An Evolving Approach to the Diagnosis of Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is a chronic allergic/immune-mediated esophageal disease. Knowledge related to the clinical presentation, pathogenesis, epidemiology, natural history, treatment, and outcomes of EoE has rapidly evolved over the past 2 decades. This article focuses on the similarly evolving diagnostic framework for EoE. In the initial clinical guidelines, diagnosis of EoE was based on symptoms of esophageal dysfunction; at least 15 eosinophils per high-power field (eos/hpf) on esophageal biopsy; and either a lack of response to high-dose proton pump inhibitor (PPI) therapy, or normal pH monitoring. The first 2 criteria have remained largely unchanged; however, the role of PPIs has been controversial, particularly due to the recognition of PPI-responsive esophageal eosinophilia (PPI-REE), in which patients with suspected EoE experience resolution of symptoms and esophageal eosinophilia with PPI therapy. A quickly expanding evidence base has found that most adult patients with EoE and PPI-REE share similar clinical, endoscopic, histologic, immunologic, and molecular characteristics prior to the use of PPIs. Because of this, the most recent diagnostic guidelines have removed the lack of response to PPIs as a diagnostic criterion; PPIs are now better considered as a treatment for esophageal eosinophilia. EoE should currently be suspected on a clinical basis when there are symptoms of esophageal dysfunction and at least 15 eos/hpf on esophageal biopsies. A history of atopy and endoscopic signs of EoE are strongly supportive of the diagnosis. However, the diagnosis cannot be confirmed until a thorough evaluation of other potential causes of esophageal eosinophilia has been performed.

Eosinophilic esophagitis (EoE) is a chronic allergic/immune-mediated clinicopathologic condition characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of the esophageal mucosa by at least 15 eosinophils per high-power field (eos/hpf) in the absence of secondary causes.[1,2] Clinical presentation varies by age; children present with predominant symptoms of abdominal pain, nausea, vomiting, regurgitation, and failure to

thrive, whereas adults and some adolescents present more commonly with solid food dysphagia and food impaction, although heartburn and noncardiac chest pain can also be seen. The dichotomy in clinical presentation is thought to be due to the natural history of the disease with progression from an inflammatory phenotype to a more fibrostenotic phenotype.[3-5]

Over the past 2 decades, the incidence of EoE has rapidly increased, with current incidence estimates ranging from 5 to 10 cases per 100,000 people per year.[6] Given the chronic nature of this disease, increasing incidence has been paralleled by growing prevalence, with current prevalence estimates ranging from 0.5 to 1 case per 1000 people.[6] EoE is now the leading cause of dysphagia and food impaction in children and young adults, and comprises more than 50% of cases of food impaction that present to the emergency department.[7-12] EoE is also commonly encountered in the outpatient setting, and is a major cause of upper gastrointestinal morbidity and increasing health care costs.[13]

EoE affects patients of all ages but is diagnosed more commonly in children and adults younger than 50 years of age.[14] Men are more commonly affected than women, with a ratio of 3 to 4:1, and the disease is also more common among white patients.[15,16] The prevalence of EoE varies by location, with a greater number of cases being reported in Western Europe, North America, and Australia; few cases are reported in Asia and the Middle East, and no cases have been reported in sub-Saharan Africa or India.[6] The rapid increase in EoE incidence as well as the geographic variation of the disease raise the question of whether environmental factors play a role in disease risk. Numerous potential risk factors have been investigated, such as aeroallergens,[17-19] food allergens,[20,21] cold or arid climates,[22] lower population density,[23] decreased rates of *Helicobacter pylori* infection,[24] use of proton pump inhibitors (PPIs),[25] and early-life exposures (eg, antibiotic exposure).[26,27]

