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Eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis is increasingly recognized in adults. The diagnosis is based on the presence of both typical symptoms and pathologic findings on esophageal biopsy. Patients usually present with dysphagia, food impaction and/or reflux-like symptoms, and biopsy of the esophagus shows more than 15 eosinophils per high-power field. In addition, it is essential to exclude the presence of known causes of tissue eosinophilia such as gastroesophageal reflux disease, infections, malignancy, collagen vascular diseases, hypersensitivity, and inflammatory bowel disease. There are no standardized protocols for the therapy of eosinophilic esophagitis. A variety of therapeutic approaches including acid suppression, dietary modifications, topical corticosteroids and endoscopic dilation can be used alone or in combination.

Key words: Eosinophilic esophagitis; Dysphagia; Endoscopic dilation; Reflux; Gastro esophageal reflux disease

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INTRODUCTION

Eosinophilic esophagitis (EE) in adults is a disease with the following clinicopathological characteristics: (1) symptoms including but not restricted to food impaction and dysphagia; (2) biopsy specimen showing more than 15 eosinophils/high-power field (HPF); and (3) other disorders associated with similar clinical, histological, or endoscopic features have been excluded[1]. EE is increasingly being recognized in adult and pediatric populations, either as a separate entity or as a part of the spectrum of eosinophilic gastroenteritis[2]. It was initially described in the 1970s[3], but subsequently most research focused on gastroesophageal reflux disease (GERD) as being the primary cause of esophageal eosinophilia. It was not until the 1990s that EE came to be regarded as a separate entity[4]. Later on, an allergic component to EE was observed as patients suspected of having EE had improvement of symptoms on either elemental diet[5,6] or on corticosteroids[7]. These features, along with normal pH study results and the relative lack of effectiveness of acid suppression therapy, resulted in EE being regarded as a clinical condition different from GERD.

EE has recently been explored in much detail within various forums. This article aims to review that literature looking at the epidemiological and clinicopathological aspects of EE, with special emphasis on diagnostic approaches and treatment options.

EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS

EE has been studied most extensively in pediatric populations and only recently has further data been compiled in adults. EE can present in the third and fourth decades of life and various studies implicate it to be more predominant in men[8,9]. Among different races and ethnic groups, EE has been seen to be more prevalent in the white population[10]. Geographic distribution is wide, with cases now being reported not only in the United States but also Europe, Canada, Brazil, Japan and Australia[11]. The preponderance of EE in developed nations has unclear etiology and could

either be secondary to the increased prevalence of atopic diseases like asthma[12] or simply because of better reporting and data collection. To probe this further, Cherian *et al*[13] conducted a blind retrospective study of western Australian children investigated for esophageal disease in 1995, 1999 and 2004 and found the prevalence of EE to be indeed increased by 18-fold during this time period. The most recent US study in 74 162 patients used a national pathology database of subjects undergoing upper endoscopy with biopsy. The data confirmed that EE is a male-predominant disorder (74%) and that it can occur at any age. Over the study period (2002-2006), an increasing prevalence was noted. Whether this reflects a true increase in prevalence or increased recognition due to heightened awareness among physicians remains to be determined[14].

Furthermore, because of the past difficulty in diagnosing EE correctly in populations with dysphagia, food impactions or GERD, studies were subsequently conducted in various nations that later found EE to be the primary cause of these symptoms[7,15]. Markowitz *et al*[6] found that 15% of patients initially suspected of having GERD were actually discovered to have EE. They used strict diagnostic criteria for EE such as > 20 eosinophils/HPF in esophageal biopsies, normal esophageal pH monitoring and a lack of response to proton pump inhibitor (PPI) therapy. These findings may warrant changing our diagnostic approach to having an early esophagogastroduodenoscopy (EGD) with subsequent esophageal biopsies if clinical reflux-like symptoms and lack of response to medical treatment continue to be an issue.

