

Role of Advanced Diagnostics for Eosinophilic Esophagitis

Ikuo Hirano

Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, Chicago, Ill., USA

Key Words

Eosinophilic esophagitis · Gastroesophageal reflux disease · Dysphagia · Endoscopy · Esophagitis · Impedance

Abstract

In eosinophilic esophagitis (EoE), diagnostic tests aid in the identification of pathophysiologic consequences and accurate detection of the disease. The EoE Endoscopic Reference Score (EREFS) classifies and grades the severity of the five major endoscopically identified esophageal features of EoE (edema, rings, exudates, furrows and strictures). The EREFS may be useful in the evaluation of disease severity and as an objective outcome of response to therapy. pH monitoring identifies the presence of abnormal degrees of acid exposure in the esophagus that characterizes gastroesophageal reflux disease. The presence of acid reflux, however, does not indicate that the reflux is responsible for esophageal eosinophilia. Esophageal manometry has not demonstrated a characteristic abnormality with sufficient sensitivity to make the test of diagnostic value in clinical practice. On the other hand, manometric characteristics of esophageal pressurization and longitudinal muscle dysfunction may help identify important pathophysiologic consequences of EoE. Esophageal impedance testing has demonstrated increased baseline mucosal impedance that correlates with increased epithelial permeability in EoE. Reduced mucosal integrity may provide intraluminal allergens access to antigen-presenting cells, serving

as an early event in the pathogenesis of EoE. The functional luminal impedance probe (FLIP) provides quantitative assessment of esophageal mural compliance, a physiologic correlate of remodeling in EoE. Studies using FLIP have associated reductions in esophageal distensibility in EoE with the important outcome of food impaction risk. Finally, confocal endomicroscopy, multiphoton fluorescence microscopy and novel eosinophil-enhancing contrast agents are emerging methods that may allow for in vivo visualization of esophageal eosinophilic inflammation, thereby improving the detection and understanding of this emerging disease.

© 2014 S. Karger AG, Basel

Introduction

The current approach to the diagnosis of eosinophilic esophagitis (EoE) relies upon the combination of clinical symptoms of esophageal dysfunction and histopathology demonstrating eosinophil-predominant esophageal mucosal inflammation [1–3]. Exclusion of secondary causes of esophageal eosinophilia is required. The clinical context is important in the consideration of diseases such as infectious esophagitis, graft-versus-host disease, connective tissue disorders and eosinophilic gastroenteritis. Endoscopy is utilized as a means for procuring esophageal biopsies, but serves an important role in the exclusion of alternate esophageal diseases that are associated with eosinophilia.

Utilization of Currently Available Tests to Improve the Diagnostic Accuracy of EoE

Can Uniform Nomenclature Improve the Diagnostic Yield of Endoscopically Identified Esophageal Features of EoE?

The presence of endoscopic features are not required for the diagnosis of EoE, but the presence of features of edema, rings, exudates and strictures increases the clinical likelihood of the histologic presence of esophageal eosinophilia. While retrospective studies report a limited sensitivity of endoscopic features for EoE, variable definitions and inconsistent reporting of features likely affected these estimates [4]. Prospective studies in EoE have identified endoscopic features in 93% of patients with EoE [5]. The substantial increment in detection of the endoscopic signs in prospective compared with retrospective studies emphasizes the importance of careful and systematic inspection and nomenclature to optimize diagnostic capabilities of endoscopy.

Endoscopic findings in patients with EoE have been shown to vary by age. Younger patients are more likely to have findings of white plaques and a normal-appearing esophagus, while adult patients are more likely to have strictures, narrow-caliber esophagus, rings and crepe-paper mucosa [6]. Fibrostenotic features including strictures and severe rings are commonly identified in adults with active EoE, but only among a minority of pediatric EoE patients. The presence of linear furrows and edema has been shown to be similar between age groups. These observations indicate a key distinction in the prevalence of fibrostenotic consequences of esophageal eosinophilia in different age groups. Furthermore, the endoscopic findings correlate with typical clinical presentations that are characterized by GERD-like symptoms in children and dysphagia in adults.