Current treatment options include medical, dietary, and endoscopic therapies. The current understanding is that EoE is the result of a Th2 cell–mediated immune response involving interleukin (IL)-4, IL-5, and IL-13 to food and/or environmental allergens.[28] Medical and dietary therapies are targeted at reducing this inflammatory process. Corticosteroids are a mainstay of pharmacologic treatment for EoE. Systemic corticosteroids are effective; however, symptoms and esophageal eosinophilia recur rapidly following corticosteroid taper.[29] Due to undesired adverse effects associated with prolonged systemic corticosteroid use, topical or swallowed corticosteroids (eg, fluticasone, budesonide) were developed.[2] Topical corticosteroids are effective in achieving histologic and clinical improvement,[30-34] and can also be effective

in maintaining EoE remission.[35-38] Dietary strategies, such as amino acid–based elemental formulas, allergy test–directed elimination diets, and nondirected empiric elimination diets, have also been shown to be effective in achieving clinical and histologic remission, and can be used as first-line nonpharmacologic therapies.[20,34,39-43] Endoscopic therapy, specifically esophageal dilation, does not affect eosinophil-induced inflammation; however, dilation plays an important role in the treatment of fibrostenotic complications of EoE and improves symptoms of dysphagia.[44-47] The evolving role of PPIs is discussed in detail in this paper. Several questions remain regarding long-term therapy, including treatment endpoints for EoE, the role of maintenance therapy, and treatment of refractory disease.[48-50] There are also numerous novel treatment options under study,[51-62] but these are beyond the scope of this paper.

Since its recognition, EoE has continued to be a heavily researched disease entity, which has led to significant insight and discovery. New discoveries have resulted in a constant evolution of the diagnostic criteria for EoE (Figure). This paper provides an update on the evolving approach to the diagnosis of EoE.

History of the Diagnosis of Eosinophilic Esophagitis

The first case of EoE was reported in the literature in 1977; a patient with comorbid asthma and hay fever presented with symptoms of esophageal spasm and was found to have eosinophilic infiltration of the esophageal mucosa.[63] Scattered case reports followed throughout the next decade, but EoE was not recognized as a distinct entity until its description was included in several seminal case series published in the early- to mid-1990s.[64-66] For the next 10 years or so, there remained substantial diagnostic variability with regard to factors such as biopsy procurement, quantification of eosinophils, threshold of the number of eosinophils to define EoE, and the use of additional testing such as esophageal pH monitoring.[67] In order to provide clarification surrounding diagnostic criteria and treatment, the first consensus recommendations for EoE were published in 2007.[68]

According to these recommendations, a patient would be diagnosed with EoE if he or she met the following criteria: (1) esophageal and/or upper gastrointestinal tract symptoms, (2) a minimum of 15 eos/hpf seen in at least 1 esophageal mucosal biopsy, and (3) either a lack of clinical or histologic response to high-dose PPI therapy, or normal pH monitoring of the distal esophagus. These diagnostic criteria recognized that EoE was isolated to the esophagus and emphasized the importance of excluding other disorders associated
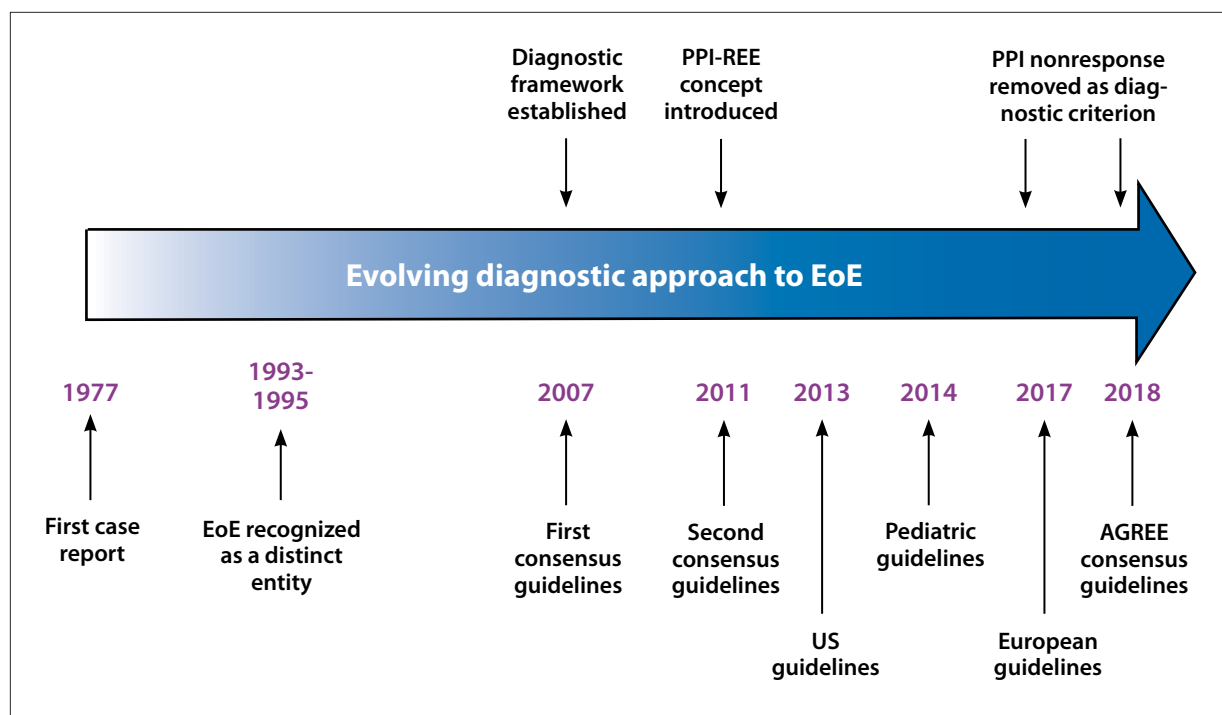
Figure. The first case report of eosinophilic esophagitis (EoE) was published in 1977; however, the condition was recognized as a distinct entity in 3 seminal publications between 1993 and 1995. The first consensus guidelines were published in 2007, establishing a diagnostic framework for EoE. These guidelines were updated in 2011, when PPI-REE was introduced as a concept. Management guidelines for the United States were published in 2013, followed by pediatric guidelines in 2014. The updated European guidelines, published in 2017, and international consensus guidelines, to be published in 2018, removed PPI nonresponse as a diagnostic criterion.

