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Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference

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Abstract

Background and Aims: Over the last decade, clinical experiences and research studies raised concerns regarding use of proton pump inhibitors (PPIs) as part of the diagnostic strategy for eosinophilic esophagitis (EoE). We aimed to clarify the use of PPIs in the evaluation and treatment of children and adults with suspected EoE in order to develop updated international consensus criteria for EoE diagnosis.

Methods: A consensus conference was convened to address the issue of PPI use for esophageal eosinophilia using a process consistent with standards described in the Appraisal of Guidelines for Research and Evaluation II. Pediatric and adult physicians and researchers from gastroenterology, allergy, and pathology subspecialties representing 14 countries utilized on-line communications, teleconferences, and a face-to-face meeting to review the literature and clinical experiences.

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Results: Substantial evidence documented that PPIs reduce esophageal eosinophilia in children, adolescents and adults, with several mechanisms potentially explaining the treatment effect. Based on these findings, an updated diagnostic algorithm for EoE was developed, with removal of the PPI trial requirement.

Conclusions: EoE should be diagnosed when there are symptoms of esophageal dysfunction and at least 15 eosinophils per high-power field (or ~60 eosinophils per mm^2) on esophageal biopsy, and after a comprehensive assessment of non-EoE disorders that could cause or potentially contribute to esophageal eosinophilia. The evidence suggests that PPIs are better classified as a treatment for esophageal eosinophilia that may be due to EoE than as a diagnostic criterion, and we have developed updated consensus criteria for EoE that reflect this change.

Keywords

eosinophilic oesophagitis; esophageal eosinophilia; proton pump inhibitor; diagnosis

INTRODUCTION

In order to provide clarity for research studies and clinical care,[1, 2] the first diagnostic guidelines on eosinophilic esophagitis (EoE) were published in 2007 and updated in 2011.[3, 4] EoE was defined as a clinicopathological condition that was immune or antigen driven, and characterized clinically by symptoms of esophageal dysfunction and histologically by ≥15 eosinophils per high power field (eos/hpf), with expert consensus determining the best approach to rule-out inflammation related to gastroesophageal reflux disease (GERD) would be with either high dose proton pump inhibitor (PPI) treatment for 8 weeks or pH monitoring. At that time EoE and GERD were felt to be mutually exclusive.

During the next decade, additional clinical experiences and research provided new insights into response to PPIs. Multiple investigators observed that a large proportion of patients with clinical symptoms and esophageal eosinophilia ≥15 eos/hpf responded to treatment with high-dose PPI, but did not have a clinical presentation consistent with GERD.[5–10] Because of this, diagnostic guidelines published in 2011, 2013, and 2014 defined a new condition termed PPI-responsive esophageal eosinophilia (PPI-REE).[4, 11, 12] Patients with PPI-REE had symptoms of esophageal dysfunction and ≥15 eos/hpf on esophageal biopsy, but improvement or resolution of symptoms and eosinophilia after a high-dose PPI trial. In these guidelines, PPI-REE was not well understood, but EoE and GERD were still felt to be two distinct conditions.[13]

However, an evolving body of research suggested that EoE and GERD were not necessarily mutually exclusive and instead shared a complex relationship (they can coexist; EoE can lead to secondary reflux due to decreased esophageal compliance or dysmotility; GERD can lead to decreased epithelial barrier integrity, allowing antigen exposure and subsequent eosinophilia).[14] In addition, a number of studies examined the clinical, endoscopic, and histologic features at baseline (prior to a PPI trial) of both EoE and PPI-REE, and found no conclusive factors could distinguish the two.[6–10, 15, 16] Concomitant atopic conditions were common in EoE and PPI-REE,[6, 8–10] allergic and inflammatory factors were found to be elevated in both,[17–19] and RNA expression profiles were largely similar between the two

conditions (and distinct from GERD) with normalization after topical steroid treatment or dietary elimination, though some differences existed.[20, 21] In addition, case reports of PPI-REE patients revealed that after stopping PPI treatment, patient symptoms and esophageal eosinophilia recurred, and subsequently responded to classical EoE treatments of diet restriction or topical steroids.[22, 23] Finally, several potential non-acid mediated mechanisms were described that could explain the PPI response in PPI-REE.[24–26] Thus, PPI-REE emerged as subtype of EoE in some patients, and a controversy developed over whether EoE and PPI-REE were in fact the same condition, whether PPI-REE was a food allergy-associated disease, whether PPIs should be considered EoE treatment, and whether a PPI trial should be removed from the diagnostic guideline.[27, 28] However, taken together, these new research advances provided a strong rationale for the consideration of removing the PPI trial from the EoE diagnostic algorithm (Table 1),