A classification and grading system to assess the endoscopic findings in EoE has been proposed. The acronym for the Endoscopic Reference Score, EREFS, designates the five major features of EoE (edema, rings, exudates, furrows and strictures) [4]. This instrument was created to standardize endoscopic assessment among endoscopists, but also incorporated grading of major esophageal findings. Edema and furrows are graded as absent (0) or present (1). Rings are graded as absent (0), mild (1, subtle circumferential ridges), moderate (2, distinct rings) and severe (3, rings that impair passage of a standard adult diagnostic endoscope). Exudates are graded as absent (0), mild (1, less than 10% of the esophageal surface area) or severe (2, greater or equal to 10%

of the esophageal surface area). Strictures are classified as absent or present with an estimation of the minimal luminal diameter. The validation of the EREFS identified a problem with the lack of a formal definition for narrow-caliber esophagus; therefore, this clinically important feature was excluded from the EREFS. Crepe-paper esophagus, while possibly a relatively more specific sign of EoE, had a low sensitivity and was also excluded from the EREFS.

The EREFS system defines commonly used nomenclature and describes standardized severity scores to facilitate the assessment of EoE disease activity, communication between physicians and comparisons of endoscopic findings among clinical trials performed at different sites. Moreover, the endoscopic evaluation incorporates not only inflammatory (edema, exudates, furrows), but also remodeling (rings, strictures) effects of EoE. Fibrosis of the lamina propria can be seen in up to 90% of EoE patients. Tissue remodeling is associated with the endoscopic findings of rings, narrow-caliber esophagus and strictures. The occurrence of food impaction, a clinically relevant symptom outcome of EoE, has recently been shown to be significantly associated with the assessment of ring severity using the EREFS system [7]. Figure 1 depicts endoscopic images and corresponding EREFS scores for esophageal mucosal findings prior to and after therapy with swallowed, topical fluticasone. The inflammatory features of exudates, edema and furrows improved with therapy while fibrostenotic features of rings and strictures persisted.

Can pH Testing Help to Differentiate Gastroesophageal Reflux Disease from EoE?

The most difficult and commonly encountered disease to differentiate from EoE is gastroesophageal reflux disease (GERD) [8]. GERD presents with symptoms of esophageal dysfunction including heartburn, chest pain and dysphagia with esophageal mucosal inflammation that can, albeit infrequently, include eosinophilia. While the endoscopic manifestations of GERD (erosions, ulceration, stricture and Barrett's esophagus) are characteristically distinct from EoE (edema, rings, exudates, furrows and strictures), none of these endoscopically detected esophageal features are specific for either disorder. Further complicating matters has been the observation that a significant proportion of patients with suspected EoE and who have these typical endoscopic features respond to a therapeutic trial of proton pump inhibitor (PPI) therapy. The distinction between EoE and GERD has clinical relevance since GERD is treated

