Role of endoscopy in eosinophilic esophagitis

Eun-Jin Yang, Kee Wook Jung

Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease involving inflammation of the esophagus. Endoscopy is essential in the diagnosis and treatment of EoE and shows typical findings, including esophageal edema, rings, exudates, furrows, and stenosis. However, studies involving pediatric and adult patients with EoE suggest that even a normally appearing esophagus can be diagnosed as EoE by endoscopic biopsy. Therefore, in patients with suspected EoE, biopsy samples should be obtained from the esophagus regardless of endoscopic appearance. Moreover, follow-up endoscopies with biopsy after therapy initiation are usually recommended to assess response. Although previous reports of endoscopic ultrasonography findings in patients with EoE have shown diffuse thickening of the esophageal wall, including lamina propria, submucosa, and muscularis propria, its role in EoE remains uncertain and requires further investigation. Endoscopic dilation or bougienage is a safe and effective procedure that can be used in combination with medical and/or dietary elimination therapy in patients with esophageal stricture for the management of dysphagia and to prevent its recurrence.

Keywords: Endoscopic dilation; Endoscopic ultrasonography; Endoscopy; Eosinophilic esophagitis

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease involving inflammation of the esophagus. It is characterized by symptoms of dysphagia and/or food impaction with esophageal biopsy showing a peak eosinophil count of ≥15 eosinophils (eos)/high power field (hpf), excluding other causes of esophageal eosinophilia. Notably, the diagnosis of EoE has evolved over the decades. The first consensus in 2007 suggested that patients with esophageal symptoms should have ≥15 eos/hpf assessed by esophageal biopsy, excluding other causes of esophageal eosinophilia. The diagnosis of EoE has evolved over the decades. The first consensus in 2007 suggested that patients with esophageal symptoms should have ≥15 eos/hpf assessed by esophageal biopsy. Additional-ly, pathologic gastroesophageal reflux disease must be absent, evidenced by normal esophageal pH monitoring or lack of response to proton pump inhibitors (PPIs). The second consensus in 2011 suggested the presence of a new condition termed PPI-responsive esophageal eosinophilia (PPI-REE). Herein, patients exhibit symptoms of esophageal dysfunction and have ≥15 eos/hpf on esophageal biopsy but achieve improvement or resolution of symptoms and eosinophilia after high-dose PPI therapy. Consequent studies showed that clinical, endoscopic, histologic, immunologic, and molecular features at baseline (pre-PPI) do not appear to distinguish or predict who may respond to PPI therapy. Moreover, no clinical or endoscopic features independently distinguished PPI-REE from EoE prior to the PPI administration. Finally, potential non-acid mediated mechanisms of PPIs were identified, including suppression of Th2-mediated eotaxin-3 secretion and improvement of the esophageal barrier function by PPIs. Since the third consensus in 2018, PPI administration has been removed from the diagnostic guideline. Thus, EoE and PPI-REE share similar clinical, endoscopic, histologic, immunologic, and molecular features prior to PPI treatment, suggesting that distinguishing these entities based on medication trials is artificial and that PPI therapy may be better positioned as a treatment for EoE.
review summarizes the role of endoscopy in the diagnosis and treatment of EoE, including endoscopic ultrasonography (EUS).

**EPIDEMIOLOGY OF EOSINOPHILIC ESOPHAGITIS IN KOREA**

EoE has an increasing incidence and prevalence trend in Western countries. Although its prevalence and incidence in Asian countries remain poorly defined, several reports have been published in Korea. According to one study, a total of 25,271 endoscopic esophageal biopsies were performed at a tertiary care center, of which 72 demonstrated EoE after pathological and clinical review of each case. Although the number of esophageal biopsies appears to have increased only slightly from 2006 to 2016, the number of patients diagnosed with EoE appears to have significantly increased over the 12 years (p<0.001). A multicenter study in Busan city and Gyeongsangnam-do province area also showed an increasing trend in EoE diagnosis. Moreover, the recent registration of the International Classification of Diseases 10th Revision code for EoE in Korea warrants further validation of this trend based on a nationwide study like achalasia.

