



Diagnosis and Treatment of Eosinophilic Esophagitis



Alex Straumann^{1,2} David A. Katzka^{1,2}

¹Swiss EoE Clinic, Praxis Römerhof, Olten, Switzerland; ²Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

Eosinophilic esophagitis (EoE) is a new disease. It is caused by a T-helper type 2 cell response to food antigens in contact with the esophageal mucosa. Although no single feature defines EoE, a constellation of compatible demographic, clinical, endoscopic, and histologic findings establish the diagnosis. Children present with symptoms and endoscopic patterns characteristic of inflammation, whereas adolescents and adults have manifestations of fibrosis and gross esophageal strictures. Clinical and endoscopic scoring systems have helped to standardize diagnosis. There is controversy in EoE research over the optimal endpoint for treatment. Although the most common endpoint is a reduced number of eosinophils in biopsies, changes in symptoms and endoscopic features are becoming important targets of therapy. We should improve our understanding of EoE progression and the need for maintenance therapy, and continue development of diagnostic tools that avoid endoscopy and biopsy analyses to more easily monitor disease activity.

Keywords: Eosinophilic Esophagitis; Esophagitis; Esophagus.

The first case of eosinophilic esophagitis (EoE) was described in 1978 and misinterpreted as achalasia.¹ In the early 1980s, the importance of esophageal eosinophilia was perceived, and esophageal eosinophilia was considered to be a diagnostic criterion for reflux disease.² It took more than a decade before EoE was described in 2 case series and recognized as a distinct disease entity characterized by symptoms of esophageal dysfunction and eosinophil infiltration.^{3,4} Both studies found EoE to be prevalent in younger males with atopic conditions, and endoscopic findings to be discreet and differ from those of gastroesophageal reflux disease (GERD). Meanwhile, EoE has been observed in children and adults, in North and South America, Europe, Asia, and Australia.⁵

Initially, EoE was regarded as rare, but soon it became evident that its incidence and prevalence were rapidly increasing.⁶ Several population-based studies from the United States^{7,8} and Europe^{9,10} have provided evidence that this is a true increase, rather than the effect of raised

awareness. Based on a recently published meta-analysis, the prevalence of EoE in adults is 32.5 and in children 30.9 patients per 100,000 inhabitants. In other words, in Westernized areas, 1 patient with EoE lives in a community of approximately 3000 inhabitants.¹¹ Although EoE mainly affects persons 20–40 years old, it is seen in all age groups.¹² The incidence and prevalence of EoE are comparable with the values of Crohn's disease.

Diagnosis

An international panel of experts in pediatric and adult gastroenterology, allergy, immunology, and pathology defined EoE as “an esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation.”⁶ Other causes of esophageal eosinophilia must be ruled out—particularly GERD. Experts had therefore recommended that patients be treated with a double dose of proton pump inhibitors (PPIs) for 2 months; the effects are used to differentiate between EoE and GERD.¹³ Unexpectedly, in a subset of patients with EoE, symptoms and histologic abnormalities resolved following PPI treatment, even in the documented absence of GERD.¹⁴ This PPI trial brought more confusion than clarification, so a panel of experts recently recommended that PPI response not be used in diagnosis.¹⁵ However, it is not clear how to differentiate reliably between EoE and GERD. Additional disorders leading to infiltration of the esophagus by eosinophils include eosinophilic gastroenteritis, celiac disease, Crohn's disease, achalasia, and drug hypersensitivity. The diagnosis of EoE is complex; therefore, clinicians should diagnose EoE based on a combination of symptoms and histologic and endoscopic

Abbreviations used in this paper: DIS, dilation of intercellular space; EoE, eosinophilic esophagitis; EREFS, edema, rings, exudates, furrows, and strictures; GERD, gastroesophageal reflux disease; HPF, high power field; IL, interleukin; PPI, proton pump inhibitor; Th, T-helper.

Most current article

© 2018 by the AGA Institute
0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2017.05.066>

findings—no single feature is sufficient to establish a definitive diagnosis.¹⁶

Symptoms in Children Vs Adults

The symptoms of EoE follow a hierarchal and pyramidal pattern from early childhood to adulthood (Table 1).^{7,17,18} This presumably follows decades of diffuse inflammation leading to esophageal fibrosis. Specifically, the symptoms of EoE in early childhood are protean and include failure to thrive, feeding difficulties, nausea, vomiting, and abdominal pain. In older children, symptoms become more esophageal, with heartburn, chest pain, and early manifestations of dysphagia (such as slow and picky eating). In adolescents and adults, symptoms become specific to esophageal narrowing, with solid food dysphagia and food impaction. On rare occasions, impaction can lead to esophageal perforation (Boerhaave’s syndrome).^{19–21}

As the population of patients with EoE increases and they are studied more carefully, it becomes clear that this timeline is not firm. For example, recent data show that chest pain may be a prominent symptom in adults, perhaps reflecting an inflammatory component.²² Similarly, heartburn may occur in adults.¹² Conversely, school-age children may present with dysphagia.¹⁸ It is not clear if these are different symptoms of a similar disease or that the degree of esophageal inflammation and fibrosis varies with age.

Symptom Scoring Systems

As for many chronic diseases, symptoms of EoE may be obvious or arise via compensatory maneuvers to cope with the disease. It is important to document the frequency and chronicity of symptoms, as well as the intensity. Several scoring systems have been developed for the comprehensive evaluation of EoE symptoms. These systems serve not only to achieve greater accuracy in grading a patient’s symptoms, but also function as a standardized objective tool that can be used to assess the disease over time and evaluate the effects of treatments or agents in clinical trials.

The EoE activity index^{16,23} is a patient-reported outcome instrument that was developed using symptoms of 183 patients in Switzerland with EoE. The system is based on a conceptual framework to assess symptoms, behavioral adaptations, and biologic activity of adult patients with EoE over periods of 1, 7, and 30 days. The score is an indicator of dysphagia. It is comprehensive, documenting the frequency,

intensity, and duration of dysphagia; the duration of dysphagia episodes and occurrence of food impaction; time required to eat a regular meal; and frequency of pain with eating. This scoring system also detects accommodating symptoms of EoE, such as slow eating, careful chewing, and food avoidance. The score is validated in a 7-day recall period, which was deemed adequate. Scores have been shown to correlate with global assessment score endoscopic and histologic findings.

The Mayo dysphagia questionnaire is a validated symptom scoring system that has been used for EoE but was originally developed for peptic esophageal strictures or general use with dysphagia. It is a 28-item instrument that takes, on average, 10 minutes to complete.²⁴ It has been used in several trials of therapeutic agents in the treatment of EoE^{25–27}; findings correlate variably with findings from histologic analysis. It is not clear if this variation is because of the inaccuracy of the scoring system for inflammation or differing presentations of peptic and EoE strictures.

Dysphagia scoring systems have also been used to evaluate pediatric patients with EoE. For example, the University of Cincinnati developed the Pediatric EoE Symptom Scoring System^{28,29}; scores correlate with findings from histology. This scoring instrument also assesses quality of life, and can include parental interpretations of symptoms.

Nevertheless, many studies have used their own non-validated indices to evaluate EoE symptoms. One problem with the scoring systems is that, although they are well suited for clinical trials, they can be cumbersome in clinical care. Some investigators have developed more patient-friendly scoring systems. For example, the Dysphagia Symptom Questionnaire³⁰ is a 3-question instrument, administered daily for 30 consecutive days; it was developed and tested in a small group of patients with EoE. The questions are: Since you woke up this morning, did you eat solid food? Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest? And, for the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief? Patient compliance and acceptance was excellent. Even though many studies use non-validated scoring systems, more concerning is a general lack of scoring system use to accurately monitoring clinical disease.