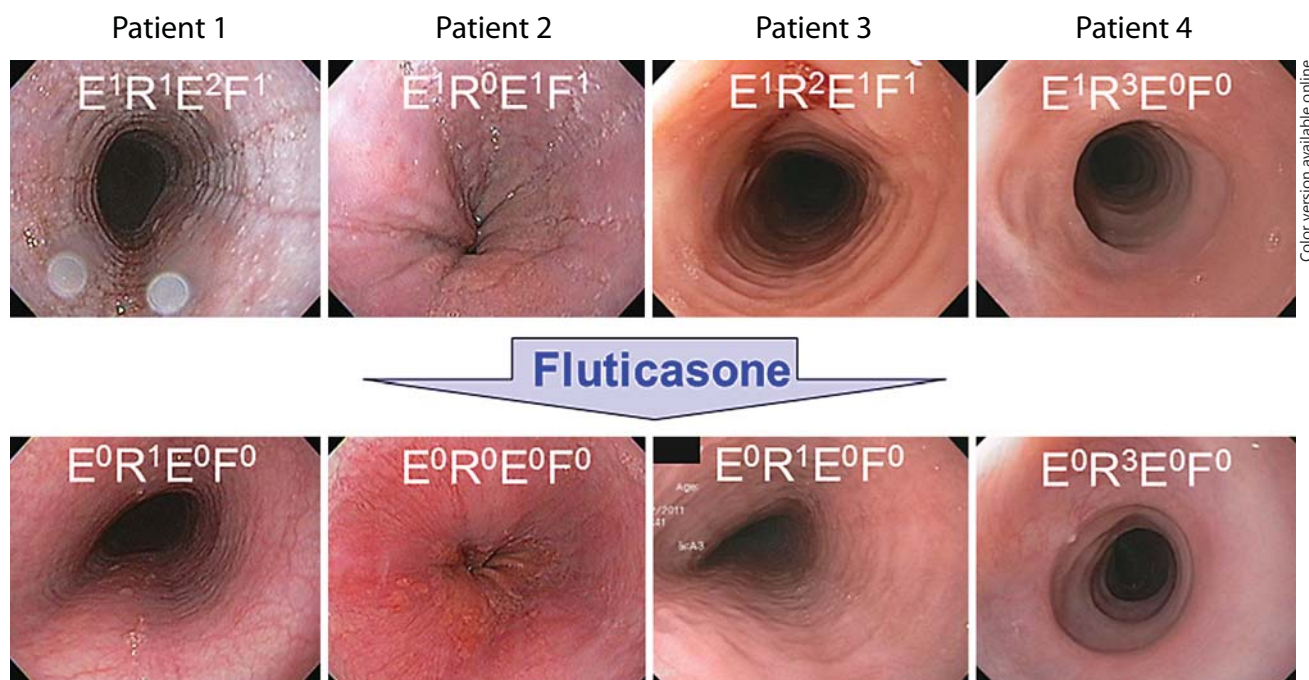


Fig. 1. Endoscopic images and corresponding endoscopic scores (EREFS) for esophageal mucosal findings prior to and after therapy with swallowed, topical fluticasone.

with acid suppression while EoE is treated with corticosteroids or elimination diet therapy [9]. Moreover, case reports have described patients who were clinically suspected of having GERD refractory to medical therapy who were treated with surgical fundoplication without improvement. The patients were subsequently recognized as having EoE. On the other hand, inadvertently labelling a patient with GERD as having EoE based on the presence of esophageal eosinophilia may unnecessarily expose GERD patients to corticosteroid therapy or restricted diets.

Ambulatory pH testing is a standardized method utilized widely for the diagnosis of GERD. Conceptually, pH testing might serve as a useful modality for the differentiation of GERD from EoE. There are, however, a number of limitations to this approach. For the diagnosis of GERD, pH testing has limitations in terms of both sensitivity and specificity. pH testing may be normal in about a quarter of patients with documented erosive esophagitis, an accepted indication of GERD. Demonstrating abnormal acid exposure does not prove that an individual patient's problem is caused by GERD. A patient may have a cough and an abnormal pH test, but this does not prove

that the cough is due to GERD. Likewise, a patient may have esophageal eosinophilia and an abnormal test, but this does not prove that the eosinophilia is caused by GERD.

For the diagnosis of EoE, limited data is available to guide the appropriate use of pH testing. Both retrospective and prospective studies have demonstrated that pH testing failed to predict a response to PPI therapy in patients with esophageal eosinophilia with a high degree of certainty [9]. Eighteen to 33% of patients with esophageal eosinophilia respond to PPI therapy in spite of a normal pH test [10]. On the other hand, 40–100% of patients with esophageal eosinophilia and an abnormal pH test demonstrated a histologic response showing a limited specificity of the pH test. Nevertheless, a greater proportion of patients with esophageal eosinophilia and abnormal pH testing have demonstrated a response to PPI therapy compared to patients with normal pH testing. Given these limitations, the role of pH testing in patients with suspected EoE is unproven, especially if the goal is to predict a response to PPI therapy.