In favor of the continued inclusion of the PPI trial were that it potentially reduces the number of endoscopies required, helps address concomitant GERD, and provides a step-wise approach for EoE diagnosis. In favor of eliminating the use of a PPI trial was that it permits ability to discuss a range of therapies (e.g. some used for classic EoE) without committing patients to a PPI from the outset. It would also help achieve broader enrollment in clinical trials, allow treatment of esophageal eosinophilia with PPIs regardless of the underlying cause, and remove medication response as a diagnostic criterion. A new European EoE guideline, published in 2017,[29] suggested that PPI-REE and EoE were on the same spectrum and that PPIs could be considered a treatment for EoE. However, an operationalized approach to EoE diagnosis was not presented. To address these issues, we convened the AGREE (A working Group on ppi-REE) Conference, which was held on May 6, 2017 in Chicago, IL.

METHODS

Scope and Purpose

We conducted a consensus building process consistent with standards described in the Appraisal of Guidelines for Research and Evaluation II.[30] Thought leaders in gastroenterology, allergy, and pathology were divided into teams to review the pertinent literature to address 3 questions that would inform the overall objective of developing new consensus diagnostic criteria for EoE:

1. What is the evidence to support the use of PPIs for suspected EoE in children, adolescents, and adults?
2. What mechanisms could explain resolution of esophageal eosinophilia by PPIs?
3. What are the sensitivity and specificity of diagnostic tests for GERD?

Methods of review

Stakeholder Involvement—This proceeding was developed by pediatric and adult physicians and researchers from gastroenterology, allergy and pathology subspecialties with extensive experience in clinical care and research activities. There were 66 participants were from 14 countries. In addition, views and preferences of patients have been sought by

soliciting input from patient advocacy groups including American Partnership for Eosinophilic Disorders (APFED), Campaign Urging Research for Eosinophilic Disease (CURED), and Eosinophilic Family Coalition (EFC). Of note, the patient advocacy groups raised important issues related to treatment response, epidemiology, clinical approach to borderline cases, and need for education about updated diagnostic criteria. The target users are primary care physicians involved in referring patients for consultation and specialty care physicians who provide initial and longitudinal care for patients affected by EoE.

Rigor of Development—We searched the PubMed database for relevant publications from inception (1966) through December 2016. Search terms included “eosinophilic esophagitis”, “esophageal eosinophilia”, “proton pump inhibitor responsive esophageal eosinophilia”. There was no language restriction. A separate search was conducted for each key question addressed in the review, using terms that addressed the specific question. We included studies of any design that reported one or more patients of any age with esophageal eosinophilia who were treated with PPIs. We excluded review articles and did not include reports with <5 cases in our PPI response summary ranges. Bibliographies of retrieved studies were reviewed to identify additional relevant citations. In addition, domain experts reviewed the retrieved citations to ensure there were no relevant omissions. While a formal quality assessment was not performed, limitations of the evidence (for example retrospective design, small sample size, non-standardized outcome metrics, sources of bias) were assessed by each team. We acknowledge that use of a single search engine and lack of a formal quality assessment tool are potential methodologic limitations.

Between January 2017 to April 2017, each topic was discussed by a team of physicians (8–12 per topic) with expertise in identified topics. Literature was distributed electronically to each team, assessed with respect to ability to address the proposed question, and then discussed electronically and by teleconference (2–4 per team). Over this series of teleconferences, initial consensus was achieved (100% agreement of teleconference participants) after ongoing discussions regarding the answer to the assigned question. On May 5, 2017, an 8 hour face-to-face meeting with 43 of the AGREE members was held during which each team presented their findings for the original questions and discussion ensued to build final consensus. Agreement was assessed by a system of hand votes on the proposed questions, and there was 100% agreement of meeting attendees to remove the PPI trial from EoE diagnostic criteria. Based on this meeting, a manuscript was written and circulated electronically. Outstanding issues, including operationalizing the criteria and the approach to cases where clinical presentations of GERD and EoE overlap (particularly an issue in pediatrics), were discussed on a series of teleconferences and email discussions to establish uniform agreement prior to the final submission. This process included all co-authors who each confirmed agreement with the consensus. Health benefits, side effects and risks of findings were discussed as a part of this proceedings. The document was not externally reviewed prior to submission. A procedure for updating recommendations is provided.