AGREE, A Working Group on PPI-REE; PPI, proton pump inhibitor; PPI-REE, PPI-responsive esophageal eosinophilia.

with similar clinical, histologic, or endoscopic features, especially gastroesophageal reflux disease (GERD). At the time, EoE and GERD were considered mutually exclusive diseases, and the purpose of a course of PPI treatment and/or pH monitoring was to rule out inflammation related to GERD as an underlying cause of symptoms and esophageal eosinophilia.[69,70] PPI therapy consisted of high-dose administration for 6 to 8 weeks followed by repeat upper endoscopy with biopsies.

In the following years, growing experience and research led to further insight regarding the etiology, pathogenesis, natural history, and treatment of EoE, and updated recommendations were published in 2011.[1] Several revisions to the original diagnostic guidelines included the acknowledgement that EoE was a chronic condition driven by an aberrant immune response; the inclusion of select patients with more than 15 eos/hpf on esophageal mucosal biopsies (possibly due to inadequate biopsy specimens, sampling error, chronic disease, or partial treatment response), and a stronger emphasis on the need for excluding other potential causes of esophageal eosinophilia beyond GERD.

At the same time, there was an increasing recognition that patients with esophageal eosinophilia could respond to PPI therapy, which was thought to represent 2 potential groups of patients: those with abnormal pH monitoring consistent with GERD who had a clinicopathologic response to PPIs, and those with normal pH monitoring who still demonstrated a clinicopathologic response to PPIs.[70-72] This latter group suggested either unreliable diagnostic testing via pH monitoring or a response to PPIs, possibly due to their inherent anti-inflammatory properties.[73,74] The ambiguity surrounding this group of patients led to the introduction of a new condition termed PPI-responsive esophageal eosinophilia (PPI-REE). Patients with PPI-REE had symptoms of esophageal dysfunction, esophageal eosinophilia (≥15 eos/hpf), and clinical and histologic response after a trial of high-dose PPI therapy. However, the pathophysiology underlying PPI-REE remained unknown; it was unclear whether it was a subtype of EoE, a manifestation of GERD, or an independent entity.