Role of Diagnostic Testing to Understand the Pathogenesis of EoE

Do the Effects of EoE Extend beneath the Esophageal Mucosa?

With standard endoscopy imaging and histology, only the squamous epithelial surface is interrogated. Standard esophageal mucosal biopsies infrequently include sufficient portions of the subepithelium and do not evaluate either the submucosal space or muscularis propria of the esophagus. Fibrosis of the subepithelial space has been demonstrated in both pediatric and adult cohorts [11, 12]. Studies in both children and adults using endoscopic ultrasonography have demonstrated significant expansion of the esophageal mucosa, submucosa and muscularis propria in EoE [13–15]. These changes reflect the remodeling consequences of EoE.

Does EoE Affect Esophageal Motor Function?

Given the expansion of the muscularis as well as reports of dysphagia in EoE in the absence of readily identified esophageal stenosis, it is logical to question whether EoE affects esophageal motor function. Interestingly, the first 2 cases of ‘eosinophilic esophagitis’ were reported in adults with major esophageal motility disorders: one having achalasia and the second having esophageal spasm. While these patients would be excluded from the current definition of EoE due to a major esophageal motility disorder and concomitant eosinophilic gastroenteritis, the concept was introduced regarding potential for esophageal eosinophilia to result in esophageal motor dysfunction. Subsequent esophageal motility studies in adult and pediatric cohorts with EoE have demonstrated clinically significant esophageal motility disorders in less than 5% of subjects. Evaluation of a cohort of 50 patients with EoE utilizing high-resolution esophageal manometry demonstrated normal peristalsis in 64%, with 36% demonstrating nonspecific esophageal motor patterns dominated by weak and frequent peristalsis [16]. The frequency of these abnormal patterns was not significantly different from the motility abnormalities in a cohort of 50 patients with GERD. Abnormal esophageal pressurization characterized by panesophageal pressurization was seen in 16% and distal esophageal pressurization in 18%. While not a specific motility disorder, the esophageal pressurization events in EoE may reflect reduced esophageal mural compliance secondary to the transmural remodeling demonstrated on endoscopic ultrasonography imaging.

Conventional esophageal motility evaluates esophageal circular muscle function, but does not assess longi-

tudinal muscle contractions that are responsible for axial shortening of the esophagus. Using high-frequency ultrasonographic imaging, Korsapati et al. [17] assessed longitudinal muscle function in patients with EoE. Compared with healthy controls, patients with EoE showed reduced longitudinal muscle peak thickness as well as duration of contraction. These results are consistent with selective longitudinal, but not circular, muscle impairment in EoE. However, an alternate explanation of the defect identified is that the longitudinal muscle is intact but that transmural remodeling alterations in EoE mechanically restrict the ability of the esophagus to shorten in the longitudinal axis.

Can GERD Contribute to the Pathogenesis of EoE?

Recent retrospective and prospective studies have reported that a third to half of patients with significant esophageal eosinophilia histologically respond to trials of PPI therapy. A potential mechanism for this response is an effect on esophageal permeability [8]. Acid exposure of the esophageal epithelium results in an increase in permeability due to dilation of intercellular spaces. Intraluminal antigens, including food allergens, can then penetrate the impaired epithelial barrier resulting in their exposure to antigen-presenting cells within the mucosa. This mechanism could serve as an inciting event in the pathogenesis of EoE. To test this hypothesis, Van Rhijn et al. [18] examined mucosal integrity by three different means: mucosal impedance, transit of fluorescein molecules across epithelial biopsies in an Ussing chamber and direct measurement of squamous epithelial intercellular gaps on electron microscopy. Following a course of PPI therapy, increased esophageal permeability improved in patients with PPI-responsive esophageal eosinophilia but not EoE.

