REVIEW ARTICLE

Eosinophilic Digestive Diseases: Eosinophilic Esophagitis, Gastroenteritis, and Colitis

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Eosinophilic digestive diseases (EDD) are relatively rare disorders associated with increased gastrointestinal eosinophilic infiltrates without any underlying primary etiology. The pathophysiology of EDD is unclear, but is suspected to be related to a hypersensitivity reaction given its correlation with other atopic disorders and clinical response to corticosteroid therapy. Given the overall relative increase of various atopic conditions, it is important for clinicians to understand the presentation and diagnosis and treatment options available. We present here a review of EDD, including the proposed pathophysiology, diagnosis and current treatment options for these disorders. [*J Formos Med Assoc* 2009;108(11):834–843]

Eosinophilic digestive diseases (EDD), including eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis, are relatively rare gastrointestinal disorders. However, these conditions are becoming increasingly recognized and an area of increasing interest of research. Although clinical presentation of the disorders varies widely, the pathophysiology underlying all three is suspected to be hypersensitivity related. Unfortunately, there are no large, randomized, controlled trials to guide treatment in EDD, and current management is extrapolated from therapies for other atopic conditions. The mainstay of therapy is corticosteroids and avoidance of food antigens.

Pathophysiology of EDD

Under normal, non-pathologic conditions, the gastrointestinal tract is the only non-hematopoietic organ to contain eosinophils,[1] with the cecal and appendiceal region having the highest concentrations.[2] Under normal conditions, the majority of gastrointestinal eosinophils reside in the lamina propria.[3] The role of eosinophilia in parasitic infections of the gastrointestinal tract has long been recognized. However, emerging evidence suggests that eosinophils may play a role in several other conditions, including EDD. The pathogenesis of eosinophilic gastrointestinal diseases is not clearly understood. But, given the high correlation with other atopic conditions, a hypersensitivity response is strongly suspected. It is postulated that exposure of the gastrointestinal mucosa to antigens promotes a Th-2 mediated immune response. Th-2 cells produce interleukin (IL)-4, IL-5 and IL-13, and promote the production of eosinophils as well as IgE.[4–6] Allergic conditions, including asthma and allergic rhinitis, are also found to have a Th-2 mediated

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response, which suggests that EDD should be included within the spectrum of atopic diseases.

Eosinophilic Esophagitis

Eosinophilic esophagitis is the most commonly recognized EDD. Patients often present with symptoms similar to gastroesophageal reflux disease; however, they are not responsive to traditional antireflux therapy. In fact, there is emerging data to suggest that use of acid-suppressive medications may predispose patients to the development of eosinophilic esophagitis.[7] The alteration of gastric pH caused by antisecretory medications has been shown to affect protein digestion, allowing a larger percentage of ingested protein to be absorbed in larger fragments, potentially inducing an immunologic response.[8] Additionally, recent studies by Mullin et al demonstrated increased permeability in the mucosa of the upper gastrointestinal tract in patients taking acid-suppressive medications.[9,10] This increased permeability may allow potentially allergenic digestion products to permeate gastric mucosa and induce an immunologic reaction.

Epidemiology
Eosinophilic esophagitis is more common in Caucasians and males.[11–13] The reported incidence is approximately six per 100,000.[14] However, increased awareness of the disease over the past several years has led to an increasing number of cases identified. A higher incidence of eosinophilic esophagitis is noted in patients with other atopic conditions.[11–14]

Clinical presentation
The main presenting complaints of eosinophilic esophagitis are similar to those of gastroesophageal reflux disease, including epigastric burning and pain, regurgitation, nausea and vomiting. However, symptoms are not responsive to standard antireflux therapy. Additionally, patients may present with symptoms of dysphagia and possible food impaction symptoms.[15]

Diagnosis
The diagnosis of eosinophilic esophagitis relies on endoscopic biopsy. Visualization of the esophagus during endoscopy may appear abnormal, including esophageal furrows (Figure 1) and strictures, white plaques, or mucosal rings.[14,16] However, in one third of patients, the appearance of the esophagus may be normal.[17] There are no pathognomonic radiologic findings in eosinophilic esophagitis. However, the most common finding on barium studies is esophageal strictures. In one retrospective analysis, 71% of patients had esophageal strictures on barium studies; 50% of these strictures were noted to be of a distinctive ring-like character, which is increasingly being recognized in association with eosinophilic esophagitis.[18]