**ENDOSCOPY AS A DIAGNOSTIC TOOL FOR EOSINOPHILIC ESOPHAGITIS**

Endoscopy is one of the initial tests to inspect the esophagus and obtain biopsies in patients suspected with EoE. Since the early 2000s, endoscopic findings, including linear furrows, feline esophagus, ring, exudates, narrowing, and crêpe-paper mucosa, are known to be correlated with EoE. However, to avoid a missed diagnosis, the timing of initial index endoscopy is crucial for the appropriate diagnosis, particularly in patients suspected with EoE. A recently published editorial on high-quality endoscopy in EoE suggests that patients should not be undergoing PPI therapy at the time of index endoscopy because it may result in normal endoscopic findings and biopsy results, leading to a missed definitive diagnosis of EoE. Therefore, the recently published British Society of Gastroenterology (BSG) and British Society of Pediatric Gastroenterology, Hepatology, and Nutrition joint consensus guidelines recommend that PPI administrations should be discontinued for at least 3 weeks for an accurate diagnosis of EoE. Moreover, during index endoscopy for patients suspected with EoE or with symptoms and/or endoscopic abnormalities, multiple biopsy sampling should be considered from the stomach and duodenum to exclude the possibility of underlying eosinophilic gastroenteritis.

The recently published American Society for Gastrointestinal Endoscopy (ASGE) consensus recommends that at least six biopsy samples should be taken from the esophagus to improve the diagnostic yield of EoE. In a study based on 66 adult patients, the sensitivity of the EoE diagnostic yield was 100% with five biopsy specimens compared to 55% with one biopsy specimen. Moreover, esophageal eosinophilia can also have a patchy distribution. Therefore, taking biopsy samples from the endoscopic mucosal abnormalities associated with higher eosinophilic infiltration might have a higher diagnostic yield.

Biopsy samples should be taken from the distal and mid-/proximal esophagus for EoE diagnosis. Similarly, the BSG consensus guideline also recommends that six biopsies taken from at least two different levels in the esophagus, with the combination of targeted biopsies from mucosal abnormal findings and random biopsies among the six biopsies to increase the diagnostic yield of EoE.

Additionally, the ASGE consensus recommends that esophageal biopsy specimens should be obtained at the time of food impaction in case of suspected EoE if it is safe to do so. A recent systematic study on 76 esophageal perforations in patients with EoE showed that obtaining biopsy samples during the endoscopy for food obstruction was not associated with an increased risk of esophageal perforation. However, biopsy samples should be obtained from the esophagus away from the area of the food impaction to ensure patient safety. Nonetheless, EoE can be diagnosed in up to 46% of patients with food bolus impaction. Moreover, endoscopic inspection with biopsy should be performed even in an outpatient clinic if the patient resolves food impaction spontaneously.

Sometimes, patients with EoE are accustomed to longstanding dysphagia and may be unaware of its presence significantly. Therefore, the questionnaires regarding imbibing fluids with meals, modifying food by cutting it into small pieces, pacing meal times, avoiding hard texture foods, chewing excessively, or turning away tablets/pills should be administered to the patients suspected with EoE.

The typical endoscopic findings of EoE are esophageal edema, rings, exudates, furrows, and stenosis. Hirano et al. characterized and validated a grading system for EoE called endoscopic reference score (EREFS) based on the above major findings and minor features, including felinization, narrowed caliber, and crêpe-paper sign (Fig. 1). The application of the
EREFS score in adult patients showed an excellent prediction of EoE with an area under the curve of 0.934 using receiver operating characteristic analysis. The EREFS score decreases with treatment, and histologic responders have significantly lower scores than non-responders. According to a meta-analysis based on 4,678 patients with EoE and 2,742 controls, the sensitivity of these endoscopic signs for EoE diagnosis was modest, with a range of 15% to 46%, whereas specificity was greater (90–95%). The positive and negative predictive values were 51% to 73% and 74% to 84%, respectively. However, in some instances, these typical endoscopic features may be subtle and require experience for the endoscopists to suspect the possibility of EoE for obtaining biopsy specimens.