Endoscopy

Patients with EoE undergo endoscopy for collection of epithelial biopsies and detection of gross abnormalities. With increasing physician recognition of the characteristic endoscopic findings, normal-appearing esophageal mucosa is found in less than 5% of patients with EoE.³¹ Findings vary among children and adults. Like symptoms, in children, endoscopic findings change with level of inflammation. Exudates, linear furrows, and edema are the most common endoscopic features of EoE in children.^{32,33} In adults, endoscopy often detects a combination of inflammation and

Table 1. Symptoms of EoE in Children vs Adults

Children	Adults
Failure to thrive	Dysphagia
Feeding difficulties	Eating slowly
Nausea and vomiting	Solid food avoidance
Abdominal pain	Avoidance of social eating
Heartburn	Chest pain
Picky eating	Heartburn

fibrosis, including rings and strictures. In an effort to standardize endoscopic findings for the purpose of monitoring disease activity and clinical trials, a graded endoscopic tool has been developed.³¹ The endoscopic reference score is calculated based on findings of edema, rings, exudates, furrows, and strictures (EREFS; see Figure 1). It is easy to calculate and incorporated in some endoscopic imaging platforms.

One of the key questions is whether EREFS score corresponds to histologically defined disease activity. Several studies have addressed this question and produced conflicting results. For example, a recent controlled trial of a topical steroid associated EREFS score with findings of active disease from histology with an area under the curve value of .934.³⁴ Other studies have shown weak to modest association between EREFS score and histology findings.^{35,36} This discrepancy might be related, in part, to the variable resolution of endoscopic findings with medical therapy, depending on whether the resolution occurs via reductions in inflammation or fibrosis. Endoscopic findings (and symptoms) might also be an important marker of disease activity, regardless of biopsy eosinophil count. At the very least, the EREFS score provides a common endoscopic language for diagnosis and monitoring of patients with EoE. Finally, the mucosa is commonly fixed with a more forceful pull of the forceps required to obtain a good mucosal sample.³⁷

Radiology

Barium esophagography is a complementary examination to endoscopy, particularly in adolescents and adults.

Although barium esophagography does not accurately detect mucosal abnormalities in patients with EoE, it detects strictures with a significantly higher level of sensitivity than endoscopy. A study that used a radiographic technique to measure esophageal diameter in adults found that endoscopy detects strictures with an esophageal diameter of less than 13 mm with a sensitivity value below 26%.³⁸ These radiographically identified strictures help determine mechanisms of dysphagia in patients with almost normal findings from endoscopy. A barium esophagram may also detect ring formation. Radiography also helps plan endoscopy and dilation in advance, particularly for narrow proximal strictures or small-caliber esophagus (Figure 2). There is limited use of barium radiography in children, but strictures detected by contrast esophagram were not seen by endoscopy in 50% of 22 children studied.³⁹

Histology

Six to 8 biopsies from the distal and mid- and/or proximal esophagus, obtained during endoscopy, are needed to identify patients with EoE with a high level of sensitivity.⁴⁰ Within these biopsies, an eosinophil count >15 in a high-power field (HPF) is the sine qua non for diagnosis of patients with active EoE.⁶ Although an ostensibly firm threshold, several considerations must be understood. The level of 15 eosinophils/HPF is somewhat arbitrary—different cut-off values were used in earlier studies. Also, the lack of a standardized diameter for the HPF on microscopes can lead to variations in determination of eosinophil density.⁴¹ Furthermore, esophageal eosinophilia is patchy in biopsies—even from patients with active disease. There has been debate about

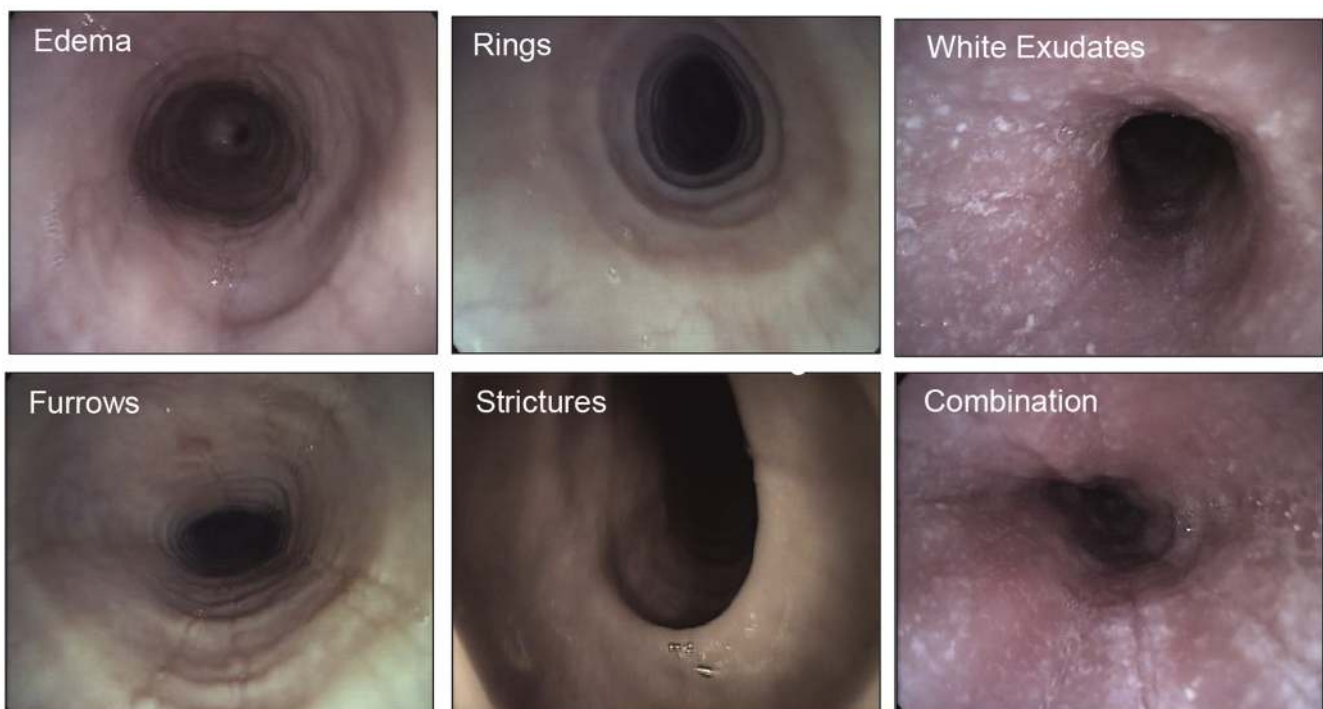


Figure 1. Endoscopic images of EoE. EREFS, endoscopy can detect edema, white exudates, and furrows, which are markers of acute inflammation, whereas rings and strictures indicate remodeling.



Figure 2. Barium esophagram demonstrating small-caliber esophagus.

how many HPFs of esophageal eosinophilia are sufficient to identify a patient with active disease and begin treatment. Studies to distinguish patients with active vs inactive EoE on the basis of mucosal impedance measurements correlated the histologic threshold of 15 eosinophils/HPF with loss of esophageal mucosal integrity.^{42,43}

Another concern with using eosinophil count is that the whole cell has undergone dissolution in the active phase and is therefore not visible with routine histologic staining. Patients can have robust staining for products of eosinophil degranulation (such as eosinophil peroxidase and eosinophil-derived neurotoxin) in esophageal biopsies, even though few eosinophils are present.^{44,45} Nevertheless, in most patients, eosinophil count associates with the presence of eosinophil degradation products.

