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Eosinophilic esophagitis: Diagnostic tests and criteria

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Abstract

Purpose of review—To present the clinical, endoscopic, and histologic features of eosinophilic esophagitis (EoE), review the current diagnostic guidelines for EoE, and present an approach for diagnosis of EoE. It will also highlight selected techniques that are under development that may useful in the future for diagnosis of EoE.

Summary—EoE is a chronic, immune-mediated disorder. Because no single symptom, endoscopic finding, or histopathologic feature is pathognomonic, diagnosis can be challenging. Recently updated guidelines emphasize that EoE is a clinicopathologic condition. Specifically, three criteria must be met to diagnose EoE: 1) clinical symptoms of esophageal dysfunction; 2) an esophageal biopsy with a maximum eosinophil count of at least 15 eosinophils per high-power microscopy field, with few exceptions; and 3) exclusion of other possible causes of esophageal eosinophilia, including proton-pump inhibitor responsive esophageal eosinophilia (PPI-REE). A PPI trial is typically required both to assess for PPI-REE and to evaluate for the presence of concomitant gastroesophageal reflux disease. In the future, symptom scores, tissue or serum biomarkers, and genetic testing may play a role in diagnosis, but these methods have yet to be validated and are not yet recommended for routine clinical use.

Keywords

Eosinophilic esophagitis; diagnosis; eosinophils; endoscopy; guidelines

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus characterized by symptoms of esophageal dysfunction and an esophageal epithelial eosinophilic infiltrate.[1] It was first described in 1978 and initially felt to be rare.[2, 3] Over the past 10 years, however, the condition has been increasingly recognized, first in children and then in adults, and now EoE is a frequently encountered cause of dysphagia and food impaction.[1, 4–8] Estimates suggest that EoE is found in 6%–15% of patients

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undergoing endoscopy, depending on the indication, and that it is the cause of food impaction in approximately half of cases.[9–14] In addition to increasing recognition by gastroenterologists,[15, 16] the incidence and prevalence of EoE appear to be rising rapidly as well,[4, 5, 7, 8] though the reasons for this are not well understood.

The pathogenesis of EoE is felt to be immune-mediated.[1] In response to antigen stimuli, either from food or environmental allergies, a Th2 inflammatory response is triggered and factors such as IL-4, IL-5, and IL-13 stimulate eotaxin-3, a potent chemokine, to traffic eosinophils to the esophageal mucosa.[17] When activated, the eosinophils cause local tissue damage and recruit other effector cells such as mast cells and fibroblasts, which play a role in esophageal remodelling.[18–21] Recent work has identified potential loci of genetic susceptibility in patients with EoE.[22, 23]

While knowledge about EoE has been increasing rapidly, diagnosis of EoE can be challenging because the symptoms and histopathologic findings are not specific. The purpose of this paper is to present the clinical, endoscopic, and histologic features of EoE, review the current diagnostic guidelines for EoE, and present an approach for diagnosis of EoE. It will also highlight selected techniques that are under development and that may be useful in the future for diagnosis of EoE.

Clinical presentation of EoE

EoE has been described in patients of all ages, though it is most common in children and adults before their 5th decade.[1, 6, 24] The condition is also more common in males and Caucasians, though the reasons for this are not known.[9–11, 25–28] Symptoms of EoE vary by patient age.[4, 7, 29, 30] In children, symptoms can be somewhat non-specific and include feeding intolerance or food refusal, poor growth, abdominal pain, nausea, vomiting, or regurgitation. In adolescents and adults, dysphagia is the hallmark of EoE. The frequency of dysphagia varies by study design and population, but rates can range from 25%–100%.[7, 9, 11, 24, 31] In cases where patients have esophageal food impaction and present to an emergency room for bolus clearance, EoE is now the leading cause, accounting for approximately 50% of such cases.[12–14]