Moreover, studies involving pediatric and adult patients with EoE suggest that in 10% to 32% of patients, even a normally appearing esophagus on endoscopy can be diagnosed as EoE. Therefore, in patients suspected with EoE, biopsy samples should be obtained from the esophagus regardless of endoscopic appearance.

If symptoms recur in patients confirmed with EoE while undergoing therapy, repeated endoscopy should be considered. The multiple causes of dysphagia in spite of treatment include patients’ nonadherence to medications, inadequate dosing of medications, progression to a fibrostenotic state, or potential sequelae of treatment such as the presence of concomitant infections such as Candida.

Sometimes, the initial histology does not show an EoE diagnosis for patients highly suspected of having an EoE. Based on the recently published BSG consensus guideline, repeated endoscopy with adequate biopsies should be considered in such cases. A retrospective case series investigated 59 patients with dysphagia without a previous diagnosis of EoE with esophageal biopsies containing 1 to 14 eos/hpf (low-grade eosinophilia). Fourteen of the 59 patients underwent repeated endoscopy, of which five (36%) met diagnostic criteria for EoE of ≥15 eos/hpf.

Moreover, endoscopists may underestimate the frequency of strictures and esophagus narrowing in EoE as they are usually difficult to detect during screening endoscopy. However, they may be more apparent on barium esophagography or functional luminal imaging probe (FLIP) distensibility testing.

Recently, an expert group suggested the Index of Severity for Eosinophilic Esophagitis (I-SEE) to reduce variability in practice patterns and aid clinicians in monitoring the clinical course of the disease. I-SEE assesses symptoms/complications, inflammatory features, and fibrostenotic features. Endoscopy aids in distinguishing the inflammatory features (edema, furrows, and/or exudates) between localized and diffuse inflammation along the esophagus. Localized inflammation is scored 1 with biopsy showing 15 to 60 eos/hpf. However, with the biopsy showing >60 eos/hpf, diffuse inflammation is scored 2. When endoscopic features of fibrostensis (rings, strictures) are noted, but the endoscope can be passed, the score is 1. When rings or strictures are present but require dilation to pass a standard endoscope, the score is 2. However when a standard size of an endoscope cannot pass and repeated dilations are required in adult patients (≥18 years old), or any dilation is required in pediatric patients (<18 years old), the score is 15.
the newly developed I-SEE requires additional data to validate its clinical efficacy.

**EUS IN EOSINOPHILIC ESOPHAGITIS**

The pathophysiology of dysphagia in EoE is complex. Chronic eosinophilic inflammation along the esophagus in patients with EoE results in fibrosis, angiogenesis, hypertrophy, and hyperplasia of multiple layers of the esophageal wall. Esophageal manometry, including high-resolution manometry with impedance, can be helpful in the diagnosis of dysphagia. However, a recently published meta-analysis suggested that the pooled prevalence of any motility abnormality confirmed by manometry was 53% (95% confidence interval [CI]: 43-63%), including minor motility disorders such as ineffective esophageal motility and fragmented peristalsis. FLIP testing can measure the passive outer distensibility of the GIT, thus complementing conventionally used manometry. Moreover, FLIP may be more efficient in the diagnosis of dysphagia in the case of EoE because patients with EoE have dysphagia due to poor distensibility associated with the diffuse fibrosis of the esophageal layer. Recent studies from a Chicago group have suggested various FLIP panometry patterns based on different EoE stages. However, FLIP is an expensive technique and is not globally available.

Previous reports of EUS findings in patients with EoE have shown diffuse thickening of the esophageal wall, including lamina propria, submucosa, and muscularis propria (Fig. 2). A recent study based on Japanese patients with esophageal eosinophilia showed that patients with symptomatic EoE had a significantly thickened lower esophageal wall than those with asymptomatic esophageal eosinophilia. In pediatric patients with EoE, Rabinowitz et al. reported that the total esophageal wall thickness correlates well with the age and height of the children. Muroi et al. used EUS and high-resolution manometry to compare pediatric patients with EoE and dysphagia with those with EoE without dysphagia. They found a significantly thicker esophageal wall layer in symptomatic patients with EoE compared to the asymptomatic patients.