Allergens play an important role in the etiology of EE. Kelly *et al*[5] first showed the association of food allergens with EE when they fed an elemental diet to 10 children with unremitting reflux symptoms and found symptomatic and histological improvement. This was later supported in different studies with successful use of either an elemental or a six-food elimination diet[16]. Aero-allergens form another potential cause of EE. Mishra *et al*[17] used a murine model to demonstrate an etiological role for inhaled allergens and eosinophils in gastrointestinal inflammation. A high degree of atopy and polysensitization to several environmental allergens was recently documented in patients with EE, suggesting that sensitization may partly be a response to inhaled allergens[18]. However multiple etiological factors are not mutually exclusive, as was presented by Plaza-Martin *et al*[19] who found evidence of poly-sensitization to aero-allergens and food allergens in their study population of patients who had EE. A familial pattern of inheritance has also been suggested to play a role in the development of EE[20].

The esophagus is normally devoid of eosinophils, however the rest of the gastrointestinal tract is populated with eosinophils beginning from the embryonal stage. Mishra *et al*[21] showed that the peptide eotaxin regulates eosinophil homing to the gastrointestinal (GI) tract during embryonal development. They also showed a connection between allergic hypersensitivity response in lung and esophagus regulated by eotaxin and interleukin (IL)-5[17,22]. It was subsequently shown that IL-13 plays a fundamental role in EE[23]. Once eosinophils have migrated to the esophagus, they release chemoattractants IL-3, IL-5 and granulocyte monocyte-colony stimulating factor (GM-CSF)[24]. Straumann *et al*[25] further confirmed the allergic nature of EE when they showed that a TH2 response, IL-5 and IgE mediated the pathogenesis of EE. However, there are inconsistencies in determining the exact nature and influence of an aero-allergic etiopathogenesis of EE. Balatsinou *et al*[26] observed EE in two patients with anticonvulsant hypersensitivity syndrome, wherein they saw reversal of endoscopic appearance after stopping carbamazepine, suggesting that oral agents could also play a role in the pathogenesis. An association with pollen has also been noted previously[27].

Dysphagia predominantly seen in EE has been attributed to both organic and non-organic (i.e. motility) disorders. Stevoff *et al*[28], in one of the first case reports on EE in octogenarians, showed circumferential but asymmetric thickening of the muscularis propria or a functional constriction related to myenteric plexus infiltration. Various other factors have been implicated in the development of dysphagia. Non-anatomic causes for dysphagia could be related to dysmotility. Nurko *et al*[29] reviewed the different causes of dysmotility that had been proposed in earlier papers, and these included eosinophil-mediated increased contraction of fibroblasts, axonal necrosis or cholinergic pathway interference, all of which contributed to esophageal dysmotility. A caveat to some of these studies is that they were either based on non-allergic models of esophagus or from studies in organ systems other than the esophagus[29].

CLINICAL FEATURES

EE usually presents with a multitude of symptoms, in part because it is a chronic disease and partly because of the gradual inflammatory involvement of the mucosa and submucosa before symptoms develop[30]. It can, however, present acutely as seen in food impactions[30]. The most common presenting symptom is dysphagia[30,31] but other symptoms such as nausea, vomiting, heartburn, chest pain or abdominal pain can also occur. Symptoms suggestive of esophageal dysmotility may indicate involvement of the muscular layers of the esophagus[32]. Occasionally, presentation of EE has been seen to be more subtle as patients adapt their chewing habits, eating food more slowly and washing down solid food with liquids, thereby decreasing the symptom incidence and leading to a delay in diagnosis[33]. Remedios *et al*[31] found an association of esophageal symptoms with exposure to certain foods even without actual consumption. Not infrequently, patients may also have additional symptoms of asthma[3], allergies or atopic dermatitis. Dauer *et al*[34] and Orenstein *et al*[35] have reported nasal symptoms and rhinosinusitis in about a quarter of patients that have EE. Laryngeal symptoms include hoarseness, cough, croup and sleep-disordered breathing[36]. Ferguson and

Table 1 Clinical presentation of eosinophilic esophagitis

Gastrointestinal symptoms	Other symptoms
Dysphagia	Chest pain
Food impaction	Rhinitis
Nausea and vomiting	Asthma
Heartburn	Allergies
Abdominal pain	Atopic dermatitis
Feeding disorders (pediatric)	Hoarseness
Failure to thrive (pediatric)	Croup, cough
	Sleep disordered breathing

Table 2 Clinical signs in eosinophilic esophagitis

Endoscopic features	Histologic features
Diminished vascular pattern	Thick epithelium with eosinophilia
Mucosal furrows	Abnormally long papillae
Thick mucosa	Fibrotic lamina propria
Exudates	Microabscesses
Strictures	Extracellular Eosinophilic granules
Rings	Increased extracellular major basic protein (MBP)
Laryngeal edema, vocal cord nodules, laryngeal ventricular obliteration	

Foxx-Orenstein divided the clinical manifestations according to age groups. Thus feeding disorders and failure to thrive were primarily seen in children below 2 years of age; vomiting, abdominal pain and reflux were seen in pediatric populations up to the age of 12; whereas adults usually present with dysphagia and food impactions[37] (Table 1).