The symptom of heartburn can be seen in both children and adults with EoE. Depending on the series, 10%–100% of EoE patients have noted heartburn or chest discomfort.[7, 9, 11, 24, 32] EoE may also be the etiology in a small proportion of patients thought to have gastroesophageal reflux disease (GERD) with symptoms refractory to proton pump inhibitor (PPI) therapy. This proportion has been reported to range from 1% to 8%.[11, 32–36] A recent analysis suggested that obtaining esophageal biopsies in PPI-refractory GERD was only cost-effective if the prevalence of EoE was at least 8%.[37]

Concomitant atopic diseases, such as asthma, atopic dermatitis, allergic rhinitis/sinusitis, and food allergies, are also seen frequently in patients with EoE. This issue has been studied in detail in children, in whom 50% to 80% have co-existing atopy.[25, 38, 39] There are fewer data in adults, but the results of available studies are similar.[7, 40, 41] There are some patients with EoE who do not have atopic disease, and the role of referral to an allergist remains controversial, with referral rates largely dependent on local expertise and practice

patterns.[1] Of note, no symptom or associated atopic disorder is specific for the diagnosis of EoE.

Endoscopic findings in EoE

When EoE is suspected clinically based on the above symptoms, esophagogastroduodenoscopy (EGD) is required to evaluate the esophagus, assess for other potential causes, and obtain esophageal biopsies. There are multiple characteristic endoscopic findings in EoE,[1] but these endoscopic findings are also not specific for diagnosis of EoE and inter- and intra-observer endoscopic agreement for these findings is only fair.[42, 43] Esophageal rings can either be fixed (this finding has previously been termed esophageal trachealization or corrugation; Figure 1A) or transient (previously termed felinization; Figure 1B). Linear or longitudinal furrows are mucosal grooves that run parallel to the long axis of the esophagus (Figure 1C) and white plaques or exudates can coat the esophagus (Figure 1D) and may mimic the appearance of candida. In some cases the mucosa appears pale, congested, or has decreased vascularity (Figures 1C and 1D). Because the mucosa is fragile it can fracture with passage of the endoscope if the esophagus is narrow in caliber, a phenomenon termed crêpe-paper mucosa (Figure 1E).

Esophageal biopsies are currently required to diagnose EoE. Because 10–20% of EoE patients can have an endoscopically normal appearing esophagus,[1, 24] it is recommended that esophageal biopsies should be obtained in all patients suspected of having EoE, including all patients who undergo upper endoscopic evaluation for unexplained dysphagia, regardless of the endoscopic appearance or findings.[1]

The approach to obtaining esophageal biopsies is informed by studies showing that esophageal eosinophilic infiltrate is EoE is patchy [44] and can vary between the proximal and distal esophagus.[45, 46] Because a single esophageal biopsy samples only a tiny fraction of the mucosal surface, increasing the number of biopsies and including tissue from different esophageal locations improves the sensitivity of diagnosis. Two studies, one in adults and one in children, suggest that sensitivity is maximized when at least 5 biopsies are obtained.[45, 47] Therefore, the current recommendation is to take at least 2–4 biopsies from the distal and 2–4 biopsies from the proximal esophagus.

Histologic features of EoE

A prominent esophageal eosinophilic infiltrate is the histopathologic hallmark of EoE (Figure 2).[1, 48, 49] This infiltrate can be seen diffusely throughout the epithelium, or there can be surface clustering of eosinophils. Frequently, the infiltrate is patchy within a biopsy and between biopsies. Other associated features include eosinophilic microabscesses (defined as clusters of at least 4 eosinophils), eosinophil degranulation (where eosinophil granule proteins are observed extracellularly), basal zone hypertrophy, and spongiosis or dilated intercellular spaces (Figure 2). If the biopsy samples happen to contain tissue from the lamina propria, fibrosis in this area can frequently be seen as well.

