REVIEW

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An Overview of Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease affecting both children and adults. The condition is characterized by an eosinophilic infiltration of the esophageal epithelium. Symptoms of esophageal dysfunction include dysphagia, food impaction and symptoms mimicking gastroesophageal reflux disease. Endoscopic examination typically reveals mucosal fragility, ring or corrugated mucosa, longitudinal furrows, whitish plaques or a small caliber esophagus. Histologic findings of >15 eosinophils per high-power field is the diagnostic hallmark of EoE. An elimination diet, topical corticosteroids or endoscopic dilation for fibrostenotic disease serve as effective therapeutic option. **(Gut Liver 2014;8:590-597)**

Key Words: Eosinophilic esophagitis; Gastroesophageal reflux; High-power field

INTRODUCTION

The occurrence of eosinophilic esophagitis (EoE) has increased recently and has become increasingly recognized in the past decade in Western countries. Since the mid-1990s, EoE has been diagnosed by both gastroenterologists and allergy specialists and EoE has rapidly emerged as a distinct disease entity in both pediatric and adult gastroenterology, and the studies of EoE have increased in number.[1-3] However, only limited studies has been published in Asian countries including Korea.[4,5]

In this paper, we discuss the data published mainly within the last 5 years on the epidemiology, pathogenesis, clinical symptoms, diagnosis, treatment, and prognosis of EoE.

EPIDEMIOLOGY

It is debatable whether the reason for the recent high prevalence of EoE is a real increase in the incidence or increased diagnosis due to increased awareness about the disease. However, a recently published 20-year prospective, population-based study from Switzerland in the absence of EoE awareness program suggests actual increase in EoE's incidence and prevalence (Table 1).[6] In a retrospective study in all patients from a Australian provincia city with otherwise unexplained eosinophillic inflammation of the squamous epithelium, no diagnosis of EoE was made between 1981 and 1994 but 12 patients were diagnosed between 1995 and 2000 and 19 patients between 2001 and 2002 indicating a clear increase in incidence of EoE in this area.[7] It is estimated that EoE in Westernized countries affects between 40 and 55 individuals per 100,000 population, similar to that of Crohn's disease.[3]

Recent meta-analysis studies that surveyed the papers published in English from 1978 to 2005 show the male-to-female ratio of 3:1 with most subjects being in the 30s and 40s.[8,9] In a

Table 1. Eosinophilic Esophagitis Incidence and Cumulative Prevalence (95% CIs) Evaluated in 3-Year Intervals

3-yr interval	Incidence per 100,000 inhabitants (95% CI)	Cumulative prevalence per 100,000 inhabitants (95% CI)
1989–1991	1.2 (0.25–3.52)	3.6 (0.75–10.56)
1992–1994	1.6 (0.42–3.98)	7.9 (3.27–16.77)
1995–1997	1.1 (0.24–3.36)	11.5 (5.51–21.14)
1998–2000	0.7 (0.09–2.74)	12.5 (7.05–23.82)
2001–2003	0.7 (0.09–2.71)	13.4 (8.60–26.40)
2004–2006	4.4 (2.30–7.77)	26.6 (18.89–42.38)
2007–2009	7.4 (4.48–11.34)	42.8 (36.96–67.33)

Incidence is reported per 100,000 inhabitants per year as the mean of a 3-year interval. Cumulative prevalence was calculated per 100,000 inhabitants at the end of the time interval. Adapted from Hruz P, *et al*. J Allergy Clin Immunol 2011;128:1349-1350.e5, with permission from Elsevier.[6]
CI, confidence interval.

