

# Pathology of Eosinophilic Esophagitis: What the Clinician Needs to Know

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**Eosinophilic esophagitis (EOE) is a clinical pathologic syndrome characterized by influx of numerous eosinophils into the esophageal epithelium. It is important for clinicians to be aware of the spectrum, as well as the characteristic location and distribution, of morphologic changes in EOE to maximize the diagnostic yield in mucosal biopsy specimens. The major pathologic features of EOE include eosinophilic microabscesses, surface layering of eosinophils often associated with surface sloughing of necrotic squamous cells, and peak eosinophil counts usually greater than 15 per high power field (hpf) within the squamous epithelium. Minor features, which are frequent but less specific, include marked basal cell hyperplasia, lengthening of lamina propria papillae, intercellular edema, and lamina propria fibrosis with chronic inflammation. The number, distribution, and location of intraepithelial eosinophils in EOE vary greatly between previously published studies. Thus, utilization of a diagnostic cutoff point for intraepithelial eosinophils in EOE, particularly in the absence of other major features of EOE, is currently considered unwise. In fact, some patients may show combined features of both gastroesophageal reflux disease (GERD) and EOE, which complicates the histologic analysis of these patients. In contrast to GERD, EOE typically involves longer lengths of the esophagus, affects the proximal equally, or even more than the distal esophagus, and the pathologic findings are often patchy in distribution. As a result, it is highly recommended that clinicians obtain biopsies from patients suspected of have EOE only after treatment with high-dose proton pump inhibitor therapy, and that biopsies be obtained from both the proximal and distal esophagus in both normal and abnormal appearing areas.**

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## INTRODUCTION

Over the past 10–15 years, a distinctive clinicopathologic type of esophagitis has emerged, termed eosinophilic esophagitis (EOE), which is characterized by influx of numerous eosinophils as the predominant morphologic manifestation of the disease process (1). This condition affects both children and adults. Clinically, infants and very young children often present with feeding difficulties, unlike older children who often present with vague symptoms, such as nausea or vomiting and adults who typically present with dysphagia (1,2). However, unlike patients with gastroesophageal reflux disease (GERD), those with EOE show no, or only minimal, response to acid suppression therapy and normal, or near normal, ambulatory esophageal pH testing. Clinicians rely heavily on pathologists' interpretation of esophageal mucosal biopsies to confirm a clinical impression of EOE in their patients, but there is some overlap in the pathologic features of EOE with GERD (3). Thus, it is equally important for clinicians to be aware of the spectrum of pathologic changes in EOE, as well

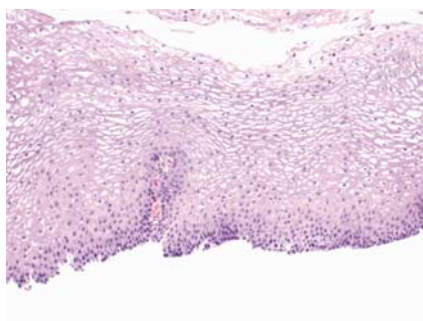
as the characteristic location and distribution of morphologic changes in the esophagus to maximize the diagnostic yield of mucosal biopsy specimens. After a brief review of normal histology and GERD-related pathology, this review will focus mainly on the current concepts and controversies regarding the pathologic features of EOE in children and adults.

## NORMAL HISTOLOGY AND RESPONSE OF THE ESOPHAGUS TO INJURY

From the lumen to the adventitia, the normal esophagus is composed of stratified squamous epithelium, an underlying lamina propria, muscularis mucosa, submucosa, and muscularis propria. The epithelium is normally composed of 1–3 layers of basal cells, with overlying suprabasal cells (4) (**Figure 1**). Above the suprabasal cell layer, the squamous cells reveal an increasing degree of maturation toward the surface of the epithelium. Under normal physiologic circumstances, the basal layer measures less than 15%, and the lamina propria papillae,

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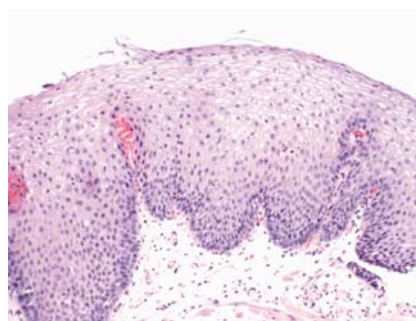
**Figure 1.** Normal esophageal squamous mucosa is characterized by a thin layer of basal and superbasal cells forming less than 15% of the thickness of the epithelium, lamina propria papillae that extend less than 50% of the thickness of the epithelium, and progressive maturation of epithelial cells to the surface.