In addition to esophageal eosinophilia, other histologic factors are associated with EoE. These include spongiosis (dilation of intercellular spaces [DIS]), increased numbers of mast cells and lymphocytes, and basal-zone hyperplasia.^{46,47} Little is known about the precise cellular and cytokine mechanisms that lead to these changes, so their relationship with disease activity is unclear. For example, a preliminary study reported that abnormal basal zone hyperplasia in biopsies from patients may persist after treatment, despite resolution of esophageal eosinophilia.⁴⁸ Basal zone hyperplasia appears to be induced by interleukin-13 (IL13) and is associated with fibrosis⁴⁹ and might serve as an endpoint of therapy. Similarly, spongiosis has been reported persist in patients with eosinophil reductions to fewer than 15/HPF.⁵⁰ It is not clear if persistent DIS is a marker of incomplete or slowly resolving inflammation, or a baseline histologic finding in some patients with EoE. The authors of this study questioned whether EoE disease activity should be further defined by normalization of all pathology findings.

Similar to the assessment of symptoms and endoscopy, a replicable histologic scoring system has recently been devised.⁴⁷ The EoE histologic scoring system evaluates 8 features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. When applied to treated and untreated patients, the score discriminates well between patients with vs without spongiosis (eosinophil surface layering and eosinophil abscess). Importantly, it gives pathologists a common language for assessment of EoE activity and for conduction of therapeutic trials.

Although pathology analysis of esophageal biopsies is essential for the diagnosis of EoE, features of the biopsies indicate variable morphologic responses to specific mechanisms of inflammation. Generally, these mechanisms are mediated by genetic, epigenetic, and environmental influences. The concept of diagnosing EoE by molecular methods has great appeal. Using cluster analysis and dimensionality reduction, Wen et al⁵¹ identified an expression pattern of 96 genes in esophageal tissues from patients with EoE that they called the EoE diagnostic panel.⁵¹ This pattern identified patients with EoE with 96% sensitivity and approximately 98% specificity, and distinguished patients with EoE in remission from controls. The EoE diagnostic panel also identified patients exposed to swallowed corticosteroids. Formalin-fixed, paraffin-embedded tissues can be used to identify the EoE diagnostic panel, which distinguished patients with EoE from those with reflux esophagitis, identified by pH-impedance testing. This test may offer an exciting alternative to routine histologic analysis of endoscopic biopsies.

New Methods of Diagnosis

Although EoE is best diagnosed by endoscopy and esophageal biopsy, the cost and risk of repeated procedures to monitor histologic response to pharmacologic or dietary interventions is burdensome. Therefore, it is important to identify alternatives that are less expensive and/or less invasive.

Transnasal Endoscopy

Transnasal endoscopy appears to be an excellent alternative to endoscopy; it is office-based, does not require sedation, and directly visualizes the esophageal mucosa. In a study of 22 children (8–17 years old) with EoE, most patients and parents favored transnasal endoscopy over standard endoscopy and would repeat the procedure.⁵² Biopsy specimens were adequate without difference in surface area compared with standard endoscopy and biopsy. Further studies are needed to determine if this is generally applicable to adult populations and young children.

Esophageal Impedance

DIS increases paracellular fluid and electrolyte flow, increasing the electrical conductance of the epithelium. Therefore, measurement of mucosal impedance is a tool that might be used to measure activity of EoE. In a study of 20

patients analyzed with an endoscopic impedance probe, point mucosal measurements identified patients with EoE with 90% sensitivity and 91% specificity, when degree of spongiosis and eosinophils/HPF were used as the reference.⁴³ Mucosal impedance can also be assessed in patients with EoE by a standard pH/impedance catheter, during the night time, when there is an absence of swallowing and fluid in the esophagus.⁵³ It is not clear whether impedance measurement will obviate the need for esophageal biopsies.

Impedance Planimetry

Stricture formation is a hallmark of esophageal disease in adults with EoE, yet visualization of this degree of fibrosis can be difficult. Biopsies collected during endoscopy might not demonstrate esophageal fibrosis because of its patchy distribution or lack of biopsies taken deep enough to find fibrotic change in the lamina propria. Furthermore, endoscopy underestimates stricture presence and extent compared with barium esophagography.⁵⁴ Impedance planimetry is used to measure esophageal distensibility via an orally passed catheter with an infinitely compliant inflatable balloon. Pressure volume characteristics are determined from step-wide inflations of the balloon and converted into a 3-dimensional color plot reflecting the degree of esophageal fibrosis. This technique can be used to easily assess esophageal distensibility, which could become an important biomarker of EoE progression.⁵⁵ The balloon catheter may be passed during endoscopy. No perforations have been reported.

Cytosponge Collection of Tissue

The ideal technique to monitor EoE would obviate the need for endoscopy yet adequately sample the esophageal mucosa for analysis. The cytosponge consists of an ingestible gelatin capsule containing a compressed mesh attached to a string. The capsule is swallowed; in the stomach, the gelatin dissolves within 5 minutes to release a 3-cm diameter spherical mesh. The mesh is withdrawn through the mouth by traction of an attached string, and a robust tissue specimen is collected from the sponge that can be analyzed by histology or immunohistochemistry. The cytosponge was invented for analysis of Barrett's esophagus.⁵⁶ In a pilot study of 20 patients, the sponge identified 11 of the 13 individuals with active EoE (83%),⁵⁷ as well as 3 cases of active EoE not identified by biopsy. The numbers of eosinophils in samples collected by the sponge correlated with those in samples collected by endoscopy. Additionally, the sponge procedure was preferred by all patients compared with endoscopy.

Esophageal String

The esophageal string device⁵⁸ consists of a capsule filled with approximately 90 cm of string. Patients swallow the capsule, which dissolves in the stomach or duodenum. After 1–12 hours (overnight), the string is withdrawn and secretions scraped from the string are analyzed for eosinophil-derived proteins. When performed in 41 children with GERD, controls, or EoE, the string test significantly distinguished children with active EoE from those with EoE in remission, GERD, or normal esophagus. Furthermore, levels of luminal eosinophil-derived proteins in string samples correlated with peak and mean numbers of esophageal eosinophils/HPF. The

test is performed bedside, is well tolerated in children, and does not require anesthesia.

Blood Markers

A simple blood test to diagnose and monitor disease activity in patients with EoE would be highly desirable. Although serum levels of C-C motif chemokine ligand 26 (also called eotaxin-3) are increased in patients with EoE, measurements of levels do not identify patients with EoE with sufficient accuracy for clinical use.⁵⁹ Other molecules increased in serum of patients with EoE include IL4, IL5, IL6, IL9, IL13, transforming growth factor alpha (TGFA), TGFB, thymic stromal lymphopoietin, proteoglycan 2 pro eosinophil major basic protein, and ribonuclease A family member 2 (also called eosinophil-derived neurotoxin). However, levels of these cannot accurately differentiate patients with active vs inactive EoE.⁶⁰

Urine Markers

Urine levels of 3-bromotyrosine, a chemical marker of eosinophil activation that is used to measure EoE activity,⁶¹ were found to be increased 93-fold in patients with EoE compared with non-atopic controls and 13-fold in patients with EoE compared with atopic controls. Cutoff thresholds were selected for 3-bromotyrosine measurement that identified non-atopic controls with 100% specificity and a negative predictive value of 100%, and atopic controls with 79% specificity and a negative predictive value of 90%. Although this test has not been used to accurately differentiate patients with active vs inactive EoE, this urine marker has potential.