Historically, there has been disagreement in the literature as to the level of esophageal eosinophilia needed to diagnose EoE.[24] Prior to 2007, there were 10 different diagnostic

cut-points in use, ranging from 5 eosinophils per high-power field (eos/hpf) to 30 eos/hpf. Moreover, because different microscopes have different high-power field sizes, for any given density of an eosinophilic infiltrate (in eos/mm^2) the eosinophil count (in eos/hpf) would vary depending on the hpf size. With the first publication of consensus diagnostic guidelines in 2007 (see below),[50] a diagnostic cut-point of at least 15 eos/hpf was established based on expert opinion. Institution of the guidelines began to improve the previously seen heterogeneity in the literature,[51] but there are few data specifically examining the appropriateness of this threshold for diagnosis of EoE. However, there is excellent intra- and interobserver reliability for determination of eosinophil counts (provided the same methodology and hpf size are used) among pathologists.[52]

Similar to the clinical symptoms and endoscopic findings of EoE, none of the histopathologic features are specific to EoE.[48, 49] Moreover, there is a differential diagnosis of esophageal eosinophilia that must be considered when eosinophils are noted on esophageal biopsy. The differential includes gastroesophageal reflux disease (GERD), other eosinophilic gastrointestinal diseases such as eosinophilic gastroenteritis, hypereosinophilic syndrome, Crohn's disease, infection (candida or parasites), achalasia, drug hypersensitivity, connective tissues disease, and others.[1] From a practical standpoint, GERD is the most commonly encountered condition that must be distinguished from EoE; the majority of other conditions on the list are not common causes of esophageal eosinophilia and can be excluded with the combination of history, endoscopic and biopsy findings, and laboratory assessment. The clinical, endoscopic, and histologic features of EoE and GERD overlap.[1, 53] Patients with either condition can have symptoms of heartburn or dysphagia; on endoscopy, erosions can be seen in both conditions and findings such as rings, furrows, and plaques are not specific; and eosinophil counts can be elevated in GERD as well, even to very high levels.[36]

Complicating the picture further is the newly recognized phenotype of PPI-responsive esophageal eosinophilia (PPI-REE). This phenomenon was first described in a series of children who had dysphagia, food impaction, vomiting, and marked esophageal eosinophilia, but who had complete symptom and histologic resolution after PPI therapy.[54] Since then, several studies have shown that approximately one-third or more of patients with esophageal eosinophilia respond to PPI therapy.[55–58] As of yet, it is unknown whether these are atypical GERD patients, whether they have a variant of EoE that responds to PPI therapy, or if there is a separate entity of PPI-REE.[59] Preliminary data suggest that PPIs might have an anti-inflammatory effect that is independent of acid.[60, 61] Because of these clinical subtleties, making a definitive diagnosis of EoE can be challenging.

Diagnostic guidelines for EoE

The first consensus diagnostic guidelines for EoE were published in 2007.[50] A key point emphasized in the 2007 guidelines was that EoE was a clinicopathologic condition. Because there was no single clinical finding or histologic feature that was pathognomonic for EoE, the sum of the clinical and histologic information had to be considered prior to making a diagnosis. To formalize this, the guidelines required three criteria to be met: 1) symptoms of esophageal dysfunction (i.e. dysphagia, food impaction, chest pain, heartburn); 2) a

maximum esophageal eosinophil count of at least 15 eos/hpf in at least one microscopy field; and 3) lack of responsiveness to high dose PPI therapy (or a negative pH study) to exclude GERD as a cause of esophageal eosinophilia.[50]

Institution of the guidelines began to improve the previously seen heterogeneity in the literature,[51] but as knowledge about EoE increased, the need to modify the guidelines was recognized. One issue concerned the requirement that reflux be excluded in order to diagnosis EoE, particularly because it became understood that the relationship between EoE, GERD, and esophageal eosinophilia was complicated and that EoE and GERD could coexist.[53] In addition, the new phenotype of PPI-REE, as noted above, needed to be addressed.