Fibrotic stenotic consequences of EoE can be visually estimated by endoscopy. The quantitative assessment at the whole organ level by measurement of esophageal mural compliance utilizing a functional luminal imaging probe (FLIP) is a novel and likely more precise approach. FLIP technology incorporates a multichannel electrical impedance catheter and manometric sensor surrounded by an infinitely compliant bag that is filled with an electrode-conducting solution. As the bag is filled with the solution, the probe simultaneously ascertains the esophageal luminal diameter and pressure at multiple points along the catheter assembly. The resulting pressure-volume curves provide a detailed interrogation of the distensibility of the esophageal wall. An initial study of FLIP in patients with EoE demonstrated a significant reduction in distensibil-

ity in EoE compared with control subjects [19]. A parameter called the distension plateau characterized the maximum ability of the esophagus to expand in spite of increasing intraluminal pressure at the point of minimal luminal diameter of the esophageal body. The distension plateau was reduced by 50% in EoE compared to controls.

Nicodème et al. [7] recently reported on the assessment of 70 patients with EoE who underwent endoscopy with esophageal biopsy and high-resolution impedance planimetry using a FLIP. These patients were followed prospectively and rates of food impaction were assessed. The study found that patients with a history of food impaction exhibited significantly lower esophageal distensibility (as measured by distensibility plateau values) than those without a history of food impaction. Decreased esophageal distensibility was found to be associated with an increased risk of food impaction and need for dilation during a 4- to 12-month follow-up period. The distensibility plateau was shown to be a more reliable predictor of food impaction risk than findings on endoscopy, although endoscopic estimations of strictures were not included in this comparison. Importantly, no correlation was found between eosinophil density and food impaction risk, need for dilation, or distensibility. The lack of correlation between esophageal distensibility and mucosal eosinophil density points to distinct roles of these two factors in the definition of EoE activity. Fibrostenosis is an important determinant of clinically relevant symptom outcomes, whereas histologic findings of eosinophilic inflammation are likely the most relevant determinant of future development of fibrostenosis [20].

Esophageal Imaging Modalities under Development

How Might Novel Esophageal Imaging Methods Improve Future Diagnostic Strategies for EoE?

Four methods have been reported in the past few years describing imaging modalities capable of microscopic imaging of gastrointestinal mucosa and have now been applied to EoE. Confocal laser endomicroscopy utilizes intravenous fluorescein to accentuate mucosal morphology and has been applied to a patient with EoE [21]. Features of dilated intercellular spaces, basal cell hyperplasia and cells morphologically similar to eosinophils were visualized in vivo. A similar technique known as reflectance confocal endomicroscopy used spectrally encoded image analysis to detect individual eosinophils within mucosal biopsies of patients with EoE [22]. A significant correlation was found between eosinophil densities calculated by

endomicroscopy and those calculated by conventional high-power microscopic imaging and routine hematoxylin/eosinophil-stained tissue (correlation: 0.76). Multiphoton microscopy also utilized autofluorescent properties of eosinophil granule proteins and was able to quantify eosinophils per unit volume in biopsies from EoE [23]. While a pilot study, the analysis did make a potentially important observation regarding the exponential decline in eosinophil density with deeper levels through the esophageal mucosa. The practical implication of this observation is that superficially oriented sections through the mucosa will yield higher estimates of eosinophil density compared with deeper or tangential sections. Technetium-labelled heparin with imaging using single-photon emission computed tomography was also applied to esophageal mucosal biopsies from EoE patients treated with an elemental diet [24]. The method takes advantage of the binding of anionic heparin to cationic eosinophil granule proteins such as major basic protein. The pilot study was able to differentiate active EoE from controls or EoE patients in remission on the elemental diet.