Clarity of Presentation—The criteria provided are specific as they pertain to both children and adult patients and options are provided.

Applicability—Results from these proceedings provide advice and a practical approach for the clinical assessment and diagnosis of children and adults with suspected EoE. Facilitators and barriers relate primarily to distribution of criteria for practice. Monitoring and auditing of criteria will be addressed in future studies.

Editorial independence—The views of the funders have not influenced the content of the guideline. Competing interests of AGREE team members have been recorded and addressed.

RESULTS

Role of PPI treatment of esophageal eosinophilia

In order to assess the role of PPI treatment in esophageal eosinophilia, we defined "suspected EoE" as symptoms of esophageal dysfunction and at least 15 eos/hpf (or ~60 eos/mm^2) on esophageal biopsy, and "confirmed EoE" as symptoms of esophageal dysfunction, at least 15 eos/hpf (or ~60 eos/mm^2) on biopsy, after evaluation for other causes of esophageal eosinophilia. We divided patients into either children or adolescents/adults based on the similarity of the clinical presentation within these age ranges (non-specific vs dysphagia-predominant symptoms).[31] Full results are presented in On-line Supplemental Materials 1.

Although there were limited reports in children, there was evidence that PPIs could be used to treat esophageal eosinophilia in suspected EoE when response was measured by histologic improvement; clinical responses were less frequently studied and it was difficult to draw conclusions about symptom benefit. Overall, histologic response ranged from 23% to 83%, and clinical responses were 23% to 82% (Supplemental Figure 1A). In a meta-analysis by Lucendo and colleagues, the pooled histologic response to PPI treatment in children with ≥15 eos/hpf was 54% (95% CI: 38–70%), though heterogeneity was high (I^2 = 66%).[32]

There was substantial evidence that PPIs can be used to treat esophageal eosinophilia in adolescents and adults with suspected EoE, when response was measured by histologic improvement. Histologic response rates ranged from 23% to 83% (Supplemental Figure 1B). The meta-analysis by Lucendo et al reported a pooled histologic response rate of 50% (95% CI: 40–59) for PPI use in adults, though there was substantial heterogeneity (I^2 = 70%).[32] In both adults and children, the wide variability in PPI responses rates is likely due to the heterogenous populations enrolled as well as heterogeneous study designs; it was not possible to determine the role of overlapping GERD in the majority of these studies.

Potential mechanisms of PPI response—The notion that resolution of symptomatic esophageal eosinophilia with PPI therapy established a diagnosis of GERD and excluded EoE was based on several assumptions: 1) gastric acid inhibition is the only important effect of PPIs; 2) acid reflux does not contribute to antigen-mediated esophageal eosinophilia; and 3) GERD is the only esophageal disease that responds to PPIs. Recent data suggest these assumptions may be flawed[14] and that several potential mechanisms may underlie PPI response (see Supplemental Figures 2 and 3). These mechanisms include anti-inflammatory

effects of PPIs unrelated to gastric acid suppression and gastric acid-inhibiting effects of PPIs including effects on barrier function (full discussion in Online Supplemental Materials 1). However, these mechanisms are primarily from in vitro data, multiple mechanisms may be involved, and the actual mechanism of action is not known in any given case.

Principles for the updated EoE diagnostic criteria

Several principles were considered as the updated diagnostic criteria were developed. First, because EoE was felt to be the same disease in children and adults[33] and any age cut-off would be arbitrary, the criteria were crafted to be applicable to all ages. Second, there was an emphasis on removing the PPI as part of the diagnostic criteria. Third, we emphasized the need to evaluate for conditions that might contribute to esophageal eosinophilia rather than require their exclusion. For patients with reflux symptoms, this would allow EoE and GERD to coexist. Fourth, there was a requirement that the criteria be operationalized in a clinically useful way. Finally, the criteria would need to have utility in both clinical practice and research trials, and would need to be applicable to patients who had been diagnosed with EoE under prior guidelines. For research, this would also imply that not every EoE patient would be appropriate for inclusion in every clinical trial, and non-response to a PPI as an entry criterion may depend on the mechanism of the therapy under investigation and the label sought.