Endoscopically, a normal-appearing esophagus is usually incompatible with a diagnosis of EE, although the findings can be subtle[8]. Typical findings on an EGD that imply the presence of EE include attenuation of subepithelial vascular pattern[38], linear furrowing[39] that may extend along the whole length of the esophagus, surface exudates composed of eosinophils or abscesses or strictures[8]. Presence of mucosal changes suggestive of ulcerations usually implies peptic injury by itself or in association with EE[40]. Schatzki ring has also been previously associated with EE[41] but one of the most characteristic and frequently quoted patterns is that of stacked circular rings or felinization[40], so called because of their presence in the cat esophagus. This has been postulated to be due to lamina propria and dermal papillary fibrosis caused by either the mediators that stimulate eosinophils or through the effect of eosinophils themselves. Previously, Vasilopoulos and Shaker described a small caliber esophagus as a major cause of dysphagia in patients with EE[42]. The esophagus was seen to have a smooth, diffusely narrow lumen shown on barium esophogram or esophagoscopy. Food impactions are also relatively frequent in patients with EE. Fox *et al*[40] have attributed these food impactions to either the strictures themselves or to decreased peristalsis secondary to underlying inflammation. Therefore, in patients with food impaction, it is worthwhile to follow EGD with biopsies for early diagnosis and treatment of this disorder. Airway endoscopy findings in patients with recurrent croup and EE include diffuse laryngeal edema, vocal fold nodules and laryngeal ventricular obliteration[36] (Table 2).

Histopathologically, EE is characterized by the presence of a thick epithelium with a large number of intraepithelial eosinophils lined near the surface, abnormally long papillae and a fibrotic lamina propria containing eosinophils[43]. Cheung *et al*[44], in their retrospective study of 42 children with dysphagia, described the presence of extracellular eosinophilic granules in patients with EE. Major basic protein (MBP) is a byproduct of eosinophil degranulation, and as such, increased deposition of MBP has been observed in pediatric and adult patients with EE[45,46].

Complications arising from EE can either be attributed to the clinical manifestations of the disease itself or to diagnostic and therapeutic interventions. Acute food impaction is one of the main reasons patients present as emergencies to the hospital. In one study, 57% of patients with EE had strictures that were successfully treated with dilatation, with subsequent resolution of symptoms[8]. More severe disease could lead to long segment narrowing which has been postulated to be in two forms[47]. The first form is referred to as trachealization[48], corrugated esophagus[48,49] or feline esophagus[50]. The second form is the small-caliber esophagus mentioned by Vasilopoulos *et al*[51], who found a diffusely narrow esophagus in three out of the five patients referred to them for chronic dysphagia. EE may also predispose to fungal and viral infections in the absence of steroid treatment or immunosuppression[47]. Straumann *et al*[52] conducted a chart review of 251 cases of esophagitis and found a case of Boerhaave's syndrome (spontaneous esophageal rupture). In their report, they recommend that all Boerhaave's cases be evaluated for EE. Chronic inflammation in EE may also lead to dysfunction of the lower esophageal sphincter and cause secondary reflux disease, as was reported by Remedios *et al*[31].

The risk of esophageal perforation is significantly increased during diagnostic or therapeutic endoscopic evaluation in a patient with EE[50]. In their chart and pathology review, Kaplan *et al*[50] found that more than half of their patients with EE had mucosal rents after simple passage of the endoscope, with one patient developing a perforation. Therefore, intense retrosternal pain after endoscopic evaluation in a patient suspected to have EE should particularly raise the suspicion of perforation and appropriate diagnostic evaluation should be undertaken[53]. The esophageal mucosa in EE is very fragile and inelastic, which Straumann *et al*[54] have termed "crepe paper mucosa" as it tore easily even with minor trauma. Consequently therapeutic interventions such as food bolus removal, dilation or biopsy can pose an even higher risk of perforation[52,55,56]. Kaplan *et al*[50] recommend about 8 wk of medical therapy before considering dilation in patients diagnosed with EE because of the high risk of perforation and the good response to medical therapy (Table 3).