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prospective study conducted in the United States, 31 patients with esophageal food impaction were evaluated for 3 years. Seventeen of 31 patients (54.8%) had >20 eosinophils/high-power field [HPF] without gender predilection.[7]

EoE was diagnosed in 3.4% of children with reflux symptoms[1] and 6.8% of children with reflux esophagitis.[8] In addition, EoE showed a higher prevalence of 68% to 94% in children with reflux symptoms not responding to proton pump inhibitors (PPIs).[10-12]

PATHOPHYSIOLOGY/PATHOGENESIS

EoE is an immune/antigen-mediated disease in which food or environmental antigens stimulate an inflammatory response. EoE is frequently associated with allergy, although the causal relationship is not known. Rates of allergic rhinitis, asthma, and eczema in patients with EoE range from 40% to 75%, 14% to 70%, and 4% to 60%, respectively.[3,13,14] The percentage of male in adults and pediatric patients is similar, 75% and 73%, respectively, while the incidence of atopic diseases including asthma, atopic dermatitis, and food allergy are more common (51% to 84%) in children than in adult patients with EoE (29% to 60%) although these diseases are prevalent in both pediatric and adult patients.[14]

In addition, seasonality associated with EoE suggests that aeroallergen may play a role in the pathogenesis of EoE.[3,13] Approximately 53% to 73% of patients with EoE are positive on the skin prick test, which is associated with exogenous allergic reactions related to serum immunoglobulin E (IgE).[14] However, the fact that 27% to 47% of patients displayed a negative skin prick test may indicate a role of endogenous nonallergic mechanisms leading to eosinophil infiltration unrelated to IgE.[9]

Eosinophilic infiltration has been reported to be related to key cytokines, such as interleukin (IL)-4, IL-5, IL-13, and eotaxin,[15-17] which stimulate the production of eotaxin-3, a potent chemokine in the esophageal mucosa. In turn, eotaxin-3 recruits and activates eosinophils to secrete proinflammatory and profibrotic mediators. IL-5 activates eosinophils, which in turn release transforming growth factor β stimulating fibroblasts and inducing fibrosis. IL-13 upregulates eotaxin-3, which recruits eosinophils in esophageal mucosa. In animal models, intratracheal administration of IL-13 induced infiltration of eosinophils in esophageal mucosa. In other words, these mediators cause eosinophilic infiltration, local tissue damage, perturb inflammatory response, and induce fibrosis, resulting in esophageal remodeling and dysfunction.[17,18]

CLINICAL FEATURES

The main clinical symptoms are vomiting, dysphagia, and abdominal pain in children, whereas dysphagia with food impaction is common in adults (Table 2).[3] Less common symptoms in adults are heartburn, noncardiac chest pain, odynophagia, and vomiting.[3,13] Peripheral eosinophilia appears in about 60% of pediatric patients and 5% to 50% of adult patients.[19] Increased serum IgE, skin prick test and positive radioallergosorbent test result are observed in 40% to 73% of patients.[3,14] Normal 24-hour esophageal pH monitoring pattern is observed in more than 90% of pediatric patients and 85% to 100% of adult patients.[14]

DIAGNOSIS

EoE can be diagnosed if eosinophilic infiltration is found in esophageal epithelium. Eosinophils are not present in normal appearing mucosa, but eosinophilic infiltration can occur from various diseases, such as gastroesophageal reflux disease (GERD), eosinophilic gastroenteritis, collagen vascular disease, achalasia, and parasitic infections.[20,21] The presence of allergic history, appropriate clinical symptoms and endoscopic findings, and histopathologic findings are helpful in excluding other diseases. Few eosinophils can be observed in the mucosa (≤4 per HPF) in GERD but typical endoscopic appearance of EoE such as longitudinal furrows may not be seen in GERD. GERD is usually responsive to acid suppression but nonresponsive to steroid therapy.[22]

In 2011, diagnostic guidelines were updated.[13] These included the followings: 1) symptoms related to esophageal dysfunction; 2) ≥15 eosinophils per HPF in at least one esophageal biopsy specimen, with few exceptions; 3) eosinophilia limited to the esophagus; and 4) other causes of esophageal eosinophilia excluded, particularly PPI-responsive esophageal eosinophilia (PPI-REE) (Table 3).[13] Several studies have shown that more than one-third of patients with esophageal eosinophilia respond to PPI treatment. However, it is unknown whether PPI-REE is a separate, new disease entity, an atypical manifestation of GERD, or a variant form of EoE that responds to PPI. In 2012, Dellon[21] suggested a novel diagnostic algorithm for EoE (Fig. 1), in which