The other important principle was that EoE remains, as conceptually defined in the 2011 guidelines, a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, defined as >15 eos/hpf (~60 eos/mm^2) in the vast majority of cases.

Overview of the updated EoE diagnostic criteria

EoE diagnostic algorithm—The updated diagnostic algorithm for EoE is shown in Figure 1, with diagnostic criteria listed in Table 2. EoE is suspected on a clinical basis with chronic symptoms of esophageal dysfunction, which could manifest in a variety of ways including but not limited to: dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain, and malnutrition. Atopic comorbidities such as asthma, atopic dermatitis, or immediate-type food allergies, as well as family history of EoE or dysphagia, should increase the clinical index of suspicion. Because these symptoms are nonspecific, patients should be treated as clinically indicated. For example, patients with dysphagia or food impaction may move to an EGD or other structural assessment as the first-line test and prior to any treatment, whereas patients with heartburn or vomiting may have other testing or medical treatment (e.g. PPI for cases of suspected reflux), with need for endoscopy determined by clinical considerations. Because EoE presents with a wide range of symptoms, this algorithm cannot anticipate every clinical possibility and provides leeway for the age-appropriate evaluation deemed necessary.

When endoscopy is performed, the practitioner should evaluate for endoscopic signs of EoE (including esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow

caliber esophagus, ideally quantified using the EoE Endoscopic Reference Score [EREFS][34]) as well as alternative esophageal disorders. In all cases where EoE is a clinical possibility (even when normal mucosa is visualized),[35, 36] esophageal biopsy specimens should be obtained. As per prior guidelines, multiple biopsies from two or more esophageal levels, targeting areas of apparent inflammation, are recommended to increase the diagnostic yield.[3, 4, 11, 37–39] Gastric and duodenal biopsies should be obtained as clinically indicated by symptoms, endoscopic findings in the stomach or duodenum, or high index of suspicion for a mucosal process. Although gastric and duodenal biopsies in the absence of symptoms or endoscopic abnormalities have a low yield in identifying other eosinophilic gastrointestinal disorders (EGIDs), they are routinely obtained in pediatric endoscopy and recommended in prior pediatric EoE guidelines.[9, 12, 40]

At this stage in the algorithm, a patient would be considered to have clinically suspected EoE if there are symptoms of esophageal dysfunction and at least 15 eos/hpf (or ~60 eos/mm^2) on biopsy. There may be patients who enter the algorithm at this step, even if EoE was not a clinical consideration prior to the endoscopy and biopsy, for example if the endoscopy was performed for a non-esophageal indication or for atypical reflux symptoms. The key point is that the presence of esophageal eosinophilia on histologic examination without further consideration of the clinical presentation is not diagnostic of EoE.[4, 11, 41]

Because of the data discussed above, a PPI trial is not required for diagnosis of EoE in this algorithm. However, use of concomitant therapies must be considered when interpreting endoscopy and biopsy results.[29, 31] A diagnosis of EoE cannot be definitively ruled out in patients who have an initial endoscopy on PPI therapy and have normal biopsies, because their biopsy results in the absence of PPI therapy are not known. For patients who respond to PPI therapy, clinicians must decide whether ongoing long-term PPI therapy should be utilized or whether further evaluation off PPI therapy should be considered. Conversely, when patients on PPI treatment come to endoscopy, they may have endoscopic findings and biopsies consistent with EoE, but still need to follow-through with the remainder of the diagnostic algorithm.