Similar to the 2007 and 2011 recommendations, updated guidelines published in 2013 defined EoE as a

clinicopathologic disorder characterized by symptoms of esophageal dysfunction, eosinophil-predominant inflammation on esophageal biopsy (≥15 eos/hpf), mucosal eosinophilia isolated to the esophagus that persisted following PPI therapy, and exclusion of secondary causes of esophageal eosinophilia.[2] These guidelines also retained the PPI-REE classification, which was becoming an area of intense research activity. Additionally, a set of EoE guidelines directed toward the pediatric population was published in 2014.[75] Similar to the adult guidelines, pediatric patients with suspected EoE were to undergo the same evaluation as adults, with an initial upper endoscopy followed by an 8-week high-dose trial of PPIs and a repeat upper endoscopy. Patients with persistent eosinophil-predominant inflammation following a PPI trial were diagnosed with EoE in the setting of the exclusion of secondary causes of esophageal eosinophilia, and patients with a response to PPI therapy were classified as having PPI-REE.

Evolving Approach to the Diagnosis of Eosinophilic Esophagitis

Prior to and following the release of the 2011 recommendations, a number of studies were published that confirmed that PPI-REE was seen in both children and adults, and that this condition was common, with PPI response rates ranging from 33% to 74%.[72,76-84] A meta-analysis found that approximately 50% of patients with esophageal eosinophilia had a histologic response to a PPI, and that an even higher proportion of patients had a symptomatic response.[85] The studies also found that EoE and PPI-REE could not be distinguished by most baseline clinical, endoscopic, or histologic features prior to a trial of PPI therapy.[72,84,86,87] In particular, patients with either EoE or PPI-REE presented predominantly with dysphagia, which was often complicated by food impaction, and experienced heartburn at comparable rates. Several studies demonstrated a similar prevalence of endoscopic abnormalities including rings, furrows, white exudates, edema, and friability in the 2 patient populations.[84,86,87] Furthermore, the degree of esophageal eosinophilia as well as the histologic findings of eosinophil degranulation and microabscess formation were found to be similar between the 2 groups.[72,84,86,87]

Further confounding the distinction between EoE and PPI-REE was that pH monitoring was unable to predict a treatment response to a PPI. Patients without pathologic acid exposure could experience a resolution of eosinophilia, whereas patients with increased acid might not.[72,76,80] There was also a recognition that the relationship between EoE and GERD was more complex than previously understood, and that EoE and GERD were not mutually exclusive.[88] In addition, it appeared that both EoE and PPI-REE had a similar Th2-driven inflammatory milieu with production of similar cytokines and tissue biomarkers (eg, IL-5, IL-13, major basic protein, eotaxin-3, tryptase).[89,90] Similar molecular profiles in the 2 groups were found when using gene expression profiling of esophageal tissue; genes that are overexpressed include those necessary for eosinophil chemotaxis, barrier function, tissue remodeling, and mast cell function.[91] In addition to demonstrating significant overlap in biomarkers and gene expression, these studies demonstrated a reversal in the Th2 signature and normalization of gene expression following PPI therapy in patients with PPI-REE in a similar manner to what was seen in patients with EoE who responded to corticosteroid therapy.[90,91]

These observations were tied together mechanistically by the knowledge that PPIs have multiple anti-inflammatory effects and are not purely antisecretory, and by the discovery that PPIs have several potential mechanisms of action that could explain the resolution of esophageal eosinophilia. One likely mechanism of action is that PPIs, at physiologic doses, were found to block Th2 cytokine–mediated secretion of eotaxin-3, the cytokine that recruits eosinophils to the esophageal mucosa.[92,93] Another is that PPIs were found to improve epithelial integrity and barrier function.[94] Third, differential PPI metabolism by the hepatic CYP enzyme system explained the loss of PPI response in some patients.[95] Finally, 2 small case series have been published that show that patients with PPI-REE can also respond to traditional EoE treatments of dietary elimination or swallowed or topical corticosteroids,[96,97] which may support the theory that PPI-REE might be antigen-mediated, similar to EoE.