The consensus diagnostic guidelines were updated in 2011,[1] and there were several notable changes. First, the guidelines provided a conceptual definition of EoE as an immune-mediated disorder with symptoms of esophageal dysfunction and eosinophil-predominant inflammation. This emphasized the clinicopathologic nature of the diagnostic process. Second, the updated guidelines still required three criteria to be met, but with some modifications: 1) clinical symptoms of esophageal dysfunction; 2) a maximum esophageal eosinophil count of at least 15 eos/hpf, *with few exceptions*; 3) exclusion of *other possible causes of esophageal eosinophilia, including PPI-REE*. These updated guidelines allowed for clinical discretion and increased flexibility. For example, a young man with food impaction, allergies, esophageal rings, furrows, and plaques, but only 12 eos/hpf could still be diagnosed with EoE. In addition, the guidelines changed the requirement that GERD must be excluded in all cases, permitted EoE and GERD to coexist, and recognized PPI-REE as an entity but highlighted the need for more studies in this patient group. Given the rapidly increasing knowledge base for EoE, it is likely the diagnostic criteria will continue to evolve.

Future diagnostic modalities in EoE

There are several avenues of research that may lead to new diagnostic approaches for EoE. Symptom scores in both children and adults have been developed to diagnose EoE on a clinical basis,[7, 62–64] but these have not been prospectively validated and cannot be recommended for use at this time. Optimizing diagnosis at the time of endoscopy is an area of active research. Use of narrow band imaging did not increase inter- or intra-observer agreement for endoscopic findings of EoE.[42] Confocal microscopy [65] and multi-photon fluorescence microscopy [66] have been proposed as techniques to detect eosinophils in the esophageal mucosal without requiring biopsy, but are still in the experimental phase. Functional luminal imaging of the esophagus has also shown promise by using measurements of the decreased esophageal compliance in EoE patients to distinguish it from GERD, but this is also not in widespread clinical use.[67] An ultimate goal would be to use biomarkers to diagnose EoE. Several tissue biomarkers have shown promise, including eosinophil granule proteins,[68–70] tryptase staining for mast cells,[20, 21] cytokine expression,[71] and gene expression.[22, 72] Non-invasive serum markers have also been explored, but with less success.[73–75] None of the biomarkers have as of yet been prospectively validated and none are in routine clinical use at this time.

Conclusion and summary of the diagnostic approach to EoE

Eosinophilic esophagitis has rapidly emerged as a major cause of dysphagia, food impaction, and upper GI symptoms in both children and adults. While there are characteristic clinical, endoscopic, and histologic features of EoE, making the correct diagnosis can be challenging because the findings are not specific to EoE. The consensus diagnostic guidelines, first published in 2007 and updated in 2011, have provided a welcome framework for both the clinician and the researcher. In order to diagnose EoE (Figure 3), the condition must be suspected clinically based on symptoms; concomitant atopic disease may also be present. Endoscopic evaluation is usually indicated for symptoms such as dysphagia, and changes in the esophagus, such as rings, furrows, and plaques, may also suggest the diagnosis. However, if EoE is clinically suspected, it is imperative that esophageal biopsies are obtained regardless of the endoscopic appearance of the esophagus. The current recommendation is to obtain at least 2–4 biopsies from both the distal and proximal esophagus to maximize diagnostic sensitivity.[1] If the biopsies show at least 15 eos/hpf in at least one hpf, then the diagnosis of EoE can be strongly considered. However, a key point is that the diagnosis is not confirmed at this junction. There must be a careful consideration of whether other causes of esophageal eosinophilia are at play, and the possible role of reflux and PPI-REE must be determined. To this end, a patient with esophageal eosinophilia is typically placed on a high dose PPI trial for 8 weeks (20–40 mg twice daily of any of the currently available medications) and the endoscopy is repeated. If there are persistent symptoms and repeat biopsies again show ≥ 15 eos/hpf, then the diagnosis of EoE is confirmed. If the patient has improved clinically and biopsies show resolution of esophageal eosinophilia, then the patient either has PPI-REE or GERD, and currently this distinction must be made clinically or with additional supportive testing such as pH/impedance monitoring. While this diagnostic process is involved for both the patient and clinician, proceeding carefully through the algorithm is necessary because the treatments, prognosis, and surveillance of patients with EoE and with other conditions diverge substantially. In the future, it is likely that improvements in endoscopic imaging and development of EoE biomarkers will streamline the diagnosis process, making it more accurate and less invasive.