Pathology
Eosinophilic esophagitis may be associated with eosinophilic gastroenteritis or may be found in isolation. Because it is not unusual to find eosinophils in mucosal biopsies of reflux esophagitis, the number of eosinophils should exceed 25/high-powered field and preferably involve submucosa for positive histologic diagnosis (Figures 2A and 2B). Patchiness of the disease may create

Figure 1. Endoscopic image from an adult male who presented with dysphagia. Esophageal biopsy demonstrated eosinophilic infiltrates.
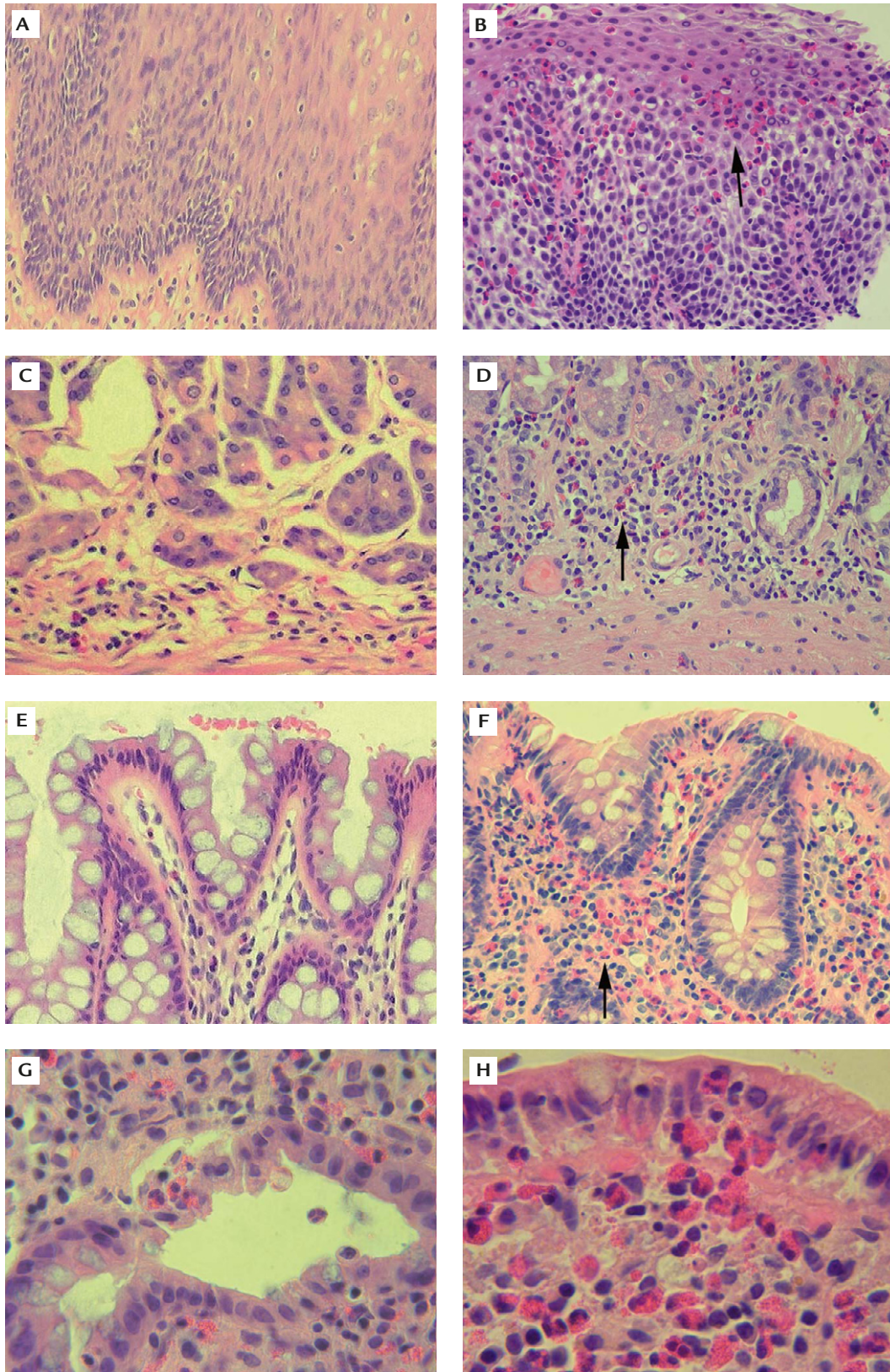
Figure 2. Cross sections of normal esophagus (A) contrasted with eosinophilic esophagitis (B). Normal gastric mucosa (C) versus gastric mucosa with eosinophilic infiltrates (D). Normal colon (E) compared with eosinophilic colitis (F). [Images A–F are at 400× magnification.] Eosinophilic cryptitis (G) at 400× magnification compared with eosinophilic cryptitis and marked infiltration of lamina propria (H) at 1000× magnification. Arrows indicate eosinophils in the abnormal specimens (B, D, F).