Challenges in Diagnosis of EoE

Unfortunately, symptoms in children and adults unreliably reflect the endoscopic and histological activity of the disease.^{16,28} Adequate diagnosis and monitoring of EoE demands endoscopic and pathologic examinations, which are invasive and expensive measures. The development of reliable non-invasive methods to determine inflammatory activity is therefore urgently needed.

Central to the diagnosis of EoE is an almost exclusive reliance on the number of eosinophils in the esophageal epithelium.⁶ Despite the prominent appearance of these late-phase inflammatory cells, little is understood about their exact role in the pathogenesis of EoE. Three studies investigated whether monoclonal antibodies against IL5, which block eosinophil recruitment, might be effective in the treatment of EoE.⁶² Although mepolizumab⁶³ and reslizumab⁶⁴ reduced blood and tissue eosinophilia by approximately 90% and 55%, respectively, symptoms persisted and numbers of other inflammatory cells, such as T cells and mast cells, did not change. In addition, a recently published case series reported on an EoE-like syndrome in members of EoE families with esophageal dysfunction, but without having eosinophils in the esophageal tissue. Interestingly, immunohistochemical and molecular analyses demonstrated tissue infiltration by T cells and mast cells, as well as a gene expression pattern resembling that of EoE.⁶⁵ These findings illustrate that although the role of

eosinophils is important, other markers of inflammation must be considered in the pathogenesis and diagnosis of EoE.

EoE is caused by allergies to specific foods; identification of culprit foods is therefore an important part of diagnosis because it opens the way to non-medical treatment options. Unfortunately, almost all established diagnostic tools are based on the detection of IgE-associated sensitization and have only minimal value in the search for causative food allergens.^{13,66} At present, the only way to identify causative food allergens is to start an empirical elimination diet and confirm histologic remission with each food addition or subtraction.^{67,68} Therefore, the development of a reliable diagnostic test to identify causative food is another unmet diagnostic need in EoE.

Treatment Endpoints

The goal of treatment of EoE is putatively to control esophageal eosinophilia and inflammation. Unfortunately, control of other parameters, such as symptoms and strictures, is also important. Different therapeutic approaches are therefore best at meeting different endpoints. For example, control of esophageal inflammation may not obviate the need for mechanical dilation to reduce dysphagia and prevent food impaction. Consequently, combinations of therapies are often needed to reach some endpoints.

Control of Esophageal Eosinophilia

The inflammatory and fibrogenic components of EoE are mediated in large part by the injurious effects of eosinophil degranulation, so control of esophageal eosinophilia is an essential endpoint of therapy (reduced to fewer than 15 eosinophils/HPF in biopsies). Although the optimal goal of therapy is to eliminate all eosinophils from the esophageal mucosa, this is achieved in only a few patients. With this caveat in mind, the biologic meaning of <5, 10, or 15 eosinophils/HPF is unclear. Although, intuitively, reducing the eosinophil count to the lowest possible number per HPF makes sense, the realistic goal of pharmacologic or diet therapy is fewer than 15 eosinophils/HPF.

Symptom Control

Control of symptoms is another essential endpoint in the treatment of EoE. In children, symptoms are principally caused by the inflammation, with relatively less fibrosis, so medical treatment alone is usually sufficient to relieve symptoms. In adults, however, fibrosis may need to be viewed as a distinct treatment endpoint.¹⁶ In medical treatment studies, the correlation of histologic to symptom improvement varies, particularly in patients with critical strictures and/or small-caliber esophagus.²⁵ Therefore, dilation is an important treatment option for adult patients with EoE, to alleviate dysphagia and prevent food impaction.

Should dilation be performed before or after initiation of medical therapy? There is no clear evidence that dilation in the presence of active esophageal eosinophilia increases risk of complications. Nevertheless, in patients with severe dysphagia and/or history of food impaction, dilation should be performed more urgently. For patients with less severe dysphagia and fewer critical strictures, a decision to perform dilation can be made after a course of medical therapy.

Prevention of Remodeling and Reversal of Fibrosis

Although the short-term goal of medical treatment is to reduce or eliminate esophageal eosinophilia, the long-term goal is to prevent and perhaps reverse esophageal fibrosis and stricture formation. Corticosteroids have been shown to reduce esophageal remodeling.⁶⁹ For example, in esophageal biopsies taken from 16 pediatric patients with EoE, 3 months of budesonide significantly reduced esophageal remodeling and reduced fibrosis, level of TGFB1, number of cells with phosphorylated SMAD2 or SMAD3, and vascular activation.⁷⁰

A follow-up study was conducted of histologic remodeling and TGFB1 expression in esophageal biopsy specimens from 32 children with EoE treated with topical corticosteroids over 10 years. Fewer than 15 eosinophils/HPF at any time correlated with lower fibrosis and endoscopic severity.⁷¹ A large retrospective study in adults associated longer durations of untreated EoE with increased risk of esophageal stricture.⁷² For example, in patients with untreated symptoms of EoE for 20 years, the chance of stricture formation was 85%.

Therapeutic Options: Drugs, Diet, and Dilation

EoE is similar to allergic airway diseases,⁷³ in that it involves a T-helper (Th)-2 cell-mediated immune response, and to gastroesophageal reflux.^{74,75} Drugs used to treat asthma and acid-suppression agents have therefore been tested as treatments of EoE. In the past, these drugs were selected based on findings from small case series or even anecdotal reports. Fortunately, in the last few years, findings from several double-blind controlled clinical trials have aided physicians in optimizing treatment decisions.

Corticosteroids

In 1998, systemic corticosteroids were first shown to be an effective treatment of active EoE in children.⁷⁶ Only a few months later, researchers reported that 4 children with EoE were treated successfully with swallowed topical corticosteroid.⁷⁷ However, it took 10 years before a prospective, controlled trial demonstrated that topical fluticasone was safer than systemic prednisolone, and as effective, in achieving and maintaining histologic and symptomatic remission.⁷⁸ Since then, more than 10

controlled clinical trials in adult and pediatric patients with EoE have confirmed that swallowed topical corticosteroids, such as budesonide, fluticasone, and ciclesonide, are highly effective in resolving the symptoms and signs of EoE.^{27,78–88} One optimal method of delivery appears to be in a viscous form, shown by scintigraphy.²⁶ Proper dosing of steroids is essential in the treatment of adults with EoE. Budesonide (1 mg) or fluticasone (800 ug) in a viscous solution, given twice daily, is recommended for initial treatment.

These studies evaluated the ability of corticosteroids to bring active EoE into remission. However, EoE is a chronic disease, and symptoms and inflammation generally relapse within few weeks after cessation of topical corticosteroid treatment.^{78,83} Therefore, many patients need long-term therapy. So far, only 1 long-term, placebo-controlled trial has evaluated this aspect; a low-dose maintenance regimen of swallowed budesonide (0.25 mg), given twice daily, maintained complete histologic remission in only 35.7% of patients over 1 year.⁸⁹

Anecdotally, many investigators have used once- or twice-daily budesonide (1 mg). The role and method of interval monitoring is unclear. Some patients are evaluated by barium swallow every 2–3 years to assess esophageal lumen diameter. Long-term management approaches to EoE require more development, but certain patient groups have been proposed as candidates for this therapeutic approach (Table 2).

