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: 1422-1430.
 49. Ruchelli E, et al. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol*, 1999;2(1):15-18.
 50. Fox VL, et al. High-resolution EUS in children with eosinophilic "allergic" esophagitis. *Gastrointest Endosc*, 2003; 57(1):30-36.
 51. Desai TK, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc*, 2005;61(7):795-801.
 52. Nostrant TT. Esophageal Dilatation / Dilators. *Curr Treat Options Gastroenterol*, 2005; 8(1):85-95.
 53. Liacouras CA, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr*, 1998;26(4):380-385.
 54. Faubion WA Jr, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr*, 1998; 27(1):90-93.
 55. Arora AS, et al. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc*, 2003;78(7):830-835.
 56. Noel RJ, Putnam PE, Collins MH, Assa'ad AH, Guajardo JR, Jameson SC, Rothenberg ME. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol*, 2004;2(7):568-575.
 57. Remedios M, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc*, 2006;63(1):3-12.
 58. Aceves SS, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*, 2005;116(3):705-706.
 59. Liacouras CA, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*, 2005;3(12): 1198-1206.
 60. Attwood SE, et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut*, 2003;52(2):181-185.
 61. Markowitz JM, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*, 2003;98(4):777-782.
 62. Garcia-Careaga M, et al. Gastrointestinal manifestations of food allergies in pediatric patients. *Nutr Clin Pract*, 2005;20(5):526-535.
 63. Spergel JM, 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(4):336-343.
 64. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BU. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*, 2006;4(9):1097-1102.
 65. Garrett JK, et al. Anti-interleukin-5 (mepolizumab) therapy for hyper-eosinophilic syndromes. *J Allergy Clin Immunol*, 2004; 113(1):115-119. (Epub, 2003).

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