Table 2. Symptoms Suggestive of Eosinophilic Esophagitis

Children	Adult
Feeding aversion/intolerance	Dysphagia
Vomiting/regurgitation	Food impaction
"GERD refractory to medical management"	"GERD refractory to medical management"
"GERD refractory to surgical management"	
Food impaction/foreign body impaction	
Epigastric abdominal pain	
Dysphagia	
Failure to thrive	

Adapted from Furuta GT, *et al*. Gastroenterology 2007;133:1342-1363, with permission from Elsevier.[3]

Table 3. Rationale for the Definition of and Diagnostic Guidelines for Eosinophilic Esophagitis

1. Change in EE abbreviation. EE often has been used as an abbreviation for erosive esophagitis. Use of the abbreviation EoE rather than EE for eosinophilic esophagitis should eliminate the potential for confusion.
2. Inclusion of the word chronic. Clinical experience supports that EoE is a chronic disease that will require long-term follow-up and treatment.
3. Inclusion of the term immune/antigen driven. An increasing body of clinical, translational, and basic evidence supports a role of an aberrant immune response (potentially reversible with treatment) as an underlying pathogenetic feature of EoE.
4. Continued use of the word clinicopathologic. No biomarker or pathognomonic element has been identified that would eliminate the need for both symptoms and an abnormal histology to make the diagnosis.
5. No change in threshold number of 15 eosinophils/HPF. Since the 2007 CR, no studies have identified a clear "lower limit of esophageal eosinophilia" or threshold number that would define EoE or have identified other histologic features or pattern of disease distribution that are pathognomonic of EoE.
6. No change in the use of HPF as the unit of measurement for eosinophilia. No studies have yet determined a standardized size of an HPF, and this might be practically unachievable. This issue is problematic because the size of an HPF can alter the reported number of eosinophils per HPF.
7. Inclusion of topical steroids/diet exclusions as a treatment. Current clinical evidence exists to include this paradigm to differentiate EoE from other diseases. Other potential therapies might exist but have not yet been supported in the literature.
8. Exclusion of GERD reference. A number of other causes of esophageal eosinophilia have been identified, and a broader statement has been included that allows for clinical discretion to be used.
9. Inclusion of patients with less than 15 eosinophils/HPF. A small number of patients with EoE (and who are treated with a PPI) might have less than the threshold number of eosinophils on their mucosal biopsy specimens associated with other features of eosinophilic inflammation, including microabscess formation, superficial layering, or extracellular eosinophil granules. Potential reasons for this finding include but are not limited to inadequate biopsy specimens, sampling error, chronic disease, or partial treatment response.
10. Inclusion of the term PPI-responsive esophageal eosinophilia. Therapeutic/basic studies and clinical experience have identified a potential anti-inflammatory or barrier-healing role for proton pump inhibition in patients with esophageal eosinophilia.

Adapted from Liacouras CA, *et al*. J Allergy Clin Immunol 2011;128:3-20.e6, with permission from Elsevier.[13]
EoE, eosinophilic esophagitis; HPF, high-power field; CR, consensus recommendation; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

EoE must be suspected clinically at first followed by endoscopy with biopsy. To differentiate the other causes of esophageal eosinophilia, in particular GERD or PPI-REE, endoscopy with biopsy is recommended after a trial of PPI for 8 weeks.

1. Endoscopic findings

A number of studies have reported several typical endoscopic features of EoE: fixed esophageal rings (corrugated rings or trachealinization), transient esophageal rings (felinization), whitish exudate or papules, longitudinal furrows, small/narrow-caliber esophagus, and mucosal laceration induced by passage of endoscope (fragile crêpe paper-like appearance).[8,23] We previously studied the concordance rate and clinical predictors of EoE in endoscopically suspected eosinophilic esophagitis (EsEoE).[23] Of 17 patients with EsEoE, five were finally confirmed as EoE by histology (diagnostic concordance rate, 29.4%). In a study by Sgouros *et al*.,[9] normal endoscopic finding was observed in only 8.8% of the patients with EoE.