which represent elongated areas of lamina propria that protrude into the epithelium, extend to only one-fourth to one-third, of the thickness of the squamous epithelium. “Mild” basal cell hyperplasia and lamina propria papillae elongation may occur, normally, in the distal 1–2 cm of the esophagus just proximal to the gastroesophageal junction (GEJ). In fact, although the normal epithelium contains no intraepithelial eosinophils (EOs), rare intraepithelial EOs may be present in this area of the esophagus as well. Although these minor pathologic changes are believed to be due to “physiologic” reflux, this theory has never been formally tested.

As a result of tissue injury from any cause, the basal cell compartment expands, increases in thickness, becomes mitotically active, and the lamina propria papillae elongate upwards toward the luminal surface. These features represent a nonspecific reaction pattern to injury from any cause, and are not specific to either GERD or EOE. In addition to basal cell hyperplasia and lamina propria elongation, other nonspecific reaction patterns to tissue injury include edema, hemorrhage, congestion, a generalized increase in inflammation by T lymphocytes (CD3+, CD8+), neutrophils, and perhaps other cells such as Langerhans cells. These changes may occur in the lamina propria as well. Depending on the degree of injury, various degrees of epithelial cell necrosis may ensue.

## GERD

The pathologic features of GERD are separated into low and high-grade changes (5). Low-grade changes include mild basal cell hyperplasia affecting <20% of the thickness of the epithelium, lengthening of the lamina propria papillae (up to one-half of the thickness of the epithelium), with congestion and edema, mild intercellular edema, regenerative changes (characterized by increased mitotic figures and nuclear hyperchromaticity), and increased intraepithelial EOs (**Figure 2**). High-grade changes include influx of neutrophils, surface erosion or ulcer, individual cell necrosis, ballooning degeneration of squamous cells, and more marked basal cell hyperplasia and



**Figure 2.** Mild gastroesophageal reflux disease (GERD) characterized by a mild degree of basal cell hyperplasia, slight elongation of the lamina propria papillae with vascular congestion, scattered eosinophils in the mid layers of the epithelium, and evidence of lack of surface maturation characterized by the presence of nucleated epithelial cells in the luminal aspect of the epithelium.

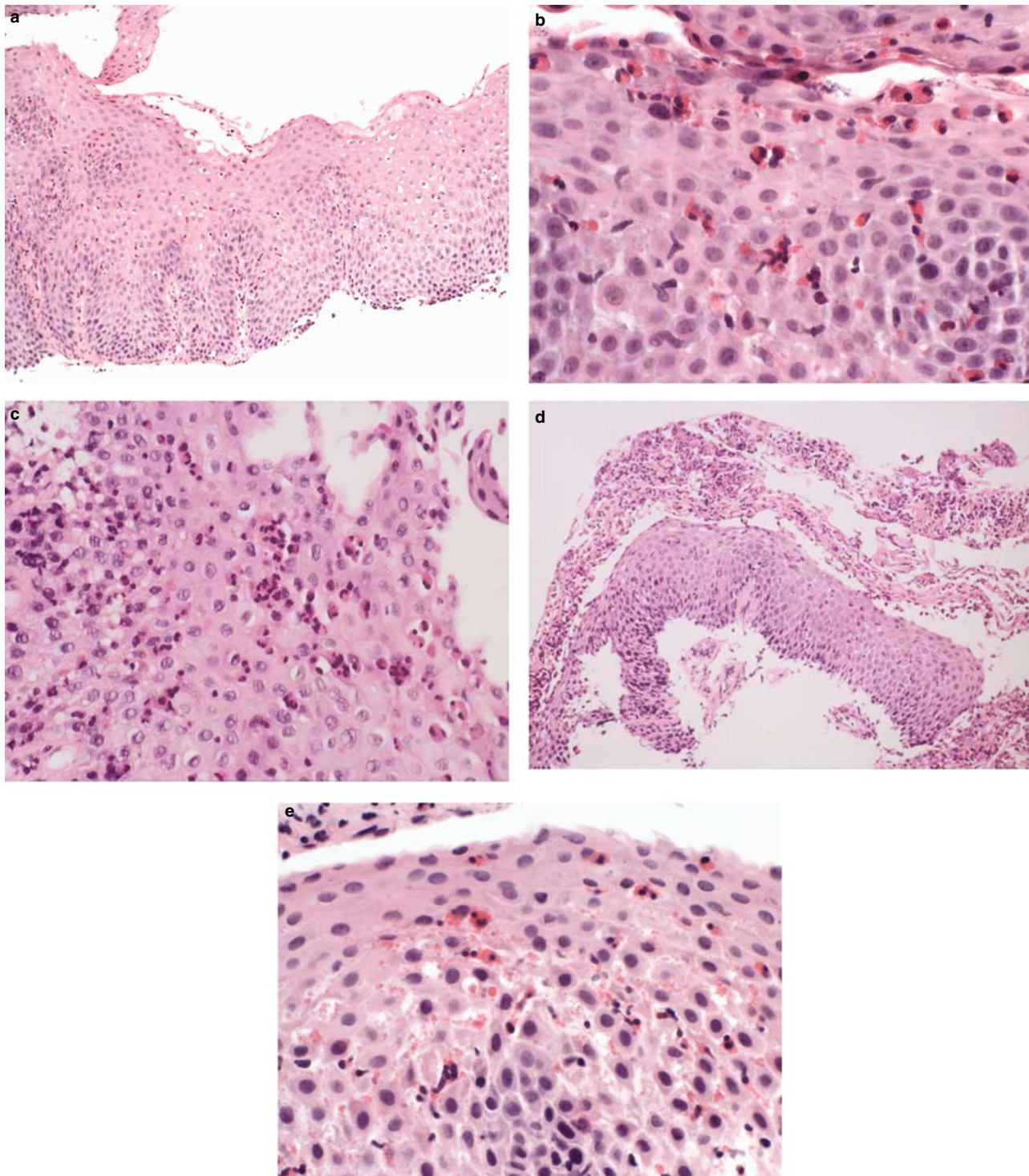
elongation of the lamina propria papillae, sometimes leading to a reactive pattern of injury referred to as pseudoepitheliomatous hyperplasia. Under normal circumstances, patients with GERD show more severe pathologic changes in the distal esophagus and GEJ region compared to the proximal esophagus (5,6).