Table 3 Complications in EE related to disease and to the interventions performed for treatment

Complications of EE	Complications of therapeutic interventions
Acute food impactions	Mucosal rents/tears
Long and short segment narrowing	Perforation
Stenosis	Infections-due to chronic use of steroids
GERD	Nutritional deficiencies
Boerhaave's syndrome	
Nutritional deficiencies	

DIAGNOSIS

EE should always be considered in the following circumstances: (1) history of food impaction; (2) persistent dysphagia especially in young individuals and in patients having a history of atopy; or (3) GERD refractory to medical therapy. Other causes of eosinophilia such as parasitic infestations, malignancy, drug hypersensitivity, collagen vascular diseases and inflammatory bowel disease need to be ruled out[57]. EE is primarily a clinicopathological condition and hence both symptoms and pathological diagnosis form an integral part of the diagnosis. The First International Gastrointestinal Eosinophilic Research Symposium (FIGERS) came up with comprehensive guidelines regarding the diagnostic criteria for EE. Accordingly, an eosinophil count of $\geqslant$ 15/HPF, along with normal gastric and duodenal biopsies, can substantiate the diagnosis of EE. Moreover, patients must have biopsies after 6-8 wk of twice daily acid suppression with PPI or have a negative pH study result[1] in order to correctly diagnose EE. At least five such biopsies must be obtained and preferably from both the proximal and the distal esophagus to account for the heterogeneous nature of the tissue eosinophilia[31,58] (Table 4).

Prasad *et al*[59] did a prospective study of 376 patients and found that mid-esophageal biopsies had a yield rate of about 10%. They thus recommend taking mid-esophageal biopsies in patients with unexplained food dysphagia. However, EE is patchy and hence increasing the number of biopsy specimens would theoretically yield a higher sensitivity and specificity in diagnosing EE[58]. Gonsalves conducted a chart review of 76 patients and found that sensitivity increased from 55% to 100% if the number of biopsies were increased from one to about five[58]. No statistically significant difference was found between the biopsies obtained from either the proximal or the distal esophagus. Thus, Collins in her article has recommended obtaining at least three pieces from two different sites in the esophagus including the distal and either mid or proximal esophagus[43]. If there is a high suspicion of the presence of EE, then biopsies should be obtained even if the esophagus endoscopically appears normal. Liacouras *et al*[60] found in their chart review that about one third of the patients with severe EE had a visually normal esophagus and they recommended that one should not rely only on the endoscopic appearance and rather aim to get biopsies for histological analysis if there is suspicion for EE.

Table 4 Diagnostic guidelines for eosinophilic esophagitis

Eosinophilic esophagitis	
Symptoms (adults)	GERD refractory to medical therapy
	Dysphagia
	Food Impaction
	Retrosternal chest pain
Endoscopy	Mucosal furrows
	Exudates
	Esophageal lumen narrowing
	Rings
Histology	Esophageal biopsies ≥15 eosinophils/HPF
	Biopsies obtained after 6-8 wk of *bid* PPI therapy or patients must have a documented negative pH study
	Normal biopsies in the rest of the GI tract

EE is thought to be primarily a TH2 inflammatory process[25,61] together with a possible allergic association, and as such, diagnosis also focuses on interleukins, eotaxin and eosinophils with their degranulation products. Research is ongoing regarding the development of non-invasive markers for EE. Gupta[62] reviewed some biomarkers that could correlate with disease presence, remission, severity and response to therapy. These include serum IgE, CD23, eotaxins, IL-5, MBP, eosinophil cationic protein (ECP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN). Baxi *et al*[63] found the presence of peripheral blood eosinophilia in 67% of EE patients. However, many of these tests are not readily available, are expensive, time consuming and, as yet, have not been recommended for routine diagnosis of EE. More research thus needs to be done to correlate these tests with disease severity and patient demographics and to establish accurate and precise laboratory investigative methods and normal values[62] before they become part of the mainstream diagnostic tool scenario.