However, the role of EUS in the diagnosis of EoE remains limited. Additionally, well-defined cut-off values to distinguish between active and asymptomatic EoE are lacking, and most previous studies have relatively small sample sizes. Therefore, further studies with large sample sizes are required to validate the role of EUS in diagnosing EoE.

**TREATMENT OF EOSINOPHILIC ESOPHAGITIS**

The treatment of EoE can be categorized into pharmacologic...
and non-pharmacologic management. Dietary elimination can be implemented in patients with EoE since a targeted elimination diet of six foods has shown good histologic and clinical efficacy. PPI therapy has shown good histologic and clinical efficacy. Additionally, the overall unweighted histological response rate in observational studies (≤15 eos/hpf) was found to be up to 42% in a recent meta-analysis. Swallowed topical steroids also have good histologic and clinical efficacy. A previous meta-analysis showed that histologic response rates were 68% (0.05-0.82) for fluticasone and 77% (0.63-0.87) for budesonide in treating EoE. Biologics are a pharmacologic option for patients unresponsive to PPI and oral corticosteroids. In 2022, the United States Food and Drug Administration approved dupilumab (a monoclonal antibody blocking interleukin [IL]-4 and IL-13) as the first-line treatment for EoE. Numerous other biologics have been investigated, including mepolizumab, reslizumab, and benralizumab (interfering with the IL-5 axis), cendakimab and dectrekumab (anti-IL-13 mAbs), tezepelumab (anti-thymic stromal lymphopoietin), and lirenlimab (anti-sig-12-sialic acid-binding Ig-like lectin 8).

ENDOSCOPY AS AN ASSESSMENT OF RESPONSE TO THERAPY

After therapy initiation, follow-up endoscopies with biopsy are usually recommended to assess response because symptoms may not always correlate with histologic findings. The recently published ASGE and BSG consensus guidelines recommend follow-up endoscopy with biopsy to assess the histologic response after initiating dietary or pharmacological treatment in patients with EoE. The follow-up endoscopy can be performed at 4 weeks after a change in dietary therapy or after 8 to 12 weeks for pharmacologic treatment to observe a significant histologic change. A clear consensus regarding the appropriate amount of biopsy samples required after EoE treatment is lacking. As with the diagnosis of EoE, at least four biopsied samples from previous lesions should be taken following EoE treatment.

ENDOSCOPY AS A TREATMENT TOOL FOR EOSINOPHILIC ESOPHAGITIS

Endoscopic dilation or bougienage in combination with medical and/or dietary treatment can be performed in patients with esophageal stricture. Previously, esophageal dilation was regarded as a risky procedure because of the fragility of the esophageal wall. A retrospective, uncontrolled, single-center study enrolling 161 EoE patients with 293 dilations reported complications, including deep mucosal tear (9.2%), major bleeding (0.3%), and immediate perforation (1.0%). Moreover, earlier studies reported higher rates of perforation and hospitalization, up to 5% and 7%, respectively. However, later studies showed that esophageal dilation was a safe and effective procedure. A recently published meta-analysis on 3,495 references with 27 studies analyzed 845 patients with EoE, including 87 pediatric patients, and a total of 1,820 esophageal dilations. They reported that dilation was effective and safe, with symptomatic improvement in 95% (95% confidence interval [CI], 90%-98%; I², 10%; 17 studies) of patients with minimal risk of perforation in 0.38% (95% CI, 0.18%-0.85%; I², 0%; 27 studies). Moreover, hospitalization due to dilation was rarely found in 0.67% of patients (95% CI, 0.3%-1.1%; I², 44%; 24 studies), and there were no dilation-related deaths (95% CI, 0%-0.2%; I², 0%; 25 studies). However, up to 75% of patients may complain of chest pain immediately after the procedure, and the pains may last for days. Therefore, experts and current guidelines have suggested that esophageal dilation should be gradually performed over several sessions. Esophageal dilation can be considered if symptoms persist despite the administration of pharmacologic therapy. However, dilation cannot improve esophageal eosinophilic inflammation and progressing mucosal changes.