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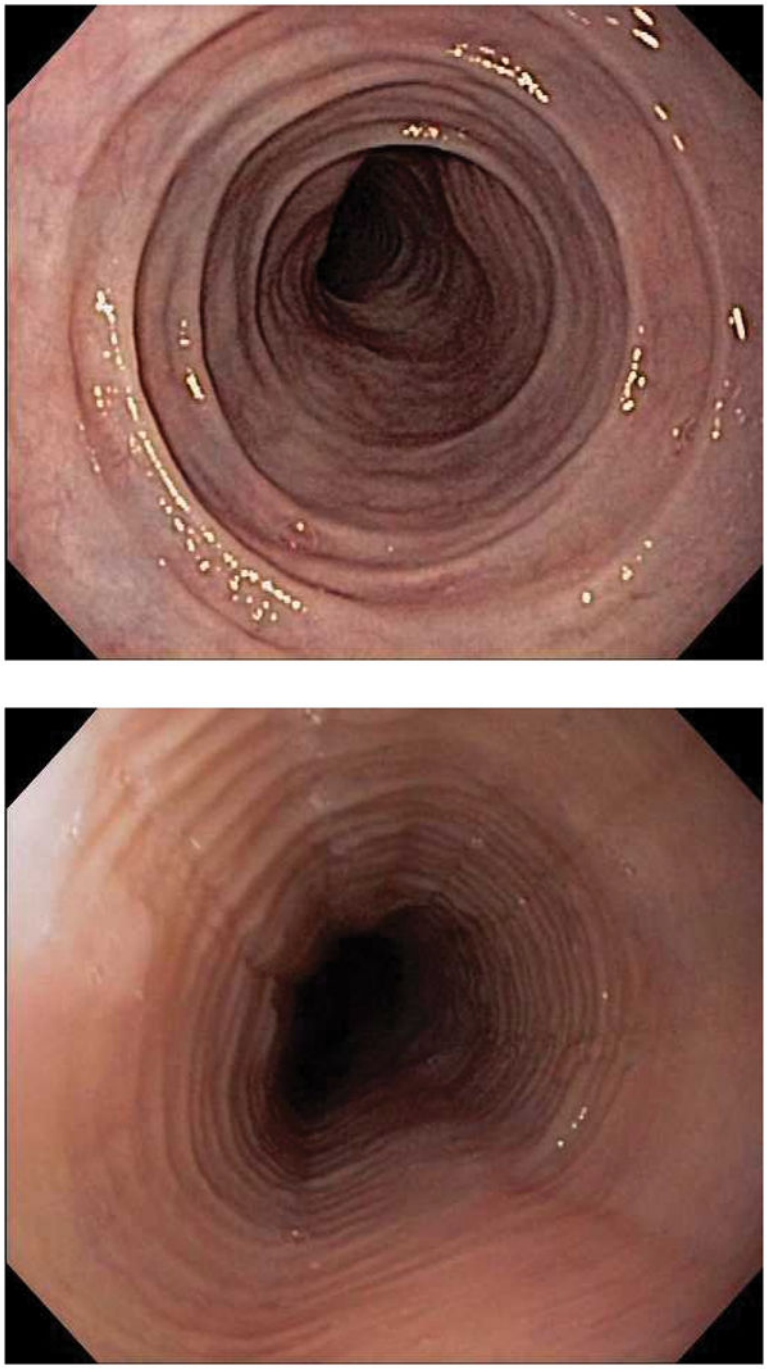