The most common endoscopic findings of EoE are mucosal or linear sheering after the passage of the endoscope (59.3%), rings or corrugated esophagus (49.2%), strictures (39.7%), whitish exudates or papules (15.7%), and narrow/small-caliber esophagus (5.3%).[8] Additionally, longitudinal furrows, diminished/lost vascularity, and fragile crêpe paper-like appearance are observed. Longitudinal furrow, as shown in Fig. 2, was the most common endoscopic finding (6/9, 66.7%), and only one of nine patients with EoE presented normal looking mucosa (11.1%).[23] We concluded that patients with dysphagia with two or more of the aforementioned endoscopic findings were more suggestive of EoE. However, we did not find positive correlation between eosinophil density in biopsy specimens, clinical symptoms, and endoscopic features.

Endoscopic ultrasonography (EUS) reveals that longitudinal furrows present as topographical changes caused by thickening of mucosa and submucosa.[24] Thickened esophageal wall combined with mucosa, submucosa, and muscularis propria was found in EoE using EUS. Therefore, causes of dysphagia and/or food impaction may be explained by thickened muscle layer consisting of muscular dysfunction.

2. Histopathologic features

EoE is characterized by a dense eosinophilic infiltrate into the

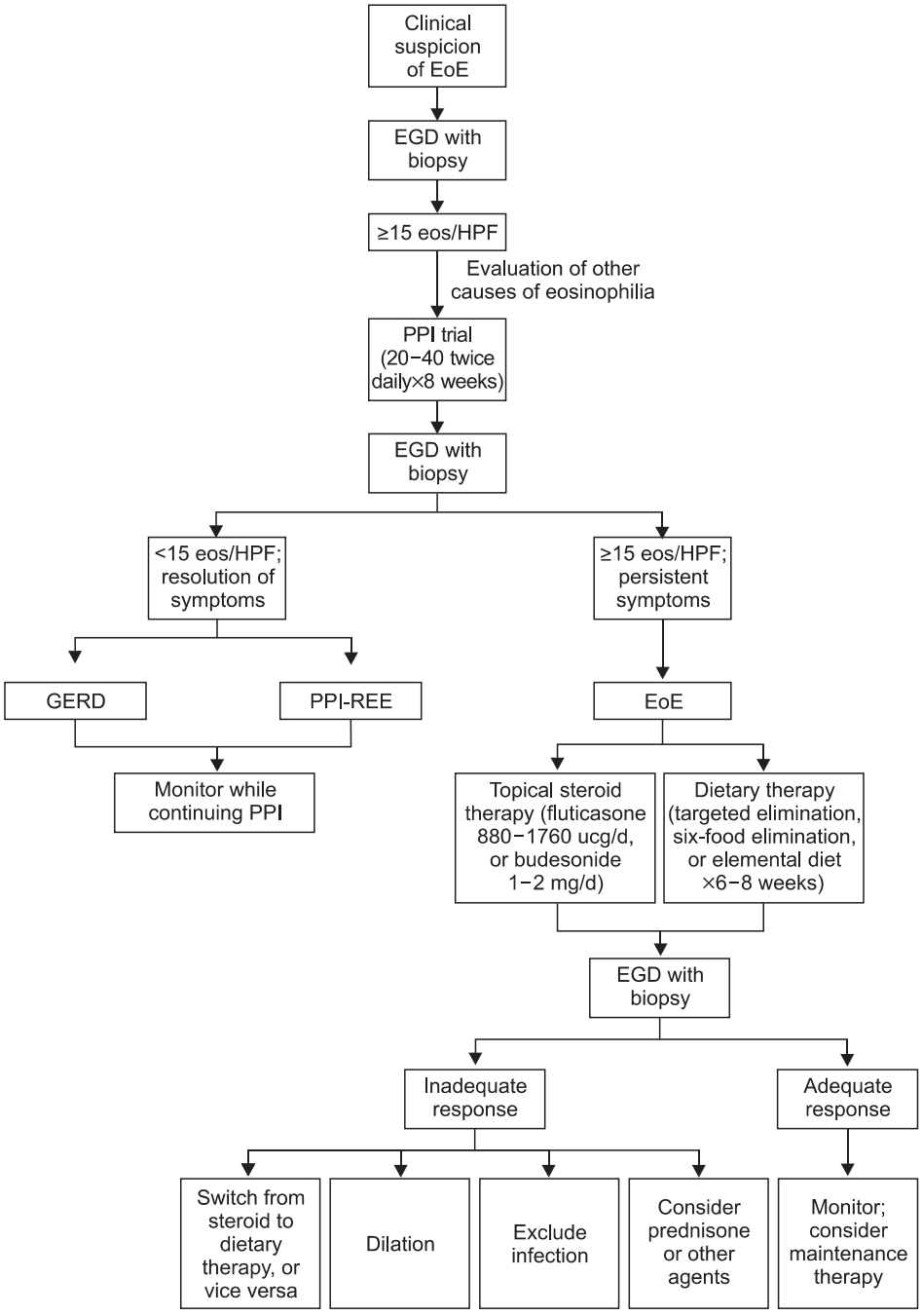

Fig. 1. A diagnostic and therapeutic algorithm of eosinophilic esophagitis (EoE). Adapted from Dellon ES. Clin Gastroenterol Hepatol 2012;10:1066-1078, with permission from Elsevier.[21]
EGD, esophagogastroduodenoscopy; eos, eosinophils; HPF, high-power field; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; PPI-REE, PPI-responsive esophageal eosinophilia.

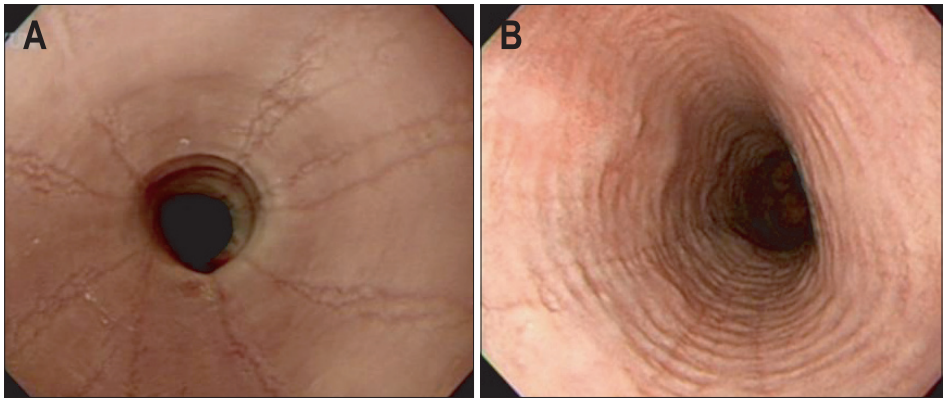

Fig. 2. Endoscopic features. (A) Longitudinal furrows. (B) Furrows and rings (spider web-like appearance).