Studies that have evaluated the number, location, and distribution of EOs in GERD have not been rigorous, and have been mainly retrospective (6–10). Most studies reveal between 1 and 10 EOs per hpf in GERD, being most numerous in the distal esophagus/GEJ region, and without a predilection for the surface layers of the epithelium (5,6,11–17). However, this data has been largely untested (in a controlled manner) and most of the GERD related studies were performed prior to the recognition of EOE as a distinct clinicopathologic entity. In fact, a wide range of intraepithelial EOs in GERD have been reported. For instance, in one study, the maximum number of EOs per hpf ranged from 20 to 168 in patients with severe or complicated GERD (18).

## EOSINOPHILIC ESOPHAGITIS

### General comments

As mentioned above, since there is clinical overlap between EOE and GERD, distinguishing these two conditions by microscopic evaluation of mucosal biopsies is considered clinically important (1). The key defining feature in patients with EOE is influx of EOs into the squamous epithelium. Unfortunately, esophageal eosinophilia is a nonspecific reaction pattern to a wide variety of potential injurious insults, such as GERD, infections, drug-induced injury (pill esophagitis), the effects of chemo and radiation therapy, Crohn’s disease, eosinophilic gastroenteritis, and malignancies (5,19). Thus, increased numbers of intraepithelial eosinophils is, essentially, a nonspecific pathologic finding, and must be interpreted in conjunction with the clinical and endoscopic features of the patient, as well as with other associated pathologic findings in the biopsy specimens from the esophagus, stomach, and duodenum.



**Figure 3.** Pathology of eosinophilic esophagitis. **(a)** Eosinophilic esophagitis characterized by prominent basal cell hyperplasia, elongation of the lamina propria papillae, presence of numerous intraepithelial eosinophils with an affinity for the surface epithelium (numbering greater than 15 per hpf in peak areas), and sloughing and degeneration of the superficial surface epithelium mixed with eosinophils. The left side of the biopsy shows abundant eosinophils, whereas the right side of the biopsy shows only a minimal eosinophilic infiltrate reminiscent of gastroesophageal reflux disease (GERD). **(b)** High power view of another area from the same case showing numerous intraepithelial eosinophils with a predilection for the surface epithelium forming early microabscesses (defined as a collection of four or more eosinophils). **(c)** High power view of another case of eosinophilic esophagitis showing more prominent eosinophilic microabscesses (image courtesy of Dr Antonioli, Beth Israel Deaconess Medical Center). **(d)** Low power view of another case of severe eosinophilic esophagitis showing prominent sloughing of epithelial necrotic debris mixed with eosinophils (image courtesy of Dr Antonioli, Beth Israel Deaconess Medical Center). **(e)** Eosinophilic esophagitis showing prominent intercellular edema, abundant intraepithelial eosinophils and prominent degranulation of eosinophils.