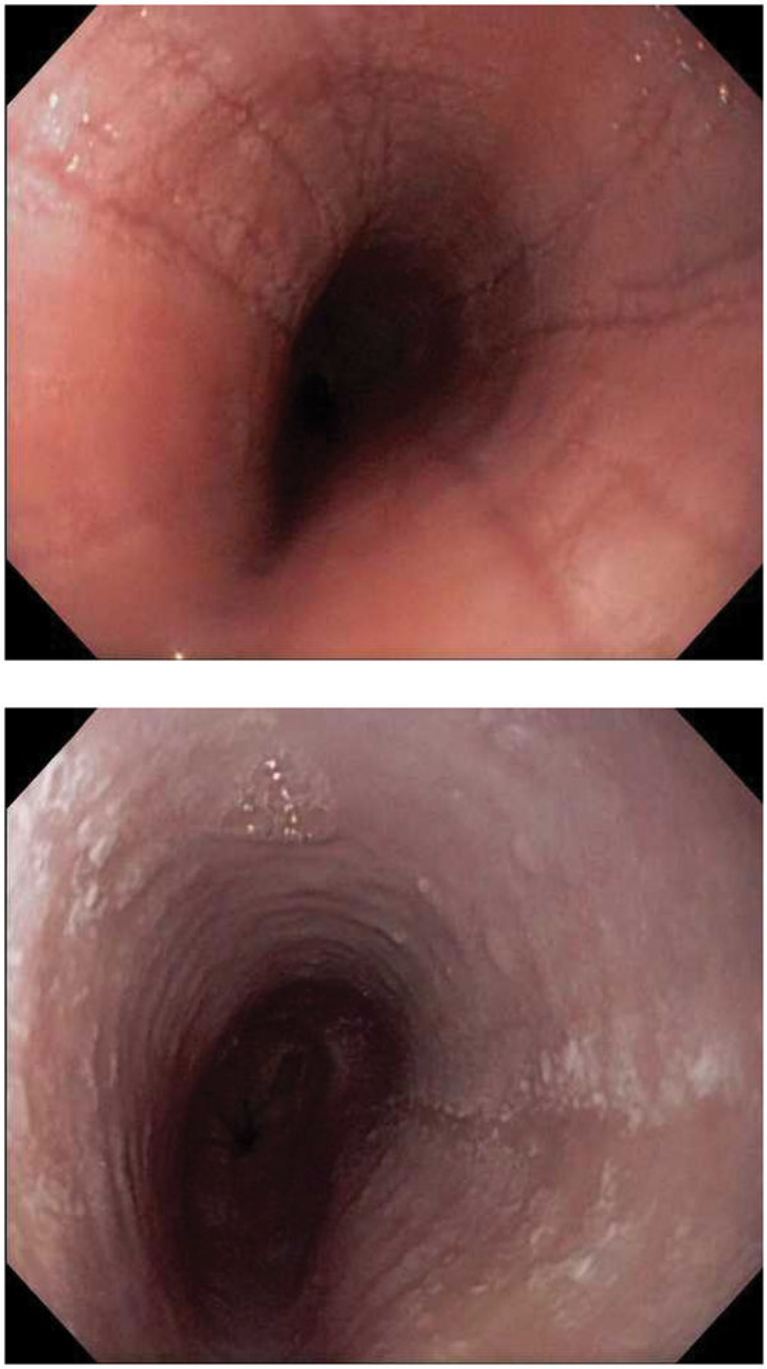
Key points