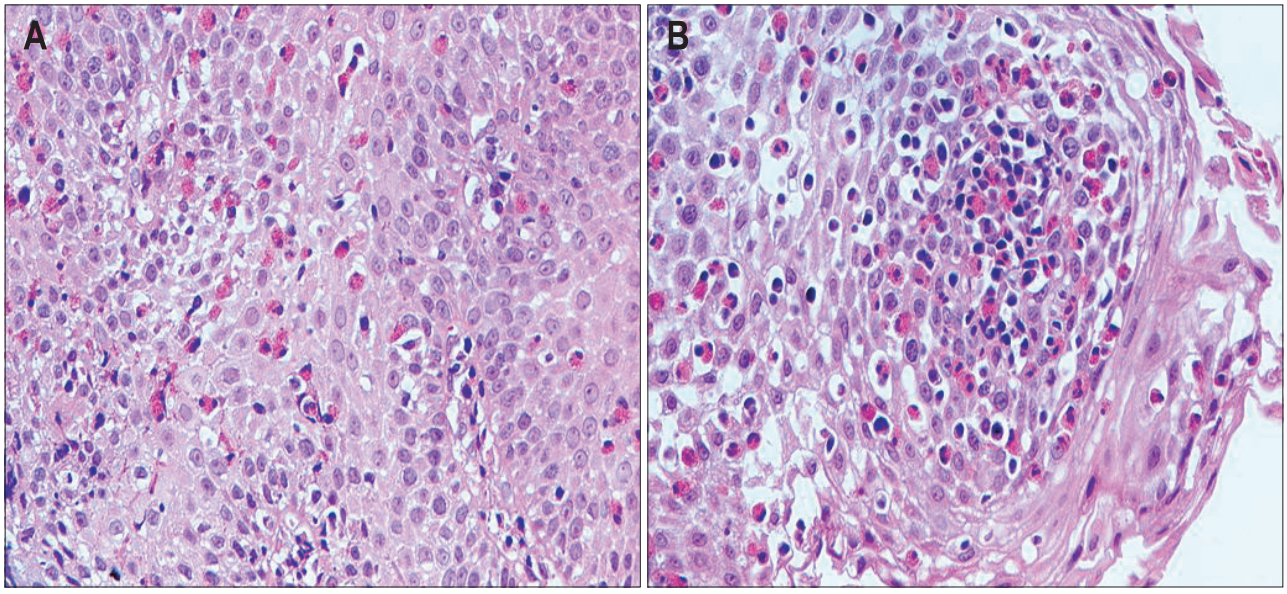

Fig. 3. Histologic findings. (A) Massive infiltration of eosinophils on the esophageal mucosa, >15 eosinophils/high-power field. (B) Eosinophilic microabscess (H&E stain, ×200).

epithelium of the squamous esophagus, as shown in Fig. 3A. To optimize pathologic diagnosis, endoscopic biopsy should be taken from the proximal and distal esophagus, since eosinophils are not evenly distributed within the esophageal mucosa.[21] Eosinophilic infiltration should be absent in gastric and duodenal mucosa. The optimal number of biopsies is essential for accurate diagnosis. The diagnostic sensitivity of 2, 3, and 6 biopsy specimens are 84%, 97%, and 100%, respectively.[13]

EoE is also characterized by the formation of microabscesses by eosinophil infiltration in the superficial layer of the esophageal epithelium, which is observed in 25% to 45% of the patients with EoE.[25,26] The histologic picture of eosinophilic microabscess is shown in Fig. 3B. It is not observed in patients with GERD or peptic esophagitis. Infiltration of the superficial layer by eosinophils lasts after acid blockade therapy for at least 2 months.[26] Noncharacteristic findings, such as basal zone hyperplasia and increased papillary size are also observed.[14] In our previous study, associated features included degranulation (100%), spongiosis (91.7%), and eosinophilic microabscess (58.3%).[27]

The 2011 diagnostic guideline describes more than 15 eosinophils/HPF in at least one esophageal biopsy specimen, with few exceptions, and eosinophilia limited to the esophagus. "Few exception" are defined as those patient with <15 eosinophils/HPF with other features of eosinophilic inflammation including microabscess formation, superficial layering or extracellular eosinophil granules.[13]

3. Esophageal motility studies

The esophageal functions have been studied by barium esophagogram, EUS, manometry, and impedance planimetry. Esophageal manometic studies detect esophageal motility disorders related to EoE. Incordination of esophageal contraction (30%), incomplete relaxation of lower esophageal sphincter, excessive contraction of the esophagus (7%), and ineffective peristalsis (4%) were mainly observed.[9] In addition, tertiary esophageal contractions, aperistalsis, multipeaked contractions, diffuse spasm are also frequently observed. About 40% of patients had shown normal manometric findings. Therefore, there are no pathognomic findings of manometry for the diagnosis of EoE. These esophageal motility disorders occur when eosinophilic infiltration affects the muscularis propria, in addition to mucosal infiltration.

The recent introduction of high resolution manometry (HRM) and impedance planimetry allowed the identification of panesophageal pressurization (by manometry) and changes in esophageal compliance with decreased distensibility (by impedance planimetry).[28,29] Roman *et al*.[28] found that 37% of EoE patients showed abnormal esophageal motility when HRM was used. The most common findings were weak peristalsis and frequent failed peristalsis, although these findings were also observed in GERD. However, panesophageal pressurization was a specific findings in EoE, which represents a manifestation of reduced esophageal compliance.