PPIs

There are at least 2 reasons that PPIs are used to treat patients with EoE. Given the high prevalence of GERD and EoE, some patients have both.¹⁸ These patients can be given PPIs as adjunct therapy. Esophageal exposure to acid causes more pain in patients with EoE than in healthy individuals.⁹⁰ Therefore, acid blockade could reduce the symptoms of EoE. Some pediatric and adult patients with typical features of EoE and pH-metric excluded GERD have symptoms and inflammation that respond to PPI monotherapy.¹⁴ A panel of experts recently agreed that PPI-responsive esophageal eosinophilia (based on its clinical, endoscopic, histologic, and molecular similarities with conventional EoE) should be regarded as a clinical sub-phenotype of EoE and not as a distinct entity.¹⁵ However, it is still unclear where to position the PPIs in the treatment algorithm of EoE (Figure 3).

Table 2. Candidates for Long-term Maintenance of Pharmacologic Therapy

1. Small caliber esophagus
2. Symptomatic or objective progression of stricture formation
3. Rapid return of symptoms off therapy
4. Recurrent food impactions
5. Co-morbid conditions increasing risk of endoscopy and dilation
6. Prior spontaneous or dilation induced perforation
7. Travel to areas where food impaction causes greater risk

Leukotriene Inhibitors

An open-label study demonstrated that high doses of montelukast reduced symptoms in patients with active EoE, but did not reduce esophageal inflammation.⁹¹ Subsequently, this drug was not found to be significantly superior to placebo in 2 trials that evaluated the efficacy of montelukast in maintaining a steroid-induced remission.^{92,93} Use of leukotriene inhibitors in induction or maintenance therapy for EoE is therefore not currently recommended.

CRTH2 Antagonists

EoE has many features of a Th2 cell-mediated immune response.^{94,95} The prostaglandin D2 receptor 2 (PTGDR2, CRTH2) is a chemoattractant receptor expressed by eosinophils and Th2 cells. This receptor mediates chemotaxis and activation of lymphocytes in response to prostaglandin D₂.⁹⁶ The small-molecule OC000459 is a first-generation selective CRTH2 antagonist that prevents prostaglandin D₂ from recruiting and activating eosinophils and Th2 cells. In a randomized placebo-controlled trial evaluating the efficacy and safety of OC000459 as a monotherapy for EoE,⁹⁷ OC000459 reduced eosinophil load by 33% in the esophagus, compared with placebo; the agent also produced mild reductions in symptoms, disease activity, and the endoscopic alterations. However, the overall effect was only moderate, and no patients achieved complete remission during the 8-week study period. Nevertheless, the excellent safety profile and the encouraging in vitro data from studies of second-generation CRTH2 antagonists warrant further investigation of these drugs.

Biologic Agents

Mepolizumab and reslizumab are highly selective, humanized antibodies against IL5 that could be promising alternatives for the treatment of eosinophilic inflammation.⁹⁸ In 3 controlled trials in children and adults with acute EoE,^{63,64,99} each drug reduced numbers of peripheral blood eosinophils by more than 90% and tissue eosinophilia by 55%. The safety profile was favorable. Unfortunately, clinical improvement was minimal and non-eosinophil inflammatory cells persisted in esophageal tissues. Therefore, mepolizumab and reslizumab are not recommended for standard treatment of EoE.

Although the squamous epithelium of the inflamed esophagus expresses high amounts of tumor necrosis factor, in an open-label study the tumor necrosis factor antagonist infliximab was not effective in reducing tissue infiltration by eosinophils or reducing symptoms in patients with EoE.¹⁰⁰

IL13 is an inflammatory cytokine secreted by Th2 cells,¹⁰¹ so antibodies against IL13 have been tested in patients with EoE. In an 8-week trial, 3 infusions of QAX576, a monoclonal antibody against IL13, reduced the numbers of esophageal eosinophils by 60%, compared with an increase of 23% in the placebo group. The reduction in esophageal eosinophils was sustained for as long as 6 months, with a trend toward reduced symptoms. An analysis of gene expression profiles of esophageal specimens from patients

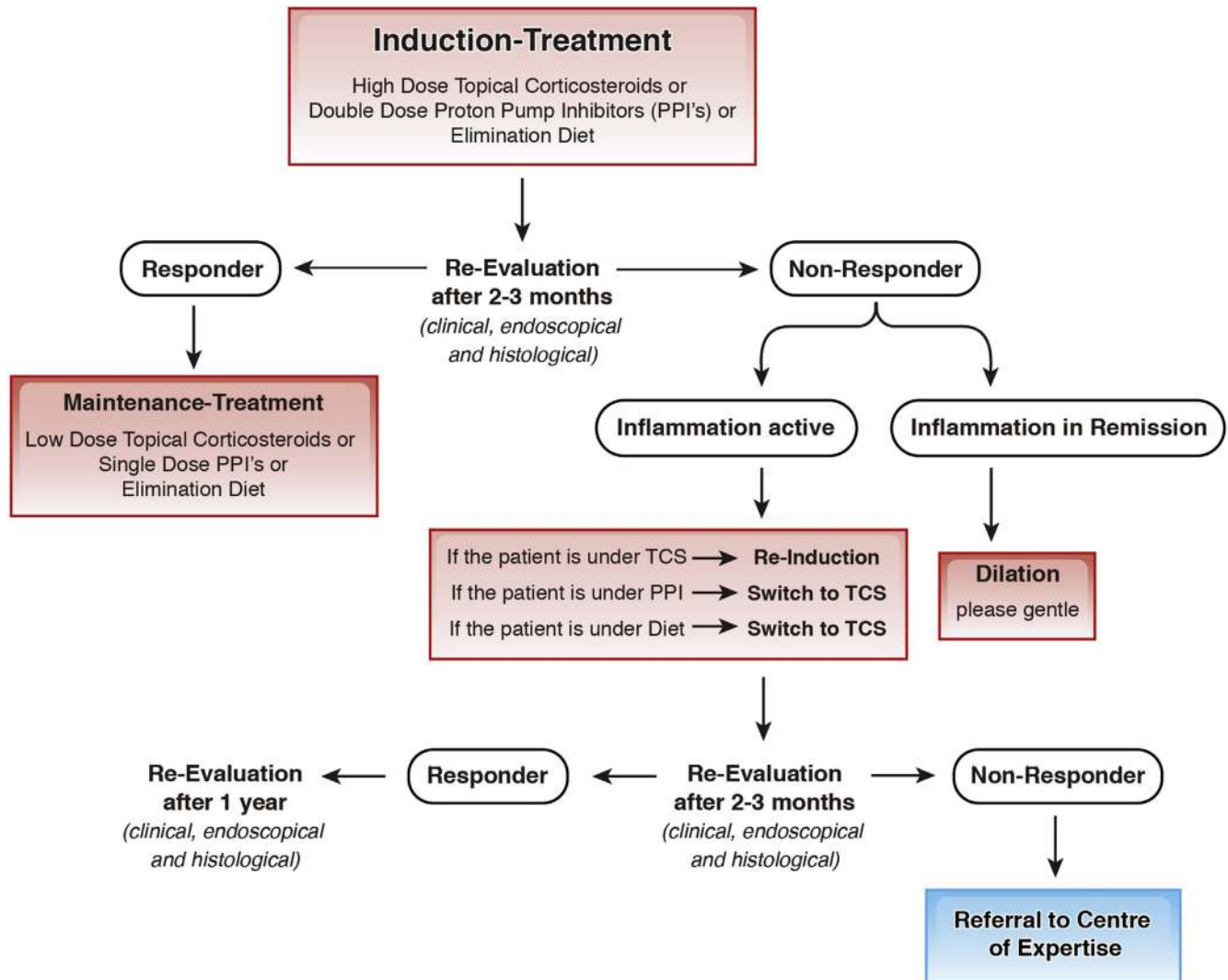


Figure 3. Treatment algorithm for EoE. The algorithm illustrates the treatment strategy for EoE. Treatment should start with an anti-inflammatory agent (swallowed topical corticosteroids), PPIs, or an elimination diet. Treatment selection depends exclusively on the patient's and physician's preference, because no comparative studies have shown any of these to be superior to the others. Dilation is indicated if symptoms persist despite successful control of inflammation. After each change of treatment strategy, symptoms, endoscopic, and histologic features should be reevaluated, because symptoms do not accurately reflect the inflammatory activity of the disease.