In this context, there is evidence to suggest that EoE and PPI-REE have more similarities than differences. Prior to PPI use, the 2 conditions have similar clinical, endoscopic, histologic, immunologic, and molecular features, and, thus, many patients with PPI-REE could potentially be considered to have EoE. These new research advances contributed to controversy within the field, particularly over the role of PPIs and the classification of PPI nonresponse as a diagnostic criterion rather than PPI use as a treatment option.[98,99] In 2017, a European guideline statement made an initial revision of the EoE diagnostic process, but it was still controversial.[100] Within this guideline, adult patients who achieve clinicopathologic remission on PPI therapy are considered to be part of the EoE continuum rather than having a separate disease entity. The authors removed PPI nonresponse as a diagnostic criterion for EoE and retracted the term PPI-REE. They further stated that PPI therapy could induce both clinical and histologic remission in a proportion of pediatric and adult patients with EoE and maintain remission

long term. Thus, PPI therapy should be considered as an alternative first-line anti-inflammatory therapy to topical corticosteroids and elimination diets.

In an attempt to build consensus, gastroenterologists, allergists, pathologists, and researchers from 14 countries convened at the AGREE (A Working Group on PPI-REE) conference to review the literature related to PPIs and esophageal eosinophilia, reach conclusions regarding the role of PPIs in the diagnosis of EoE, and operationalize a new EoE diagnostic algorithm. This statement is forthcoming, but the main conclusions were to remove the PPI trial as a diagnostic criterion for EoE and to consider PPIs as a treatment for esophageal eosinophilia and EoE.

Current Diagnosis of Eosinophilic Esophagitis

At present, based on both the 2017 European guidelines and the consensus from the AGREE conference, EoE should be suspected on a clinical basis when there are symptoms of esophageal dysfunction and when esophageal biopsies show at least 15 eos/hpf. A history of atopy and endoscopic signs of EoE are strongly supportive of the diagnosis. However, at this point, the diagnosis would not be confirmed until a careful and thorough consideration of other potential causes of esophageal eosinophilia has been performed.

Esophageal eosinophilia remains a histologic finding that must be interpreted within the clinical context of each patient. Numerous other diseases with distinct clinical and histologic features have also been associated with esophageal eosinophilia. These diseases include GERD, eosinophilic gastrointestinal diseases, celiac disease, Crohn's disease, infectious esophagitis, pill esophagitis, hypereosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, pemphigus, connective tissue diseases, and graft vs host disease. Therefore, providers must carefully consider and rule out other potential causes for esophageal eosinophilia before arriving at a diagnosis of EoE. In addition, there are some patients with esophageal eosinophilia greater than 15 eos/hpf who have either very mild endoscopic findings of EoE or a normal esophagus. Further research is required to understand where these patients fall in the spectrum of EoE.

The role of GERD deserves special mention in this context, particularly because it is now known that EoE and GERD can coexist and that the interaction between the 2 diseases can be complex.[88,101] Although a patient may have both EoE and GERD that are unrelated, EoE can cause secondary reflux (both from decreased esophageal compliance and dysmotility).[88,102,103] It is also possible that acid exposure from GERD and reflux of food contents might cause esophageal epithelial damage, resulting in penetration of allergic antigens that trigger an eosinophilic response.[88,102,103] Additionally, it is important to recognize that GERD itself can be associated with Th1-mediated esophageal eosinophilia.[91] Indeed, low levels of esophageal eosinophilia were first felt to be a marker of GERD,[69] although in some patients, even high levels of eosinophils can be due to reflux.[70]

Future Directions in the Diagnosis of Eosinophilic Esophagitis

Currently, the diagnosis of EoE requires upper endoscopy with multiple biopsies of esophageal mucosa, and management requires repeat upper endoscopies to assess mucosal and histologic response to treatment. Patients also undergo additional endoscopies for an evaluation of new, worsening, or recurrent symptoms. This invasive method of diagnosis and long-term monitoring is associated with risks of sedation and anesthesia, procedural complications, financial burden to the patient, missed time from work, and high health care costs. The development of less invasive tests to predict or monitor EoE would allow for selective testing in high-risk patients and reduce the number of endoscopies performed, which would also allow for a more cost-effective method of caring for patients with EoE.