All patients with esophageal eosinophilia of ≥15 eos/hpf (~60 eos/mm^2) should be evaluated for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia. GERD continues to present a unique situation (see below). Hypereosinophilic syndrome, non-EoE EGIDs, achalasia, Crohn’s disease, infections, connective tissue disorders and drug hypersensitivity reactions (Table 3) have been associated with esophageal eosinophilia but are uncommon or present with clinical features that readily distinguish them from EoE.[4, 11]

EoE is finally diagnosed after evaluation shows there are no other etiologies substantially contributing to symptoms and esophageal eosinophilia. We define confirmed EoE as symptoms of esophageal dysfunction, at least 15 eos/hpf (or ~60 eos/mm^2) on biopsy, and evaluation showing no significant other causes of symptoms and/or esophageal eosinophilia. It is important that the definition of esophageal eosinophilia and EoE is uniform among adult and pediatric gastroenterologists, allergists, and pathologists, as well as among both clinicians and researchers.

Complexities in EoE diagnosis

Phenotypic variability—A major complexity in EoE diagnosis is that there is substantial phenotypic variability in presentation based on age and duration of disease.[31, 42–45] Diagnosis may be straightforward in a young man with food and environmental allergies, a long-standing history of dysphagia and food impaction, endoscopy showing rings, furrows, edema, and exudates, and esophageal eosinophilia. However, a child or adult presenting with heartburn, nausea/vomiting, or epigastric pain, who has an endoscopy with subtle edema and biopsies with esophageal eosinophilia (≥15 eos/hpf), presents a distinctly different challenge. It is therefore key to understand the various presentations of esophageal eosinophilia and EoE, and that the finding of increased eosinophils on biopsy cannot in isolation be equated with a definite diagnosis of EoE. In addition, we provide a set of illustrative cases (Supplemental Materials 2) across the age and phenotypic spectrum, to highlight how individual patients may fit into the presented diagnostic algorithm.

Evaluating for the contribution of GERD—GERD is defined as a condition that develops when reflux of gastric contents causes troublesome symptoms and/or complications.[46] The lack of one single “gold standard” for the diagnosis of GERD makes attempts at defining the accuracy of any individual test problematic. Composite definitions of GERD using a combination of reflux esophagitis, abnormal pH testing, symptom association probability metrics, and symptom response to PPI therapy have reported 42–65% sensitivity and 70% specificity for validated symptom instruments for the diagnosis of GERD.[47] However, endoscopic features of GERD,[48, 49] histologic features of basal zone hyperplasia, papillary elongation, inflammatory cell infiltrate and dilated intercellular spaces, and symptom response to PPI therapy [47, 50] have limitations in both sensitivity and specificity. In some patients, because it may be difficult to ascertain the precise contribution of GERD to esophageal eosinophilia, clinical evaluation for GERD could be undertaken in concordance with published GERD guidelines prior to a definitive diagnosis of EoE.[51, 52]

Available studies examining the distinction between GERD and EoE (Supplemental Materials 3) are limited by study design, absence of comprehensive testing modalities, and the lack of a gold standard to define either condition. Furthermore, the high background prevalence of GERD (10–20%) confounds efforts to differentiate GERD and EoE.[46] Adding PPI-REE to this discussion is a further complexity. Some patients with PPI-REE appear to have an increased GERD signature as evidenced by a higher degree of abnormal pH testing, symptoms of GERD, manometric features consistent with GERD, and fewer endoscopic features of EoE.[6, 8–10, 53] Assessing GERD features using tissue biomarkers or mucosal impedance may be useful in the future, as preliminary studies have been promising,[17, 54–58] as have been some symptoms scores.[42, 59–62] Molecular studies show a substantial overlap in gene expression between EoE and PPI-REE and identify a molecular signature for the pathogenesis of EoE that is distinct from GERD.[20, 21, 63–65] At this time, though, there is no single test that can be used clinically to reliably distinguish EoE from GERD, and clinicians will need to take into account individual patient features and perform clinically indicated testing as needed. For example, a patient with erosive esophagitis and a peptic stricture might present with symptoms suggestive of EoE (dysphagia, heartburn) and have esophageal eosinophilia, but GERD would be the primarily diagnosis. Additionally, when GERD and

EoE overlap, patients will need management and follow-up of GERD and coexisting Barrett's esophagus, if present, as per published guidelines.[51, 66]