false-positive results unless generous multiple samples are obtained.

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis is a rare condition involving eosinophilic infiltrates of gastrointestinal tissue causing a wide array of gastrointestinal symptoms. The diagnosis of eosinophilic gastroenteritis requires a high degree of clinical suspicion, given the relatively nonspecific history and physical examination findings. Eosinophilic gastroenteritis should be considered in the differential diagnoses of any patient who presents with abdominal pain or other nonspecific gastrointestinal complaints without any clear etiology on diagnostic evaluation. A definitive diagnosis can be made by endoscopic biopsy displaying increased eosinophilic infiltrates and exclusion of any primary etiology causing hypereosinophilia.

Epidemiology

Eosinophilic gastroenteritis is a rare disease, with a peak incidence between the ages of 20 and 50 years.[19] While the actual incidence is unknown, there have been several case reports in the literature, particularly in the past 30–40 years, with the initial case report published in 1937.[20] Given the wide variety of presentations in addition to the relatively nonspecific symptoms of this disease, the incidence has likely been underreported. There is an increased incidence of eosinophilic gastrointestinal disease in patients with other atopic conditions, such as asthma, allergic rhinitis, atopic dermatitis, and food and environmental allergies. This may relate to the similar underlying reactive processes of these disorders, including increased eosinophils, mast cells, IL-4, IL-5, IL-13 and chemokines.[21]

Clinical features

The clinical features seen in eosinophilic gastroenteritis vary based on the region and depth of the gastrointestinal tract affected by eosinophilic infiltration.

Mucosal eosinophilic gastroenteritis

Symptoms of mucosal eosinophilic gastroenteritis include nonspecific complaints such as abdominal pain, nausea, vomiting and diarrhea as well as anemia due to fecal occult blood loss and protein wasting enteropathy.[22] Given these nonspecific symptoms, the diagnosis of mucosal eosinophilic gastroenteritis requires high clinical suspicion. The prevalence of mucosal eosinophilic gastroenteritis varies widely between studies (25–100%). However, the higher incidence of this subtype may be due to the more relative ease of diagnosis via endoscopic biopsy.[23,24]

Muscularis eosinophilic gastroenteritis

Muscular eosinophilic gastroenteritis often presents with signs and symptoms of gastric outlet and intestinal obstruction, and typically colicky abdominal pain.[25,26] Muscular eosinophilic gastroenteritis is the second most common subtype, found in 13–70% of cases.[23]

Subserosal eosinophilic gastroenteritis

Subserosal eosinophilic gastroenteritis is the least common subtype, accounting for only 12–40% of cases.[23] Subserosal eosinophilic gastroenteritis frequently presents with ascites and bloating,[27] and often has a higher level of peripheral eosinophilia.[28] This subset of patients typically has better clinical response to steroid treatment, but often with a more significant number of relapses.[28]