Symptom scores and predictive models for EoE have been studied,[104-107] and, given the high rates of symptom overlap between EoE and GERD, models have been aimed at distinguishing between these 2 diseases. One scoring system has been validated in adults and can be used either before or after biopsy.[108] Two other studies describe scores or clinical models using laboratory and/or clinical data to distinguish EoE from GERD before endoscopy is performed, but they are not yet validated.[105,106]

With the rise of molecular technology, a gene expression panel (the EoE diagnostic panel; EDP) that comprises 94 genes was developed and has the ability to detect pediatric and adult patients with EoE with a 96% sensitivity and 98% specificity.[109] The EDP was also able to distinguish between patients with EoE in remission from controls and from patients with GERD, and could possibly identify patients with disease relapse following treatment. The EDP was further found to have high diagnostic utility in distinguishing EoE from non-EoE controls, and scores reliably improved following treatment response, suggesting that the EDP could be used to monitor disease status.[110] In addition to gene expression profiling, several studies have identified biomarkers in esophageal biopsy samples that are specific for EoE, such as eosinophil granule proteins, mast cell enzymes, cytokines, and chemokines.[111-113] Although the EDP or tissue biomarkers still require upper endoscopy with

biopsies, these tests could potentially increase diagnostic accuracy and reduce the number of biopsies needed.

Less invasive tests include transnasal endoscopy and mucosal impedance measurement. Transnasal endoscopy has the advantages of being able to be performed in the outpatient setting without anesthesia or sedation, while allowing for collection of esophageal biopsy specimens. Assessment of the esophageal mucosa with mucosal impedance has been demonstrated to distinguish inflammation patterns in EoE from those in GERD, as well as active vs inactive EoE.[114,115] Although mucosal impedance testing allows for avoidance of biopsies, one limitation of mucosal impedance is that the placement of the catheter currently requires an upper endoscopy to be performed.

An even less invasive assessment of the esophageal mucosa can be achieved via the Esophageal String Test (EST; EnteroTrack) and Cytosponge (University of Cambridge) test. These tests allow for the evaluation of esophageal contents by having the patient swallow a dissolvable capsule containing either a string or a sponge. The EST captures secretions of eosinophil-derived granule proteins and related Th2 cytokines, which strongly correlate with levels measured in esophageal mucosal biopsies.[116] The Cytosponge captures an epithelial sample that can be analyzed with standard histopathologic techiques.[117] Eosinophil counts from the sponge strongly correlate with those from standard esophageal biopsies.[118] Both of these methods are promising, but they are not yet available for routine clinical use.

Based on the current understanding of EoE pathogenesis, investigators have evaluated a number of potential serologic biomarkers, including absolute eosinophil count, as well as specific cytokines (eg, IL-4, IL-5, IL-13) and chemokines (eg, eotaxin-3, eosinophil granule proteins, mast cell tryptase) to establish a diagnosis of EoE and to monitor the condition.[119-122] However, although panels of these biomarkers have been created, none have been validated or are being used in the clinical setting. Additional studies have evaluated salivary IL-4 and IL-5, exhaled nitric oxide, urine 3-bromotyrosine, and stool eosinophil-derived neurotoxin, and have shown some potential as noninvasive markers of EoE, but these also must be validated in larger prospective studies.[120,123-127]

Conclusion

Knowledge related to the clinical presentation, pathogenesis, epidemiology, natural history, treatment, and outcomes of EoE has rapidly evolved over the past 2 decades. With this, the diagnostic framework of EoE has evolved. When the disease was first described, no guidelines existed, and there was substantial variability in diagnosis, with resulting heterogeneity in the patient cohorts that

were described. A series of diagnostic guidelines, each building on the prior, have presented clear diagnostic criteria and led to a standardization of reporting in the field. A major area of controversy over the past decade has been the role of PPIs and their use as a diagnostic criterion, as well as the resultant description of patients with PPI-REE. The most recent diagnostic guidelines continue this evolution by acknowledging that PPI-REE, in many cases, is actually in the EoE spectrum, and that PPIs should not be a diagnostic criterion but rather play an important role in the treatment of EoE through their anti-inflammatory properties. As knowledge related to EoE matures, diagnostic algorithms will continue to adapt. In the near future, minimally invasive and noninvasive techniques will come into clinical practice, likely relying on immunologic or molecular tests. These should further streamline and simplify EoE diagnosis, allowing patients to benefit and move from diagnosis to treatment.

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