### Pathologic features

The pathologic features of EOE can be broadly separated into “major” and “minor.” Major features are considered characteristic and necessary to establish a diagnosis, but not pathognomonic, of EOE. Minor features are often helpful for pathologists but, essentially, are nonspecific and occur in a wide variety of disorders. Major features include increased intraepithelial eosinophils (greater than 15 per hpf in areas of peak density), eosinophilic microabscesses (defined as a collection of four or more EOs within the epithelium), a particular affiliation of EOs to aggregate in the surface layers of the epithelium (“surface layering”), surface sloughing of squamous cells and EOs, and EO degranulation (3,20) (Figure 3). Minor features include “marked” basal cell hyperplasia (generally greater than 20% of the thickness of the epithelium), lengthening of the lamina propria papillae (often greater than 75% of the thickness of the epithelium), increased intraepithelial lymphocytes and mast cells, increased intercellular edema, and increased lamina propria fibrosis and chronic inflammation (3,20–22). Influx of neutrophils, and the development of ulcers or erosions, are unusual in EOE, unless complicated by another unrelated disorder such as GERD, pill esophagitis, or infection.

### Eosinophils in EOE

Unfortunately, the number, distribution, and location of intraepithelial EOs considered supportive and/or diagnostic of EOE varies greatly between previously published studies (1,17,23). This may be due to a variety of factors, such as variability in the methods used to evaluate EOs in different studies (such as variation in the location of biopsies, or biopsies obtained only from the distal esophagus/GEJ region in which the effects of GERD are most pronounced), absence of reporting of the anatomic site of the biopsy, minimal (or no) clinical information or manometry test results, lack of information on anti-GERD therapy, or inclusion of information on EOs regardless of their distribution in the mucosa or location in the esophagus (3,23). Furthermore, the method of enumerating EOs has been widely variable and this is primarily due to a lack of consensus on this issue and lack of uniformly accepted pathologic criteria. For instance, some early reports did not quantify EOs, whereas others counted only one hpf, others counted many hpfs (1,3,23). Some studies counted EOs only in areas with the highest density of EOs, others have averaged the numbers of EOs in all hpfs regardless of the density of the cells. Finally, the size of an hpf is dependent on the particular ocular characteristics of the microscope used for study, and this has also differed widely between studies.

The first objective definition of EOE was put forth in a case series of 12 patients, in which >20 EOs per hpf was determined as the diagnostic cut off point. More recently, in a Medline review of 116 papers, 39 abstracts, and 69 review articles between 1950 and 2006, Dellon *et al.* (23) reported a great degree of variability in the methods and criteria used to define EOE. In that study, the authors cited 10 different histologic definitions of EOE that ranged from 5 to 30 EOs per hpf. In fact, 35% of reported

studies did not state the pathologic criteria used for evaluation of EOE. In addition, in the 13 original articles that reported the number of EOs per hpf, the EO density (per mm squared) varied 23-fold. Nineteen articles used greater than 15 EOs per hpf as a diagnostic “cut-off” point for EOE, 30 used more than 20 EOs per hpf, 17 more than 24, and 3 greater than 25 EOs per hpf. Nevertheless, most authorities advocate counting EOs in areas of mucosa with the highest density of cells (representing the peak counts) and expressing the number of EOs per hpf in this context (1,3). However, at present, there is no consensus regarding the correct method of counting EOs, but given that intraepithelial EOs are not typically uniformly distributed in the esophagus (2,3,17,21,24), and sometimes not even within a single biopsy specimen, it is recommended that counts be obtained from the most densely populated areas using greater than 15 EOs per hpf as the “minimum” cut-off to suggest a diagnosis of EOE.