Diagnosis

The diagnosis of eosinophilic gastroenteritis requires a high index of suspicion, given its wide array of nonspecific symptoms and relatively low incidence. A clinical history of other atopic conditions such as asthma, atopic dermatitis, and food and environmental allergies should heighten suspicion for eosinophilic gastroenteritis. Patients with eosinophilic gastroenteritis may appear chronically ill on physical examination, with signs of malnutrition due to malabsorption. Suggestive findings on laboratory data are peripheral eosinophilia. But this finding is extremely variable.[19] Radiographic changes in patients with eosinophilic

gastroenteritis are also variable and are absent in up to 40% of cases.[29] Upper gastrointestinal series may show an irregular and lacy antral surface of the stomach or thickening of the circular folds and wall of the small bowel.[30] Additionally, strictures secondary to eosinophilic gastroenteritis may be evident on imaging. The endoscopic appearance of eosinophilic gastroenteritis is relatively nonspecific and most notable in the mucosal subtype. Abnormalities include erythema, ulcerations or focal erosions, and thickening of folds and friability.[31]

Pathology

Definitive diagnosis is made by histological evidence of eosinophilic infiltration on biopsy. The majority of studies have used a definition of > 20 eosinophils/high-powered field in the lamina propria for eosinophilic gastroenteritis (Figures 2C and 2D).[19] Involvement of gastric mucosa is often patchy and multiple biopsies should be obtained from various regions to improve yield. It involves all layers of the wall and is typically associated with edema (especially in the submucosa and muscle), increased vascularity, and fibrosis. Other inflammatory cells are also increased. In particular, increased number and degranulation of mast cells have come to attention more recently. Occasionally, necrotizing granulomata are noted. Involvement of subserosa may be associated with eosinophilic ascites and peritonitis.

Since endoscopic biopsies are typically limited to mucosa, pathologic findings in this region carry special significance for everyday diagnosis. Significant patchy or diffuse eosinophilic infiltration of lamina propria is a frequent finding. However, the number of eosinophils varies considerably in normal mucosa. Thus, other findings such as epithelial infiltration, eosinophilic cryptitis and degranulation, and involvement of muscularis mucosa and submucosa are important to increase the reliability of histologic diagnosis. In addition, the frequently patchy nature of the disease creates high false-negative rate unless generous and multiple biopsies are obtained.

Once a diagnosis of eosinophilic gastroenteritis is made, some clinicians elect to perform allergy evaluation to determine the inciting antigen. Methods of allergy testing include skin prick or patch tests and radioallergosorbent tests to detect IgE antibody formation against various ingested antigens. This can assist in development of an elimination diet to avoid antigen exposure.

Eosinophilic Colitis

Eosinophilic colitis is the least common EDD and varies in clinical presentation depending on the region and layer of colon affected. Diagnosis of eosinophilic colitis also relies on biopsy with pathologic evaluation.

Epidemiology

Eosinophilic colitis is the rarest EDD. It mainly affects neonates and young adults. Eosinophilic colitis appears to affect both sexes equally.[32]

Clinical presentation

The clinical symptoms of eosinophilic colitis may vary depending on the intestinal layer affected, similar to eosinophilic gastroenteritis. Eosinophilic colitis affecting the mucosa often presents with malabsorption, diarrhea, and protein wasting, whereas disease affecting the muscularis often manifests as intestinal obstruction and colonic thickening. Eosinophilic colitis affecting the serosa mainly presents as ascites with fluid analysis showing the majority of cells to be eosinophils.[33–35]

Diagnosis

The mainstay of diagnosis for eosinophilic colitis is biopsy. A small number of eosinophils may be seen in various regions of the colon under normal conditions, and at present there is no general consensus for differentiating normal versus abnormal levels of eosinophilia in the colon. Radiologic findings of eosinophilic colitis also depend on the region and layer affected, but may show strictures or thickening of the bowel wall.[33]