- Eosinophilic esophagitis is a clinicopathologic diagnosis; because symptoms, endoscopic findings, and histologic features are non-specific, the entire clinical picture must be considered in order to make the diagnosis.
- The finding of eosinophilia on esophageal biopsy does not, in and of itself, establish a diagnosis of eosinophilic esophagitis.
- Current diagnostic criteria require three components for diagnosis of eosinophilic esophagitis: 1) Clinical symptoms of esophageal dysfunction; 2) a maximum esophageal eosinophil count of at least 15 eos/hpf, with few exceptions; and 3) exclusion of other possible causes of esophageal eosinophilia.





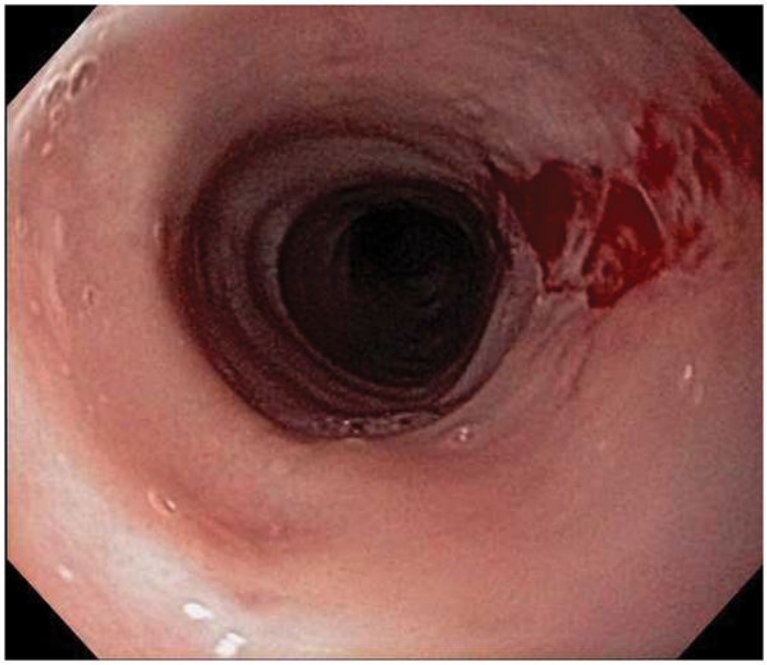


Figure 1.
Typical endoscopic findings in EoE. (A) Fixed esophageal rings, previously termed corrugation or trachealization. (B) Transient esophageal rings, previously termed felinization. (C) Linear furrows, as well as mucosal pallor, congestion, and loss of vascularity. (D) White plaques and exudates, as well as mucosal pallor, congestion, and loss of vascularity. (E) Crêpe-paper mucosa with a mucosal rent after passage of the endoscope through a narrow caliber esophagus. This occurred without endoscopic dilation.