Conclusions

Advances in the utilization of currently available and novel technologies have improved both the diagnosis and understanding of the pathogenesis of EoE. Since pH testing currently has an unproven role in the clinical determination of the PPI-responsive form of esophageal eosinophilia, further validation is needed. Endoscopic ultrasonography has demonstrated significant structural alterations in EoE that extend beneath the mucosa to both the submucosa and muscularis propria. Esophageal motility aberrations have implications regarding the pathophysiology of EoE. Functional luminal imaging has identified substantial reductions in esophageal mural distensibility in EoE with clinical correlation with outcomes of food impaction. Esophageal mucosal impedance tests have been utilized to detect impaired esophageal barrier function in EoE compared with controls. Finally, novel imaging modalities show great promise for the visualization of eosinophilic inflammation of the esophageal mucosa in vivo.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

References

- 1 Liacouras CA, et al: Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.e6, quiz 21–22.
- 2 Furuta GT, et al: Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–1363.
- 3 Dellon ES, et al: ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;108:679–692, quiz 693.
- 4 Hirano I, et al: Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489–495.
- 5 Kim HP, et al: The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:988–996.e5.
- 6 Straumann A, et al: Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;67:477–490.
- 7 Nicodème F, et al: Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2013;11:1101–1107.e1.
- 8 Spechler SJ, Genta RM, Souza RF: Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 2007;102:1301–1306.
- 9 Hirano I: Eosinophilic esophagitis and gastroesophageal reflux disease: there and back again. *Clin Gastroenterol Hepatol* 2011;9:99–101.
- 10 Molina-Infante J, et al: Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110–117.
- 11 Aceves SS, Ackerman SJ: Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2009;29:197–211, xiii–xiv.
- 12 Aceves SS: Tissue remodeling in patients with eosinophilic esophagitis: what lies beneath the surface? *J Allergy Clin Immunol* 2011;128:1047–1049.
- 13 Fox VL, et al: High-resolution EUS in children with eosinophilic ‘allergic’ esophagitis. *Gastrointest Endosc* 2003;57:30–36.
- 14 Straumann A, et al: Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–409.e1.
- 15 Stevoff C, et al: EUS and histopathologic correlates in eosinophilic esophagitis. *Gastrointest Endosc* 2001;54:373–377.
- 16 Roman S, et al: Manometric features of eosinophilic esophagitis in esophageal pressure topography. *Neurogastroenterol Motil* 2011;23:208–214, e111.
- 17 Korsapati H, et al: Dysfunction of the longitudinal muscles of the oesophagus in eosinophilic oesophagitis. *Gut* 2009;58:1056–1062.
- 18 Van Rhijn BD, et al: Acid suppression restores impaired esophageal mucosal integrity in patients with esophageal eosinophilia (abstract). *Gastroenterology* 2013;144(suppl 1):s155.
- 19 Kwiatak MA, et al: Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011;140:82–90.
- 20 Hirano I: Therapeutic end points in eosinophilic esophagitis: is elimination of esophageal eosinophils enough? *Clin Gastroenterol Hepatol* 2012;10:750–752.
- 21 Neumann H, et al: First description of eosinophilic esophagitis using confocal laser endomicroscopy (with video). *Endoscopy* 2011;43(suppl 2 UCTN):E66.
- 22 Yoo H, et al: Reflectance confocal microscopy for the diagnosis of eosinophilic esophagitis: a pilot study conducted on biopsy specimens. *Gastrointest Endosc* 2011;74:992–1000.
- 23 Safdarian N, et al: Quantifying human eosinophils using three-dimensional volumetric images collected with multiphoton fluorescence microscopy. *Gastroenterology* 2012;142:15–20.e1.
- 24 Saffari H, et al: ^{99m}Tc-hexatium-labeled heparin: a new approach to detection of eosinophilic esophagitis-associated inflammation. *J Allergy Clin Immunol* 2013, E-pub ahead of print.