Pathology

Eosinophilic colitis is more problematic to diagnose because of marked variability in the number of eosinophils in the normal population and in various geographic sites. The concentration of eosinophils is variable depending on the region of the colon. Eosinophils are more concentrated in the cecum and ascending as compared to the left colon. Eosinophils comprise up to 3% of the inflammatory cells in normal colonic mucosa (Figure 2E), and this percentage may increase significantly without any correlating clinical complaint or disease. Thus, the presence of edema in the muscularis and submucosa, presence of eosinophils (Figure 2F) in the epithelium of the crypts (Figure 2G), degranulation, and involvement of muscularis mucosa and submucosa (Figure 2H) are particularly important in formulating a diagnosis of eosinophilic colitis. Generous and multiple biopsy samples are necessary for diagnosis. Often, eosinophilic cryptitis is observed in association with chronic inflammatory bowel disease, particularly Crohn's disease, and this is important in the differential diagnosis for eosinophilic colitis. On rare occasions, eosinophilic colitis or gastroenteritis manifest themselves as localized tumor masses and may present with a clinical picture of obstruction. In such cases, eosinophilic venulitis may dominate the pathology.

Differential Diagnosis

Eosinophilic infiltration of the gastrointestinal mucosa can be seen secondary to a variety of other conditions. It is important to evaluate patients for secondary causes prior to diagnosis of primary EDD. The classic association is in the setting of parasitic infections, such as *Ascaris*, *Anisakis*, *Trichuris*, schistosomiasis, *Ancylostoma caninum* (hook worm), and *Enterobius vermicularis* (pinworm).[36–41] Case reports of *Toxocara canis* and *Strongyloides* causing eosinophilic ascites have been reported as well.[42,43] Evaluation of stool for ova and parasites or larvae identified on biopsy confirms primary parasitic infection as the etiology

for eosinophilic infiltration in these cases. Additionally, several medications have been implicated in eosinophilic infiltration of gastric mucosa. The more commonly utilized medications that have been implicated include azathioprine, gemfibrozil, enalapril, and carbamazepine.[44–47] Other causes of secondary gastrointestinal eosinophilia include connective tissue diseases and vasculitis.[48,49] Occasionally, inflammatory bowel disease may be associated with gastrointestinal eosinophilic infiltrates as well as peripheral eosinophilia, as a component of the inflammatory response in inflammatory bowel disease.[50] Hypereosinophilia syndrome may also be a secondary cause of eosinophilic gastroenteritis. Hypereosinophilia syndrome is a rare condition with significant peripheral eosinophilia for an extended period of time (> 6 months) and associated infiltration and end-organ damage related to hypereosinophilia.[51] Clinically, patients with eosinophilic esophagitis present with complaints similar to gastroesophageal reflux disease. A recent study by Sayej et al revealed that high-dose proton pump inhibitor therapy may be useful in differentiating patients with eosinophilic esophagitis from those with non-eosinophilic esophagitis.[52] An additional study by Dellon et al identified a variety of clinical, endoscopic and histologic findings that may aid in distinguishing eosinophilic esophagitis from gastroesophageal reflux disease. They retrospectively reviewed 377 patients with either gastroesophageal reflux disease or eosinophilic esophagitis and found that younger age, symptoms of dysphagia, history of food allergies, endoscopic evidence of esophageal rings, linear furrows, white plaques or exudates, and absence of hiatal hernia, as well as pathologic evidence of higher maximum eosinophil count and presence of eosinophil degranulation independently predicted eosinophilic esophagitis.[53]

Treatment of EDD

At present, there are no large, randomized, controlled trials to guide treatment in eosinophilic

gastroenteritis. The majority of data is from smaller case series or extrapolated from the management of other atopic conditions. Corticosteroid therapy plays a large role in the treatment of this condition. Given the suspected inflammatory and hypersensitivity pathology of EDD, steroids are a reasonable treatment option. Several small, uncontrolled studies have evaluated the efficacy of steroids in the various types of EDD and shown significant improvement in symptom management. However, no histologic correlation has been shown.[27,54,55] The optimal duration of corticosteroid therapy has not yet been established. Often, a dosing strategy similar to that used in inflammatory bowel disease has been utilized (1–2 mg/kg/day for 8 weeks followed by a gradual taper).[23] Topical corticosteroid treatment has also been utilized in patients with eosinophilic esophagitis. A small study of 21 adult patients evaluated the effects of a 12-month course of oral fluticasone propionate.[56] All patients in this trial had complete resolution of their dysphagia symptoms per assessment at 4 months post-completion of therapy. However, a second study that evaluated patients who had received oral fluticasone treatment approximately 3 years after completion of therapy found that 91% of patients had experienced recurrence of their dysphagia symptoms.[57]