receiving QAX576 revealed changes in levels of EoE-associated mRNAs, including those encoding eotaxin-3, periostin, and markers of mast cells and barrier function. A placebo-controlled phase 2 study of RPC4046, another humanized antibody against IL13¹⁰² in adults with active EoE resulted in a significant reduction in numbers of esophageal eosinophils and improved endoscopic features. Furthermore, RPC4046 reduced dysphagia. The efficacy and safety profile of these compounds supports the development of IL13 antagonists for the treatment of patients with severe EoE.

Immune Modulators

A small pilot study found that treatment with azathioprine and 6-mercaptopurine was effective in inducing and maintaining a remission in 3 patients with

steroid-refractory EoE.¹⁰³ No further controlled trials with these drugs have been performed.

Elimination Diets

Diet therapy is attractive for several reasons. With adequate nutrition, there are no potential side effects. An elimination diet, as first-line therapy, is less expensive than steroids.¹⁰⁴ A meta-analysis demonstrated that a food elimination diet is effective in a similar proportion of patients (67.2%) to corticosteroid therapy (63.3%).⁶⁶ Nevertheless, several factors mitigate against using diet therapy for EoE. These include effects on quality of life and social activities because patients must avoid ubiquitous food antigens such as gluten and milk. Furthermore, there is no test other than endoscopy to assess the response to changes in food antigen exposure.

The 6-food elimination diet was the first elimination diet to be used in the treatment of patients with EoE. Although studies in the United States have tested diets that eliminate gluten, milk, soy, egg, nuts, and seafood as, in that order,⁶⁷ studies from Spain have strongly implicated legumes as a common antigen.¹⁰⁵ In most studies, gluten and milk were found to be the most frequent causes of EoE. Whereas diet therapy typically starts with avoidance of the 6 foods, with measured food reintroduction, the difficulty of this diet has forced new strategies. Investigators recently studied the effects of a 4-food elimination diet,¹⁰⁶ and found that it led to remission in 28 of 52 patients (54%), based on clinical and histologic features. Most notably, all patients were found to have just 1 or 2 food triggers, with milk as a only trigger for 27% of patients. Step-up rather than step-down therapy, starting with elimination of milk and/or gluten and then removal of additional foods, as needed, might be the best approach.

Elemental Diet

Although expensive and unpalatable, the elemental diet makes the most intuitive sense because it is devoid of all food antigens that cause eosinophil infiltration and inflammation. In children, an elemental diet produces nearly complete remission of EoE.¹⁰⁷ Although it is not as effective in adults with EoE, the elemental diet led to remission in 80% and 90% of subjects.^{108,109} Unfortunately, the dropout rate is substantial in trials of adults. Furthermore, the influence of GERD (reducing the role of food allergy) is likely more prominent in adults.

Endoscopic Therapy

Dilation with bougienage or balloons is the only available endoscopic treatment for EoE. Dilation of esophageal strictures can lead to long-lasting reductions in dysphagia in adults and children with EoE.^{110–112} Early studies reported perforations after dilation of EoE-induced strictures, causing this therapy to be considered risky.¹¹³ However, a meta-analysis of data from 468 patients who underwent a total of 671 dilations reported only 1 perforation (0.1%).¹¹⁴ This rate is comparable with that of esophageal dilation for strictures other than those caused by EoE (risk of approximately 0.1% to 0.2%). Patients should therefore be informed accordingly prior to the procedure.

The main drawback of esophageal dilation is the fact that it does not control the chronic inflammation that contributes to esophageal remodeling.¹¹⁵ Therefore, esophageal dilation should not be used as the only first-line therapy. It is generally used for persistent dysphagia after medical treatment, up front in patients with severe dysphagia and/or history of food impactions, or as the only treatment for patients who did not respond to anti-inflammatory agents, based on histologic analysis and symptoms.¹¹⁶ Dilation should be performed gradually, using rules of 3 and often over several sessions, depending on symptoms and the initial esophageal lumen diameter. After dilation, 75% of patients have considerable chest pain that may last several days.¹¹⁵

Extra-Esophageal Allergies

Animal models of EoE have been developed, via instillation of *Aspergillus* to lungs of mice.¹¹⁷ Different types of studies have linked the activity of extraesophageal allergies with EoE. For example, many patients have an EoE flare during times of the year when levels of aeroallergens are high.¹¹⁸ Interestingly, as in the mouse model, in which lung inflammation precedes esophageal eosinophilia, many patients with EoE have a history of rhinitis for up to 10 years.¹¹⁹ Airway exposure to common household allergens, such as dust mites, cockroaches, and mold, can also induce esophageal eosinophilia.¹²⁰ There are also reports of initiation and exacerbation of EoE with immunotherapy.¹²¹ Some plant aeroallergens have similar antigenic epitopes to common foods, so patients with EoE might have immune cells that cross-react with plant and food allergens; certain plant allergens might cause EoE through direct exposure to the esophageal epithelium.¹²² Unfortunately, there is little data that demonstrate that control of extraesophageal allergies modulate EoE activity.¹²³

Patients With Refractory Disease

The definition of refractory EoE varies; patients can be considered to have refractory EoE if they have persistent esophageal eosinophilia, symptoms, or both. Lack of histologic response occurs in 5%–40% of patients treated with topical steroids.^{22,124} Some of these patients may respond to longer courses of steroids.¹²⁵ Anecdotally, some clinicians give patients a combination of PPIs and steroids. Patients may also be refractory to treatment because they have a critical stricture or small-caliber esophagus. These patients will likely need a series of dilations to achieve an esophageal diameter that allows reasonable oral intake.

Future Directions

EoE is a relatively new disease that was once considered rare but is now commonplace—diagnosis and therapy must progress with prevalence. We need to develop easy and inexpensive tests that can be performed bedside to assess EoE activity. It will also be important to learn more about the type and length of time esophageal antigen exposure is required to induce esophageal eosinophilia, to guide dietary therapies. If we can increase our understanding of the subtypes of EoE, it might be possible to estimate risk of disease progression for specific patients, and identify those that require intensive and/or chronic maintenance therapy. Therapeutic agents are needed that have been developed specifically for patients with EoE, with FDA approval. Additionally, it is important to better define the long-term side effects of topical steroids in patients with EoE, which is often a chronic relapsing disease. Similarly, we need to continue to follow large cohorts of patients with EoE carefully, as we strive to understand the course of their disease beyond 10–20 years—particularly because many are children and young adults.