TREATMENT

Treatment modalities for patients with EE include pharmacological, endoscopic or dietary interventions used either singly or in combination. Endpoints of treatment are still not clear regarding whether relief of symptoms or esophageal inflammation need to be resolved. Clinicopathologically, EE involves esophageal eosinophilia and other causes of esophageal eosinophilia such as inflammatory bowel disease, parasitic infestation and GERD need to be ruled out[64].

Acid suppression

The association between GERD and EE is as yet unclear. Persistent reflux disease may cause esophageal eosinophilia, or EE may lead to secondary GERD[47] or simply, they may co-exist[31]. Acid suppression with PPIs helps to exclude GERD because EE is defined by a lack of response to PPI therapy[1]. There is some controversy as to this definition since Molina-Infante *et al*[65] showed that clinical response to PPIs does not completely rule

out quiescent EE. Furthermore, pathological diagnosis of EE should be done after a patient has been on PPI therapy for at least 4 wk. An important role of the use of PPI in patients with EE is symptomatic relief because of the multilayer involvement of the esophagus and the possibility of secondary GERD[64].

Systemic steroids

Systemic steroids are effective in managing EE. Liacouras *et al*[60] conducted a 10-year retrospective study of 381 patients diagnosed with EE and found that systemic corticosteroids significantly improved clinical symptoms and esophageal histology. Unfortunately EE recurred after withdrawal of steroids. Thus, side effects and recurrence after withdrawal limit their usage in management of EE.

Topical steroids

Arora *et al* evaluated 21 patients with dysphagia and treated them with swallowed fluticasone. Relief of dysphagia occurred in all and symptom relief lasted at least 4 mo. Schaefer *et al*[66] compared oral prednisone and swallowed fluticasone and found no clinical advantage of prednisone over fluticasone. Symptom relief and histological improvement were observed in both treatment groups. Symptom relapse was seen in both groups upon discontinuation of therapy, thus necessitating the need for long-term maintenance protocols. Because of the higher risk of systemic side effects and the need for maintenance therapy, topical therapy may actually turn out to be a better option. Currently, there are no steroids developed specifically for EE. Aceves *et al*[67] described a case series of two children who benefited from treatment with a viscous suspension of budesonide but not with fluticasone. However, studies to determine the efficacy of different topical steroids, methods of preparation and long-term maintenance need to be performed to recommend any one steroid over another.

Leukotriene inhibitors

Leukotrienes are eosinophil chemoattractants and hence one would expect that blocking leukotrienes may decrease eosinophilic migration and accumulation. Attwood *et al*[68] studied 12 patients who hitherto had been unresponsive to conventional therapy and started eight of them on montelukast. Six of these patients reported complete subjective improvement. Preceding this, there had been reports of an association between zafirlukast, another leukotriene inhibitor, and Churg-Strauss syndrome[69,70]. This association has not yet been seen with montelukast, but further studies are needed to determine the risks and benefits of using leukotriene inhibitors in patients with EE.

Biologics

IL-5 is a cytokine that plays a role in eosinophil regulation[71], and as such, inhibiting IL-5 could play a role in decreasing eosinophil-mediated inflammation. Garrett *et al*[72] performed an open label trial of mepolizumab, a humanized blocking monoclonal antibody against IL-5, in four patients with hypereosinophilic syndrome, and found it to be effective and safe with steroid-sparing properties. This was later corroborated by Stein *et al*[73] and anti-IL-5 seems to be a promising new therapy in patients with EE.

Immunomodulators

Netzer *et al*[74] evaluated three patients with corticosteroid-dependant EE and found that azathioprine and 6-mercaptopurine induced clinical and histological remission in all of them. More studies are indicated in this area, especially since treatment with immunomodulators can potentially help in decreasing the side effects associated with chronic steroid use.