Alternative immune-modifying medications, including mast cell inhibitors (sodium cromoglycate, 200 mg four times daily)[58] and leukotriene receptor antagonists have also been evaluated in this condition. These studies are largely observational and the medications were often evaluated in combination with other treatment modalities.[59–61] In one case report by Urek et al, montelukast 10 mg/day provided symptom improvement in an adolescent male with eosinophilic gastroenteritis.[62] Additional case reports also demonstrated symptom improvement.[63,64] However there are no large randomized trials evaluating efficacy or correlating histologic improvement. Leukotriene receptor antagonists have been shown in multiple case reports to improve symptoms and provide an alternative to corticosteroids for chronic

maintenance therapy. The majority of case reports involved children with eosinophilic gastroenteritis or eosinophilic esophagitis and used dosages of montelukast ranging from 10 mg daily to 40 mg daily.[64–66] Additionally, Friesen et al reported a double-blinded, randomized, controlled study evaluating the efficacy of montelukast (10 mg daily) in 40 children and adolescents with eosinophilic duodenitis. Their results showed significant symptom improvement in the montelukast arm (62%) versus the placebo arm (32%).[67]

As mentioned above, it is postulated that EDD are triggered by food antigen exposure. Allergy testing can aid in the identification of specific antigens and development of an elimination diet. The majority of data evaluating diet modification have been obtained from the pediatric population. In a large study, specific elimination diets based on food sensitivities resulted in improvement in symptoms and esophageal biopsy in 75% of patients.[68] However, allergy testing has low sensitivity and specificity with high false-positive rates and should be cautiously interpreted. Other studies have evaluated the effect of a trial of empiric elimination diet, with removal of the six most common food allergens (milk, soy, egg, wheat, nuts and seafood). In a small study of 35 patients who were placed on an empiric elimination diet for a 6-week trial, 74% showed improvement on esophageal biopsy.[69]

Given the relative lack of data at this time, there is no definitive treatment regimen for patients with EDD. However, it is reasonable to consider a course of corticosteroid treatment (1–2 mg/kg/day for 8 weeks followed by a gradual taper) for the management of acute symptoms in the appropriate clinical setting. Topical steroids, including oral fluticasone (fluticasone inhaler 220 mmol/puff, two puffs twice daily), may also be considered as a treatment option. Some patients may require chronic maintenance therapy and steroid-sparing options, including mast cell inhibitors (sodium cromoglycate, 200 mg four times daily) and leukotriene receptor antagonists (montelukast 10–40 mg daily). Empiric diet

modification or allergy testing with specific diet modifications may be an alternative option in motivated patients.

Conclusion

EDD, including eosinophilic esophagitis, eosinophilic gastroenteritis and eosinophilic colitis, are rare conditions involving gastrointestinal eosinophilic infiltrates and associated gastrointestinal symptoms without a primary etiology for hypereosinophilic infiltrates. The pathophysiology of this condition is not well understood, but a hypersensitivity mechanism is suspected given its increased association with other atopic conditions and clinical improvement with corticosteroids. The definitive diagnosis of EDD is made with endoscopic biopsy displaying increased eosinophilic infiltrates and the absence of any primary disorders that may cause secondary eosinophilic infiltrates. At this time, there is minimal data to guide EDD treatment. Treatment regimens are extrapolated from therapies for other atopic disorders and current evidence for efficacy is limited to case reports and smaller studies. Based on this data, it is reasonable to use corticosteroids in the acute setting and, if necessary, mast cell inhibitors, leukotriene receptor antagonists and diet modification for chronic maintenance. Additional studies are needed to further delineate the pathophysiology of EDD, and larger randomized, controlled studies are needed to determine optimal treatment regimens.

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