References

- Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology* 1978;74:1298–1301.
- Winter HS, Madara JL, Stafford RJ, et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology* 1982;83:818–823.
- Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109–116.
- Straumann A, Spichtin HP, Bernoulli R, et al. [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. *Schweiz Med Wochenschr* 1994;124:1419–1429; [Article in German].
- Furuta GT, Katzka DA. Eosinophilic Esophagitis. *N Engl J Med* 2015;373:1640–1648.
- Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20 e6; quiz 21–22.
- Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–941.
- Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009;7:1055–1061.
- Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol* 2011;128:1349–1350 e5.
- van Rhijn BD, Verheij J, Smout AJ, et al. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013;25:47–52 e5.
- Arias A, Perez-Martinez I, Tenias JM, et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther* 2016;43:3–15.
- Kapel RC, Miller JK, Torres C, et al. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008;134:1316–1321.
- Simon D, Cianferoni A, Spergel JM, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016;71:611–620.
- Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110–117.
- Molina-Infante J, Bredenoord AJ, Cheng E, et al. PPI-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016;65:524–531.
- Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. *Gastroenterology* 2016;150:581–590 e4.
- Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:1066–1078.
- Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–1363.
- Lucendo AJ, Frigal-Ruiz AB, Rodriguez B. Boerhaave's syndrome as the primary manifestation of adult eosinophilic esophagitis. Two case reports and a review of the literature. *Dis Esophagus* 2011;24:E11–E15.
- Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol* 2008;6:598–600.
- Jackson WE, Mehendiratta V, Palazzo J, et al. Boerhaave's syndrome as an initial presentation of eosinophilic esophagitis: a case series. *Ann Gastroenterol* 2013;26:166–169.
- Dellon ES, Katzka DA, Collins MH, et al. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. *Gastroenterology* 2017;152:776–786.e5.
- Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology* 2014;147:1255–1266 e21.
- Grudell AB, Alexander JA, Enders FB, et al. Validation of the Mayo Dysphagia questionnaire. *Dis Esophagus* 2007;20:202–205.
- Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:742–749 e1.
- Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012;143:321–324 e1.
- Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol* 2013;108:366–372.
- Pentiuk S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009;48:152–160.
- Franciosi JP, Hommel KA, Greenberg AB, et al. Development of the Pediatric Quality of Life Inventory Eosinophilic Esophagitis module items: qualitative methods. *BMC Gastroenterol* 2012;12:135.
- Dellon ES, Irani AM, Hill MR, et al. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. *Aliment Pharmacol Ther* 2013;38:634–642.
- Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic

- oesophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489–495.
32. Kim HP, Vance RB, Shaheen NJ, et al. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:988–996 e5.
 33. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2009;7:1305–1313; quiz 1261.
 34. Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the Eosinophilic Esophagitis Endoscopic Reference Score in diagnosis and determining response to treatment. *Clin Gastroenterol Hepatol* 2016;14:31–39.
 35. van Rhijn BD, Verheij J, Smout AJ, et al. The Endoscopic Reference Score shows modest accuracy to predict histologic remission in adult patients with eosinophilic esophagitis. *Neurogastroenterol Motil* 2016;28:1714–1722.
 36. Rodriguez-Sanchez J, Barrio-Andres J, Nantes Castillejo O, et al. The Endoscopic Reference Score shows modest accuracy to predict either clinical or histological activity in adult patients with eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2017;45:300–309.
 37. Moawad FJ, Robinson CL, Veerappan GR, et al. The tug sign: an endoscopic feature of eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:1938–1939.
 38. Podboy A, Katzka DA, Enders F, et al. Oesophageal narrowing on barium oesophagram is more common in adult patients with eosinophilic oesophagitis than PPI-responsive oesophageal eosinophilia. *Aliment Pharmacol Ther* 2016;43:1168–1177.
 39. Menard-Katcher C, Swerdlow MP, Mehta P, et al. Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2015;61:541–546.
 40. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;64:313–319.
 41. Sperry SL, Shaheen NJ, Dellon ES. Toward uniformity in the diagnosis of eosinophilic esophagitis (EoE): the effect of guidelines on variability of diagnostic criteria for EoE. *Am J Gastroenterol* 2011;106:824–832; quiz 833.
 42. van Rhijn BD, Verheij J, van den Bergh Weerman MA, et al. Histological response to fluticasone propionate in patients with eosinophilic esophagitis is associated with improved functional esophageal mucosal integrity. *Am J Gastroenterol* 2015;110:1289–1297.
 43. Katzka DA, Ravi K, Geno DM, et al. Endoscopic mucosal impedance measurements correlate with eosinophilia and dilation of intercellular spaces in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:1242–1248 e1.
 44. Protheroe C, Woodruff SA, de Petris G, et al. A novel histologic scoring system to evaluate mucosal biopsies from patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2009;7:749–755 e11.
 45. Sridhara S, Ravi K, Smyrk TC, et al. Increased numbers of eosinophils, rather than only etiology, predict histologic changes in patients with esophageal eosinophilia. *Clin Gastroenterol Hepatol* 2012;10:735–741.
 46. Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. *Am J Gastroenterol* 2009;104:485–490.
 47. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus* 2017;30:1–8.
 48. Godwin B, Whelan K, Benitez A, et al. Persistent epithelial changes in inactive eosinophilic esophagitis: is inactive really inactive? *Gastroenterology* 2016;150:S136.
 49. Jiang M, Ku WY, Zhou Z, et al. BMP-driven NRF2 activation in esophageal basal cell differentiation and eosinophilic esophagitis. *J Clin Invest* 2015;125:1557–1568.
 50. Katzka DA, Tadi R, Smyrk TC, et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1824–1829 e1.
 51. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology* 2013;145:1289–1299.
 52. Friedlander JA, DeBoer EM, Soden JS, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. *Gastrointest Endosc* 2016;83:299–306 e1.
 53. van Rhijn BD, Kessing BF, Smout AJ, et al. Oesophageal baseline impedance values are decreased in patients with eosinophilic oesophagitis. *United European Gastroenterol J* 2013;1:242–248.
 54. Lee J, Huprich J, Kujath C, et al. Esophageal diameter is decreased in some patients with eosinophilic esophagitis and might increase with topical corticosteroid therapy. *Clin Gastroenterol Hepatol* 2012;10:481–486.
 55. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011;140:82–90.
 56. Kadri SR, Lao-Sirieix P, O'Donovan M, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *BMJ* 2010;341:c4372.
 57. Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:77–83 e2.
 58. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut* 2013;62:1395–1405.
 59. Konikoff MR, Blanchard C, Kirby C, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1328–1336.
 60. Dellon ES, Rusin S, Gebhart JH, et al. Utility of a noninvasive serum biomarker panel for diagnosis and monitoring of eosinophilic esophagitis: a prospective study. *Am J Gastroenterol* 2015;110:821–827.