4. Laboratory findings

Peripheral eosinophilia is found in 40% to 50% of patients with EoE, and its count decreases after successful treatment with topical corticosteroids.[3,13] Peripheral eosinophilia is correlated with the number of esophageal eosinophils. Serum total IgE levels are increased in 50% to 60% of patients with EoE,[20,21] although its level does not reflect either histologic inflammation

or predictor of therapeutic response. The skin prick test (SPT) is an immediate type allergic test for food allergen and aeroallergen.[20,21] SPT is warranted in detecting food allergy associated with EoE, although the usefulness of therapeutic application including specific food avoidance by its positivity is still limited and requires more study to validate its significance.

TREATMENTS

It is helpful to identify the algorithmic process for diagnosis and proper treatment, prior to undertaking major treatment including corticosteroids.[21] The goal of the treatment would be complete symptom relief and resolution of esophageal eosinophilia. To exclude other causes of esophageal eosinophilia such as GERD and PPI-REE, an 8-week trial of high-dose PPI and repeat endoscopy are recommended. PPIs have anti-inflammatory effects by reducing eosinophils by decreasing Th2 cytokine-stimulated eotaxin-3 mRNA expression and protein secretion independent of the effects on acid production.[30,31] In fact, several studies have reported that one-third or more patients with esophageal eosinophilia responded to PPI treatment.[5] Therefore, it has been suggested that PPIs might not distinguish EoE from GERD.

If EoE is confirmed, diet therapy and topical corticosteroid to suppress immune response will be initiated.[32] When evidence of fibrostenotic disease, such as narrow-caliber esophagus or stricture, is present, endoscopic dilation is effective in improving the symptoms. After the treatment, symptoms and eosinophil counts are generally improved, but endoscopic findings may not be improved, indicating that deformity of esophageal structure, or remodeling due to eosinophilic inflammation is irreversible.

1. Diet

Food allergy has been commonly observed in 15% to 43% of subjects with EoE.[33] Therefore, it has been suggested that identification and elimination of potential food antigens which cause antibody response and eosinophilic infiltration would be an effective preventive ad therapeutic approaches.[13,19,20] SPT and patch testing were used to identify the potential food antigens, and the patients were advised to avoid positive foods as identified by these tests. In this study, 18 patients had a concurrent improvement in biopsy and clinical response, and six patients had partial improvement.[34] According to the proposal of Markowitz and Liacouras,[22] the foods that trigger allergy by testing or past history should be eliminated and if the food allergens are not identified, the foods to which patients are most likely to be allergic (i.e., cow's milk, soy, eggs, wheat, and peanuts) are empirically eliminated.

A diet eliminating milk, egg, soy, wheat, nuts, and seafood (six food elimination diet, SFED) has been reported to be an effective therapy in EoE. Gonsalves *et al*.[35] demonstrated that SFED significantly improved symptoms, endoscopic features, and histopathology, and reintroduction of food reproduced EoE confirming a role for food allergens.

2. Corticosteroids

The use of steroids is one of the mainstays of pharmacologic treatment. Oral corticosteroid therapy improves the symptoms within 1 week when administered for 1 month,[10] but systemic steroids use is associated with side effects. Whereas topical steroids, such as flucatisone and budesonide, known as swallowed inhaled steroid therapy, are effective treatments for improvement of symptoms and resolution of esophageal eosinophilia. In a study in adults that included 21 patients who were administered topical steroids for 6 weeks, all patients had relief of dysphagia that lasted a minimum of months.[17] Dry mouth was the only adverse effect noted and esophageal candidiasis was not reported. Three patients relapsed after 4 months.[18] Recommended doses of corticosteroid treatment protocol for EoE are shown in Table 4.[13] If topical steroids are stopped after initial treatment, most of them recurred. But, there is little data regarding the effectiveness of maintenance treatment. Long-term maintenance treatment with low dose budesonide (0.5 mg/day) for 50 weeks was more effective than placebo in maintaining EoE in clinical and histologic remission,[36] although the optimal duration and dose of budesonide are not yet clarified.[37]