Elemental and elimination diet

Infiltration of the esophagus with eosinophils forms the hallmark of EE. Because of the close association of EE with other allergic disorders, avoidance of presumed allergens provides a rationale for the use of an elimination diet in patients with EE. An elemental diet is one in which all solid foods are replaced with a nutritionally complete elemental formula and the protein source is comprised entirely of synthetic amino acids[75], whereas an elimination diet attempts to avoid including possible food allergens in a person's daily diet. Kelly *et al*[5] studied 10 children with GERD refractory to standard medications and fed them elemental diet followed by repeat endoscopy and food challenges. Symptomatic improvement with a decrease in eosinophils was seen in all patients. Symptoms relapsed after these patients were exposed to food challenges. This pioneering work formed the basis for many follow-up trials, which reported success with elimination diets. Markowitz *et al*[6] found that patients responded symptomatically and histologically to an elemental diet. Further confirmation of the success of an elemental diet was also confirmed using more formal evaluation with skin prick and atopy patch testing[76,77]. Sugnanam *et al*[78] then analyzed prospectively the sensitization profile of food and inhalant allergens in their cohort of patients with EE, by performing skin prick and patch testing. They found that younger patients showed more IgE and patch sensitization to food allergens. Spergel *et al*[77], in their retrospective study analyzing the relation between skin prick and atopy patch testing and food elimination diet in patients with EE, found that a large number of their patient population had normalization of biopsy results on elimination and reoccurrence on reintroduction. Kagalwalla *et al*[16] used a six-food elimination diet rather than the conventional elemental diet and found it to be associated with good clinical and histological response. The major problem with an elemental diet is the lack of palatability and thus a six-food elimination diet offers the advantage of better acceptability and compliance[16]. Elemental formulae do not contain fiber, and other nutrients may not be available based on the formula used in any particular patient. In these situations, fiber supplementation may be useful, especially in children or those who are prone to constipation, and other nutrients may be provided by other foods[75]. It is also beneficial

to have a registered dietician or a nutritionist involved because elimination diets may have a significant impact on the whole family who will need to be educated on the type of food that the patient can safely eat and on balancing the daily nutritional requirements of the individual. Food reintroduction forms an important aspect of management. Spergel and Shuker, in their article on nutritional management of EE, advocate reintroducing the least allergic foods followed by the most allergic ones. Periodic endoscopies are performed to assure symptomatic and histological improvement. If symptoms reappear, then that food is avoided, but by using this approach, patients can go back to an appropriate diet acceptable to the patient and the family[75].

Endoscopic dilatation

EE is characterized by eosinophilic infiltration that may extend into deeper layers of the esophagus[1] and by subsequent chronic inflammation causing tissue remodeling including subepithelial fibrosis[45]. Endoscopically, this may present as luminal narrowing, stricture formation or decreased tissue compliance[40], wherein, patients typically present with chronic dysphagia or foreign-body impaction. Food impaction is one of the commonest causes of dysphagia, and is considered an alarm symptom warranting immediate evaluation. The push technique has previously been advocated in acute esophageal food impaction[79,80]. Recent reports have suggested a prevalence of EE in at least 50% of patients with esophageal food impaction[81,82]. EE therefore is now increasingly being considered in patients presenting with the above symptoms. However, Kaplan *et al*[50] reported that tearing of the esophagus can occur even with routine passage of the endoscope, and because of this, dilatation was recommended after careful consideration only in those patients non-responsive to medical therapy and having rings obstructing the lumen. Fox in his article reported that longitudinal tearing or splitting of the mucosa is occasionally appreciated only during withdrawal of the endoscope[40], thus extreme care is warranted is selecting patients for endoscopic evaluation and dilatation. In a recent article, Straumann cautions against food bolus removal with rigid endoscopy in patients suspected of having EE, because of the high rate of perforation[52]. Other reports, however, suggest endoscopic dilatation to be a relatively safe procedure. Croese *et al*[8] found that 87% of their patients with EE had tears but none had serious complications, thus indicating dilation to be a safe intervention in patients with strictures. It will be worthwhile to conduct trials to evaluate whether the frequency of endoscopic dilations or the risk of complications with endoscopic maneuvers decrease if patients have prior medical treatment.

CONCLUSION

Eosinophilic esophagitis is increasingly being recognized in the adult population. It can present with a variety of symptoms including dysphagia and food impaction, along with other nasal and trachea-bronchial symptoms. Long-term sequelae of EE may include secondary malnutrition, weight loss, and acute esophageal perforations. Diagnosis of EE involves clinicopathological criteria and endoscopic biopsies. Because of the absence of a single known factor involved in the pathogenesis of EE, treatment options are multiple and include acid suppression, steroids, leukotriene inhibitors, elemental and elimination diets, and endoscopic dilations. Careful selection of patients must be done before the initiation of therapy because of the inherent risks and acceptability involved in each of them.

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