61. Cunnion KM, Willis LK, Minto HB, et al. Eosinophil quantitated urine kinetic: a novel assay for assessment of eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2016;116:435–439.
62. Conus S, Straumann A, Bettler E, et al. Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;126:175–177.
63. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intra-epithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology* 2011;141:1593–1604.
64. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012;129:456–463. e1–e3.
65. Straumann A, Blanchard C, Radonjic-Hoesli S, et al. A new eosinophilic esophagitis (EoE)-like disease without tissue eosinophilia found in EoE families. *Allergy* 2016;71:889–900.
66. Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;146:1639–1648.
67. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;142:1451–1459 e1; quiz e14–e15.
68. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797–804.
69. Aceves SS. Tissue remodeling in patients with eosinophilic esophagitis: what lies beneath the surface? *J Allergy Clin Immunol* 2011;128:1047–1049.
70. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010;65:109–116.
71. Rajan J, Newbury RO, Anilkumar A, et al. Long-term assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids. *J Allergy Clin Immunol* 2016;137:147–156 e8.
72. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145:1230–1236 e1–e2.
73. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? *Clin Gastroenterol Hepatol* 2004;2:523–530.
74. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–1512.
75. van Rhijn BD, Weijenborg PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1815–1823 e2.
76. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380–385.
77. Faubion WA Jr, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;27:90–93.
78. Schaefer ET, Fitzgerald JF, Mollleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008;6:165–173.
79. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002;122:1216–1225.
80. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003;78:830–835.
81. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–1391.
82. Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;2:568–575.
83. Remedios M, Campbell C, Jones DM, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* 2006;63:3–12.
84. Peterson KA, Thomas KL, Hilden K, et al. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci* 2010;55:1313–1319.
85. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010;139:418–429.
86. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526–1537.e1.
87. Schroeder S, Fleischer DM, Masterson JC, et al. Successful treatment of eosinophilic esophagitis with ciclesonide. *J Allergy Clin Immunol* 2012;129:1419–1421.
88. Albert D, Heifert TA, Min SB, et al. Comparisons of fluticasone to budesonide in the treatment of eosinophilic esophagitis. *Dig Dis Sci* 2016;61:1996–2001.
89. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–409 e1.
90. Krarup AL, Villadsen GE, Mejlgaard E, et al. Acid hypersensitivity in patients with eosinophilic oesophagitis. *Scand J Gastroenterol* 2010;45:273–281.

91. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003;52:181–185.
92. Lucendo AJ, De Rezende LC, Jimenez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* 2011;56:3551–3558.
93. Alexander JA, Ravi K, Enders FT, et al. Montelukast does not maintain symptom remission after topical steroid therapy for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2017;15:214–221 e2.
94. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–961.
95. Gupta SK, Fitzgerald JF, Kondratyuk T, et al. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2006;42:22–26.
96. Pettipher R. The roles of the prostaglandin D(2) receptors DP(1) and CRTH2 in promoting allergic responses. *Br J Pharmacol* 2008;153(suppl 1):S191–S199.
97. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013;68:375–385.
98. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144–2148.
99. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;59:21–30.
100. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008;122:425–427.
101. Blanchard C, Rothenberg ME. Basic pathogenesis of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;18:133–143; x.
102. Dellon ES, Collins M, Assouline-Dayyan Y, et al. A randomized, double-blind, placebo-controlled trial of a novel recombinant, humanized, anti-interleukin-13 monoclonal antibody (RPC4046) in patients with active eosinophilic esophagitis: results of the HEROES study. *Am J Gastroenterol* 2016;111:S186.
103. Netzer P, Gschossmann JM, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* 2007;19:865–869.
104. Cotton CC, Erim D, Eluri S, et al. Cost utility analysis of topical steroids compared with dietary elimination for treatment of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2017;15:841–849.e1.
105. Lucendo AJ, Arias A. Treatment of adult eosinophilic esophagitis with diet. *Dig Dis* 2014;32:120–125.
106. Molina-Infante J, Arias A, Barrio J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin Immunol* 2014;134:1093–1099 e1.
107. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003;98:777–782.
108. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:759–766.
109. Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. *Aliment Pharmacol Ther* 2017;45:777–787.
110. Schoepfer AM, Gschossmann J, Scheurer U, et al. Esophageal strictures in adult eosinophilic esophagitis: dilation is an effective and safe alternative after failure of topical corticosteroids. *Endoscopy* 2008;40:161–164.
111. Robles-Medrande C, Villard F, le Gall C, et al. Severe dysphagia in children with eosinophilic esophagitis and esophageal stricture: an indication for balloon dilation? *J Pediatr Gastroenterol Nutr* 2010;50:516–520.
112. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20 e6; quiz 21–22.
113. Lucendo AJ, De Rezende L. Endoscopic dilation in eosinophilic esophagitis: a treatment strategy associated with a high risk of perforation. *Endoscopy* 2007;39:376; author reply 377.
114. Jacobs JW Jr, Spechler SJ. A systematic review of the risk of perforation during esophageal dilation for patients with eosinophilic esophagitis. *Dig Dis Sci* 2010;55:1512–1515.
115. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol* 2010;105:1062–1070.
116. Richter JE. Current Management of eosinophilic esophagitis 2015. *J Clin Gastroenterol* 2016;50:99–110.
117. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009;137:1238–1249.
118. Dellon ES, Erichsen R, Baron JA, et al. The increasing incidence and prevalence of eosinophilic oesophagitis outpaces changes in endoscopic and biopsy practice: national population-based estimates from Denmark. *Aliment Pharmacol Ther* 2015;41:662–670.
119. Simon D, Marti H, Heer P, et al. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;115:1090–1092.
120. Rayapudi M, Mavi P, Zhu X, et al. Indoor insect allergens are potent inducers of experimental eosinophilic esophagitis in mice. *J Leukoc Biol* 2010;88:337–346.
121. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for

- food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;113:624–629.
122. Simon D, Straumann A, Dahinden C, et al. Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy* 2013;68:945–948.
123. Harer KN, Enders FT, Lim KG, et al. An allergic phenotype and the use of steroid inhalers predict eosinophilic oesophagitis in patients with asthma. *Aliment Pharmacol Ther* 2013;37:107–113.
124. Sawas T, Dhalla S, Sayyar M, et al. Systematic review with meta-analysis: pharmacological interventions for eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2015; 41:797–806.
125. DiGiovanni EL, Champeaux AL, Arroyo MR, et al. Esophageal eosinophilia treated with long-duration proton pump inhibitor therapy. *ACG Case Rep J* 2016; 3:95–97.

Received April 11, 2017. Accepted May 19, 2017.

Reprint requests

Address requests for reprints to: David A. Katzka, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Ave., S.W., Rochester, MN 55905. e-mail: Katzka.david@mayo.edu; fax: (507) 266-0350.

Conflicts of interest

The authors disclose no conflicts.

GASTROENTEROLOGY ARTICLE OF THE WEEK
April 5, 2018

*Straumann A, Katzka DA. **Diagnosis and treatment of eosinophilic esophagitis.** Gastroenterology 2018;154:346-359.*

1. Typical histologic findings of EoE include
 - a. eosinophil count >15 eos/HPF
 - d. Basal-zone cell dysplasia
 - c. Dilation of intercellular spaces between squamous cells
 - d. Gastric metaplasia of esophageal epithelium
2. The ideal number of esophageal biopsies to diagnose EoE is:
 - a. 2 distal, 2 mid/proximal
 - b. 3-4 distal, 3-4 mid/proximal
 - c. 4 distal, 4 mid, 4 proximal
 - d. 3 mid/proximal

True or False

3. Realistic goal of therapy for EoE is to reduced esophageal eosinophil count to <15/HPF
4. Skin patch testing for food allergens is a good way to detect foods that should be avoided by EoE patients
5. Correct dosing of topical steroids should be fluticasone 800ug or budesonide 1mg given bid as initial therapy
6. Leukotriene inhibitors (ie montelukast) is an effective second line agent for corticosteroid non-responders
7. Milk and gluten appear to be the most common dietary triggers in EoE
8. The efficacy of immune modulators (ie. azathioprine and 6-MP) in the treatment of EoE remains unknown
9. If a patient has aeroallergens (for example allergy to grasses), immunotherapy to control those allergies improves EoE.
10. Barium esophagram is more sensitive than endoscopy in detecting less sever esophageal narrowing and strictures
11. Resolution of eosinophilia in esophageal biopsies after an 8-week trial of PPI excludes diagnosis of EoE
12. Low dose (0.25mg) of budesonide bid is effective in maintaining remission
13. Up to 75% of patients have chest pain after dilation. If pain lasts >4 hours, perforation is likely