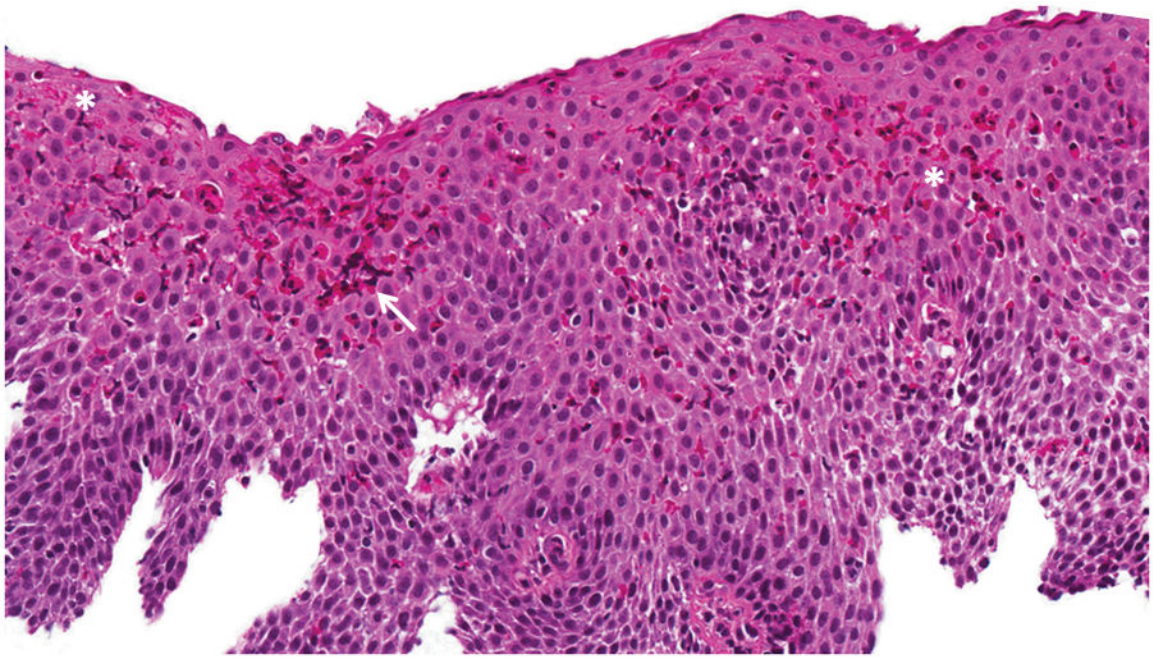


Figure 2.

Typical histologic features of EoE. In this esophageal biopsy specimen, a marked infiltrate of eosinophils is noted in the epithelium. In addition to the increased number of cells, eosinophilic microabscesses are noted (white arrow) and there is eosinophil degranulation (white asterisks). The basal layer is also substantially hypertrophied.

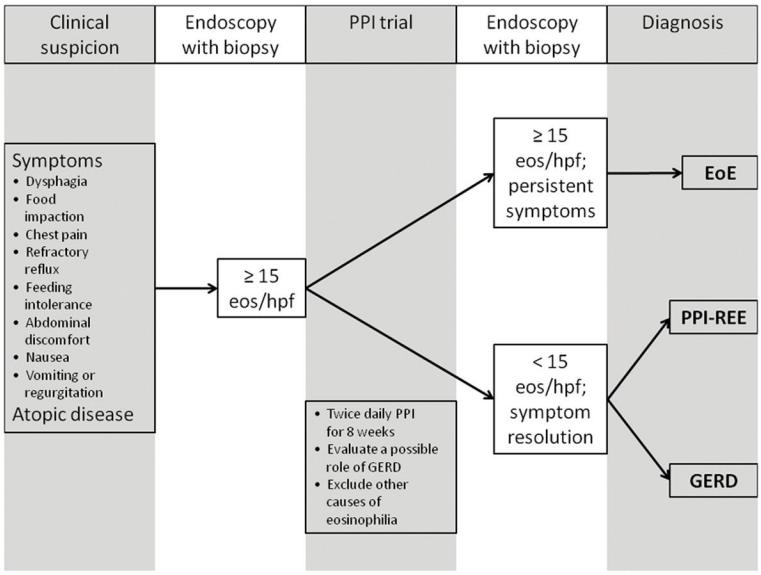


Figure 3.

A diagnostic algorithm for EoE. First, the condition must be suspected clinically, and on endoscopy it is imperative that esophageal biopsies are obtained regardless of the endoscopic appearance of the esophagus. If the biopsies show at least 15 eos/hpf, then the diagnosis of EoE is a possibility, but it is not confirmed. The other causes of esophageal eosinophilia, in particular GERD and PPI-REE must be assessed, which is best done by treating with a high dose PPI trial for 8 weeks. The endoscopy is then repeated. If there are persistent symptoms and biopsies again show ≥ 15 eos/hpf, then the diagnosis of EoE is confirmed. If the biopsies show resolution of esophageal eosinophilia, then the patient either has PPI-REE or GERD.