Regardless of the method used to count EOs, it is noteworthy that one recently reported study showed significant overlap in the number, location, and grouping of EOs in the esophagus in patients with EOE vs. GERD. In a study of 40 patients, all of whom were selected from a large cohort of 3,648 patients on the basis of finding at least one biopsy with >20 EOs per hpf, by Rodrigo *et al.* (18), 6(15%) had EOE, 2(5%) had coincident EOE and GERD, and 28(70%) had GERD. The remaining four patients had other non-GERD, and non-EOE-related esophageal disorders. In that study, the maximum number of EOs (and range), the number of patients with  $\geq 2$  biopsies (levels) with >20 EOs per hpf, the presence of EO microabscesses, and surface layering of EOs, did not differ significantly between the three groups of patients. However, the cohort of patients used for the study were obtained from a somewhat biased high risk referral center for GERD, without controls, and the paper did not cite whether patients were treated with high dose anti-GERD therapy prior to endoscopy with biopsies. Furthermore, even in this high risk population, biased toward patients with severe and complicated GERD, only 1.1% of patients in their entire cohort had >20 EOs per hpf indicating the rarity of this finding in this patient population.

### Other “major” features

Other, often disregarded, but equally important pathologic features of EOE include the distribution of disease and the findings in the stomach and duodenum (3,21,24,25). As opposed to GERD-induced esophagitis, EOE often involves long segments of the esophagus, may be patchy/focal (which leads to an increased chance for sampling error) and typically involves the proximal esophagus equally, or more so, than the distal esophagus/GEJ region. For instance, in one study by Gonsalves *et al.* (25), the mean number of EOs per hpf was similar in the proximal, compared to the distal, esophagus (68 vs. 82), and the number of patients with at least one biopsy showing  $\geq 15$  EOs per hpf was also similar (80% vs. 100%). This is in stark contrast to patients with GERD, who typically reveal higher EO counts in the distal, compared to the proximal, esophagus. Gonsalves

*et al.* also noted characteristic “focality” of eosinophilic infiltrates in EOE. In that study, the findings in one biopsy showed a sensitivity for EOE of 55% compared to 100% when five biopsies from different levels of the esophagus were obtained. In a similar study by Walsh *et al.* (22), biopsies obtained  $\geq 10$  cm proximal to the GEJ averaged 32 EOs per hpf in patients with EOE, compared to only 1 EO per hpf in a control group of GERD patients. In that study, both eosinophilic microabscesses and superficial layering of EOs were only present in patients with EOE. Similarly, in a study by Bhattacharya *et al.* (26), the number of EOs per hpf was 55 in patients with EOE compared to 6 in patients with GERD. Eosinophilic microabscesses were present in 79% of the former, but 0% of the latter.

Finally, from both the clinical and pathologic point of view, eosinophilic gastroenteritis (EOG) may mimic EOE. Many of these patients reveal numerous esophageal intraepithelial EOs, have an allergic history and show peripheral eosinophils. However, as opposed to EOE, patients with EOG typically reveal gastric, and less often duodenal, involvement. Thus, obtaining biopsies from the stomach and duodenum may be considered to rule out EOG in diagnostically difficult cases.

#### Minor pathologic features

Other features, such as basal cell hyperplasia, lengthening of the lamina propria papillae, lamina propria fibrosis and chronic inflammation, lack of neutrophils and/or ulcers, and prominent intercellular edema are common in GERD, and in other types of esophagitis as well, but have been reported to be more pronounced in patients with EOE (3,17,21,22,27). Eosinophilic degranulation is also common in EOE, but this feature has not been rigorously evaluated in patients with GERD (22). In the study noted above by Walsh *et al.* (22), marked basal cell hyperplasia and lamina propria lengthening were present in all of patients with EOE, but in none of the control patients with GERD. Unfortunately, evaluation of basal cell hyperplasia and lamina propria papillae lengthening is highly dependent on proper tissue orientation, which is often a limitation when evaluating mucosal biopsies of the esophagus. Furthermore, the features may occur in a wide variety of esophageal inflammatory disorders, so that in individual patients they are considered “supportive” but not “diagnostic” of EOE.

#### Other cell types in EOE

Some studies have reported an increase in other types of inflammatory cells and inflammatory mediators in patients with EOE as well (21,28–33). For instance, increased CD3 positive T lymphocytes, increased CD8 and CD1A lymphocytes, mast cells, dendritic cells, and increased expression of interleukin 5 and 13 have all been reported in patients with EOE. Eotaxin levels, particularly eotaxin 3, and its receptor CCR-3, have been shown to be markedly increased in EOE by immunohistochemistry, and by mRNA and protein analysis. Some of these parameters have been evaluated for use in differentiating EOE from GERD in mucosal biopsies, but at this point in time, are still considered investigational.