Dilation may be the most effective treatment modality in patients with a diffusely narrowed lumen or multiple esophageal strictures (severe strictures with <10 mm in diameter). The goal of improved diameter by dilation is usually an esophageal diameter ≥15 mm. However, the immediate endpoint during endoscopic dilation could be mucosal disruption when approaching the targeted diameter. Previous studies investigating esophageal dilation success factors identified predilation stricture diameter, location, and extent of the fibrostenotic disease, evidence of inflammation, the presence of blood on a dilator, or mucosal disruption as potential success factors.

In adult patients with EoE, an ideal esophageal diameter resolving dysphagia and food impaction is usually at least 16 mm and can be achieved over ≥1 session during dilation. A retrospective study investigated the effectiveness of esophageal dilation among 207 adult patients with EoE. They found that an increase in the mean esophageal diameter from 11±3 (4–15) mm to 16±2 (11–20) mm was associated with a significant symptomatic improvement of dysphagia. However, cautious
serial dilations and appropriate choice of the initial dilator with repeated endoscopic inspections identifying esophageal tears are recommended for safe dilation.63,64 When serial dilations are required, >3 mm in a single dilation session is not recommended.13,66

Effective management of esophageal inflammation is necessary to minimize repeated esophageal dilation because active esophageal eosinophilic infiltration in patients with EoE can progress to esophageal fibrosis, stricture, and stenosis.13,65,66 One study observed that patients with a histologic response to steroids showed a 65% decrease in the need for subsequent dilation.62 Similarly, another study showed that the maintenance therapy in patients with EoE decreased the need for repeated esophageal dilation.67

Endoscopists can opt for various dilation methods in patients with EoE, such as bougies or through-the-scope balloons, which are equally efficacious.59,68 Bougie dilation can dilate the entire esophagus with a fixed diameter.13 Savary bougies can be used for a more narrowed esophagus.13 Similarly, through-the-scope balloon dilation is used for esophageal dilation.69

Dilation therapy is usually recommended with concomitant medical or diet elimination therapy for the management of dysphagia to prevent recurrent dysphagia.13 A study of 55 patients with EoE who underwent initial esophageal dilation with topical steroid therapy showed that 27 histologic responders required significantly fewer esophageal dilations than 28 non-responders (1.6 vs. 4.6, p=0.03).62

EoE patients with perforation are usually managed and improved by conservative therapy alone.13,20,70 Other invasive management, including endoscopic and surgical interventions, are rarely required.70 Moreover, in the case of early detection, small-sized perforations can be managed by fasting in combination with antibiotics.71 Endoscopic clipping may be attempted but is usually unsuccessful due to EoE-associated fibrosis.70 Sometimes, the short duration of stent insertion may also be considered in the case of large-sized perforations.70 However, when esophageal perforation with exposure of fluid and food material outside the esophageal lumen occurs, invasive management, including surgical intervention with drainage, is required.70

**CONCLUSIONS**

Endoscopy is crucial for EoE diagnosis and treatment. It is one of the initial tests performed in patients suspected with EoE to inspect the esophagus and obtain biopsies. EUS findings in patients with EoE have shown diffuse thickening of the esophageal wall, including lamina propria, submucosa, and muscularis propria. However, the role of EUS in EoE remains uncertain and requires further investigation with larger sample sizes of patients with EoE. Follow-up endoscopies with biopsy are usually recommended after initiation of therapy to assess response. Moreover, endoscopic dilation or bougienage can be used in combination with medical and/or dietary treatment in patients with esophageal stricture for the management of dysphagia and to prevent its recurrence.

**Conflicts of Interest**

The authors have no potential conflicts of interest.

**Funding**

None

**Author Contributions**

Conceptualization: all authors; Data curation: all authors; Formal analysis: all authors; Investigation: all authors; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors.

**ORCID**

Eun-Jin Yang https://orcid.org/0009-0004-9168-8011
Kee Wook Jung https://orcid.org/0000-0002-3771-3691

**REFERENCES**


64. Lipka S, Keshishian J, Boyce HW, et al. The natural history of steroid-naive eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. Gastrointest Endosc 2014;80:592–598.