3. Leukotriene antagonist, mast cell stabilizer, and other biologic drugs

Immunotherapy related to allergic medications includes the leukotriene D4 receptor antagonist and anti-IL-5.[38] Montelukast, a selective inhibitor of the leukotriene D4 receptor, is also used

Table 4. Recommended Doses of Corticosteroids for Eosinophilic Esophagitis

Topical swallowed corticosteroids
Initial doses (see references for preparation and administration information)
Fluticasone (puffed and swallowed through a metered-dose inhaler)
Adults: 440–880 μg twice daily
Children: 88–440 μg twice to 4 times daily (to a maximal adult dose)
Budesonide (as a viscous suspension)
Children (<10 yr): 1 mg daily
Older children and adults: 2 mg daily
Systemic corticosteroids
For severe cases (e.g., small-caliber esophagus, weight loss, and hospitalization)
Prednisone: 1–2 mg/kg

Adapted from Liacouras CA, *et al*. J Allergy Clin Immunol 2011;128: 3-20.e6, with permission from Elsevier.[13]

for the treatment of asthma in adults. In a study reported by Attwood *et al*.,[39] eight adult patients with EoE was started on 10 mg per day dose of montelukast but the dose was increased up to 100 mg daily if required. Once symptom was relieved, the dose was reduced to maintenance levels between 20 and 40 mg per day. Six of eight patients reported complete subjective improvement and five patients remained completely asymptomatic. However, the safety of the high dose used in this study is unclear.[26] Montelukast could not completely treat the infiltration of eosinophils in the esophageal tissue.[39]

Cromolyn sodium, a mast cell stabilizer, is not thought to have apparent therapeutic benefit in patients with EoE.[38] A study conducted with mepolizumab, a humanized monoclonal antibody against IL-5, suggested improvement in patient with EoE in clinical symptoms, endoscopic findings, and histologic findings. However, the long-term effect or safety of this drug need to be further investigated.[40] Additionally, anti-IL-13 monoclonal antibodies, antieotaxin-3, anti-IgE antibodies and anti-inflammatory drugs have been used either to treat EoE or under development.[37,38] However, these biologic agents are not yet in clinical practice in patients and require further scientific evidence.

4. Endoscopic dilation

Endoscopic dilation with balloon is effective for relieving symptoms of dysphagia with the evidence of ring or stricture. Since it does not affect eosinophilic infiltration and inflammation, medical therapy and/or dietary therapy should be undertaken after dilation.[21,38] A total of 83% of patients experienced immediate symptomatic improvement after esophageal dilation, but some patients experienced symptomatic recurrences after 3 to 8 months in a long-term follow-up.[9]

NATURAL HISTORY AND PROGNOSIS

EoE is a chronic disease, in which symptoms and inflammation relapse after cessation of successful treatment, is common.[41] EoE does not seem to limit life expectancy, but impairs the quality of life. In an 11.5-year follow-up study, the eosinophilic inflammatory process remained confined to the esophagus without transition to eosinophilic gastroenteritis or other disease.[42] It has not been associated with increased risk of malignant conditions. But many uncertainties still exist, particularly natural history and prognosis.[37]

CONCLUSIONS

EoE is a chronic, immune/antigen-mediated esophageal disease characterized by eosinophilic infiltration and typical clinical presentation includes dysphagia and food impaction due to fibrostenosis associated with inflammatory changes and alteration of biomechanical properties. Endoscopic examination reveals mucosal fragility, longitudinal furrows, ring or corrugated mucosa, whitish papules, or small caliber esophagus. After exclusion of other causes of esophageal eosinophilia including PPI-REE or GERD, the tailored treatment of diet therapy, corticosteroids, and/or endoscopic dilation is considered according to its phenotype of whether inflammatory and/or fibrostenotic changes in the esophagus. Further basic and clinical research data are needed to understand its pathophysiology, biomarkers, clinical courses and to update the diagnostic algorithm and develop novel treatments.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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