#### Combined GERD and EOE

Recently, it has been suggested that EOE and GERD may coexist in some patients and this may, of course, further complicate the clinical and histologic analysis of biopsy specimens (34,35). For instance, it was recently proposed that EOE may predispose patients to GERD by releasing secretory products that cause altered esophageal motility or structural changes, which may, in turn, lead to increased susceptibility to the negative effects of acid. In contrast, GERD may contribute to the development of EOE by causing acid-induced epithelial damage, which may result in increased intercellular permeability to large-sized antigens and the subsequent recruitment of immune cells. Ngo *et al.* recently reported three patients with clinical, endoscopic, and histologic features highly suggestive of EOE (with  $>20$  EOs per hpf in biopsies) whose findings resolved completely upon treatment with high dose proton pump inhibitors. As suggested by Spechler *et al.*, one cannot rule out the possibility that GERD helped induce EOE in these patients. Regardless, it is critically important for clinicians to treat patients with suspected EOE with vigorous anti-GERD therapy, to decrease or eliminate the potential esophageal changes (or effects) of GERD on the esophagus, prior to evaluation of mucosal biopsies (1,3).

#### Diagnostic criteria and helpful hints for gastroenterologists

Recently, a multidisciplinary task force of 31 physicians was assembled to discuss specific criteria, and make recommendations, for evaluation and treatment of patients with EOE based on an extensive literature review and expert opinion (1) (**Table 1**). This group defined EOE as a clinicopathologic disease with symptoms including, but not restricted to, food impaction/dysphagia in adults or feeding intolerance/GERD symptoms in children combined with the finding of greater than 15 EOs per 1 hpf (in areas of most dense EOs, representing the “peak” EOs counts), after exclusion of other disorders (especially GERD) by high dose proton pump inhibitor therapy or documentation of normal pH or near normal ambulatory esophageal pH testing (see **Table 1**). In that consensus review, it was noted that pathologic changes may occur in grossly normal-appearing mucosa, so that it is important to obtain biopsies not only from the proximal esophagus, but in areas of normal-appearing mucosa as well. It was noted that tissue specimens should not be fixed in Bouin’s, because of the difficulty of evaluating EOs in specimens fixed in this solution. Multiple biopsies should be obtained from both the proximal and distal esophagus (even if endoscopically normal), and from grossly abnormal areas although this approach has not yet been evaluated systematically in prospective studies. In addition, in diagnostically difficult cases, biopsies may be obtained from both the stomach and duodenum to rule out other disorders, such as EOG, that can also lead to prominent esophageal eosinophilia. After treatment with high dose proton pump inhibitor therapy, and utilizing the clinical and endoscopic methods, outlined above, biopsies that reveal eosinophilic microabscesses and superficial layering of EOs,

**Table 1. Diagnostic approach to patients with suspected eosinophilic esophagitis**

1. Clinical	Food impaction/dysphagia in adults
	Feeding intolerance/GERD symptoms in young children
	High dose PPI therapy×2 months to exclude GERD
2. Endoscopic	Rings, pinpoint white mucosal exudates, linear furrows, strictures
	Obtain multiple biopsies from proximal and distal esophagus
	Biopsy normal and abnormal areas
3. Pathologic	Biopsy stomach and duodenum if Eosinophilic gastroenteritis is in the differential
	Avoid Bouin's fixative
	Evaluate for EO microabscesses, surface layering and slough, EO degranulation
	Count EOs per hpf in peak (most dense) areas to obtain mean count
EO, eosinophil; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.	
Data based on review by Furuta <i>et al.</i> (1).	

either with or without sloughing of necrotic squamous cells and EOs, may be considered highly suggestive (virtually diagnostic) of EOE. In the absence of these findings, biopsies that reveal a peak count of  $\geq 15$  EOs per hpf, particularly in combination with other (minor) pathologic features noted above, and especially if equally or more severe in the proximal compared to the distal esophagus, are considered suspicious of EOE. Although using a fixed cut-off value of 15 EOs per hpf was considered unwise by this study group, the combination of these pathologic findings in patients who have fulfilled the clinical and endoscopic criteria are, in fact, quite rare in patients with GERD. Nevertheless, documentation of a clinical and pathologic response to therapy is considered the ultimate confirmation of the patient's diagnosis.

#### CONFLICT OF INTEREST

**Guarantor of the article:** Robert Odze, MD, FRCPC.

**Specific author contributions:** Dr Odze reviewed the literature, drafted the paper, and edited the paper for intellectual content.

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