Initial treatment and follow-up after EoE is confirmed—It is beyond the scope of this paper to provide comprehensive recommendations for the treatment of EoE.[29, 31] To date, no prospective double-blind randomized trial has compared the efficacies of steroids to PPI, or diet to PPI. However, due to low cost, good safety profile, convenience, and a large body of literature describing PPI response in patients with esophageal eosinophilia and endoscopic findings suggestive of EoE, a PPI should be considered as a potential early or initial treatment, although swallowed steroids or dietary elimination may also be considered.[27,29, 32] If diet or steroid therapy is used as a first line therapy but is ineffective on follow-up endoscopy with biopsy, PPI therapy should be considered as there is a good chance that this will be successful.[67] It is also necessary to realize that because GERD and EoE may coexist, some patients may need to be treated with both a PPI and different anti-inflammatory treatment (e.g. dietary elimination or a topical steroids) in order to optimally treat both conditions, though there are few data on combination therapy. Finally, treatment decisions must be made with the understanding that the majority of data on response rates for topical steroids, dietary elimination, and novel/emerging treatments in EoE are largely in the patient population that has failed to respond to PPI treatment previously.[31, 68, 69]

Because there are limited long-term treatment data available, patients with esophageal eosinophilia and EoE need to have close and structured follow-up with symptomatic, endoscopic, and histologic assessment. For those who respond to a PPI and are maintained on these medications, regular clinical follow-up, including future endoscopies with biopsy, may be indicated as a proportion may lose response over time,[70, 71] as can happen with other EoE therapies.[72–76] There are no data on outcomes in truly asymptomatic patients with esophageal eosinophilia. Because of concerns of progression from inflammation to fibrosis,[43–45, 77] these patients also merit clinical follow-up.

Approach to clinical trials and regulatory agencies—As noted above, one of the principles in updating EoE diagnostic criteria was to ensure that patients previously treated in clinical trials for EoE would still meet criteria for EoE diagnosis. Indeed, patients diagnosed with EoE as per prior guidelines (with failure to respond to a PPI trial) would still meet criteria as having EoE as per the updated guidelines, provided that other causes of and contributions to esophageal eosinophilia had been assessed. Going forward, however, a clinical trial design must specify and provide the rationale for the subtype of EoE population being included, be it PPI-non-responsive, PPI-responsive, or PPI-naive. Similar considerations would be needed for other EoE treatments as well. These criteria will also allow new research and clinical trials to be conducted that will move the field forward. For example, patients who were previously diagnosed with PPI-REE might be reclassified as having EoE, and could be enrolled into clinical trials.

Future research directions

With updating the diagnostic algorithm for EoE and reviewing the literature related to the treatment effect of PPIs on esophageal eosinophilia, multiple gaps in knowledge and

important research questions were identified (Table 4). This new algorithm acknowledges that in some cases there may be clinical ambiguity between EoE and GERD, or esophageal eosinophilia without symptoms, and in these situations ongoing close follow-up is mandatory. This document challenge researchers to continue to identify clinical phenotypes and understand the biology and clinical role of PPIs in patients with esophageal eosinophilia and EoE. In addition, understanding the mechanism of the dramatic effect of PPI therapy on type 2 allergic inflammation holds promise for treating EoE and other diseases characterized by similar processes. Together, this knowledge will help guide regulatory agencies, industry partners, and patient advocacy groups to understand the best sub-populations of EoE to study for drug and other therapeutic development, in order to continue to improve outcomes for all EoE patients.

CONCLUSION

A tremendous amount of progress has been made in the understanding of EoE in the last two decades spanning clinical presentation, epidemiology, genetics, pathogenesis, treatment, and outcomes. With such a rapid evolution of knowledge, diagnostic criteria must also evolve. While EoE and GERD were first felt to be distinct and separable by a PPI trial, there was increasing recognition that the relationship was far more complex, that they could co-exist, and that each might influence the other. With the identification of patients who responded to PPI treatment, it was not initially known if PPI-REE was a sub-type of EoE, an atypical manifestation of GERD, or a unique entity. Now, the evidence suggests that in many cases PPI-REE is indistinguishable from EoE, and PPIs are better classified as a treatment for esophageal eosinophilia that may be due to EoE than as a diagnostic criterion. These updated international consensus criteria reflect this concept. As the field continues to develop and the research questions identified during this process are answered, the criteria presented here will evolve in the context of new data and advances.

Supplementary Material

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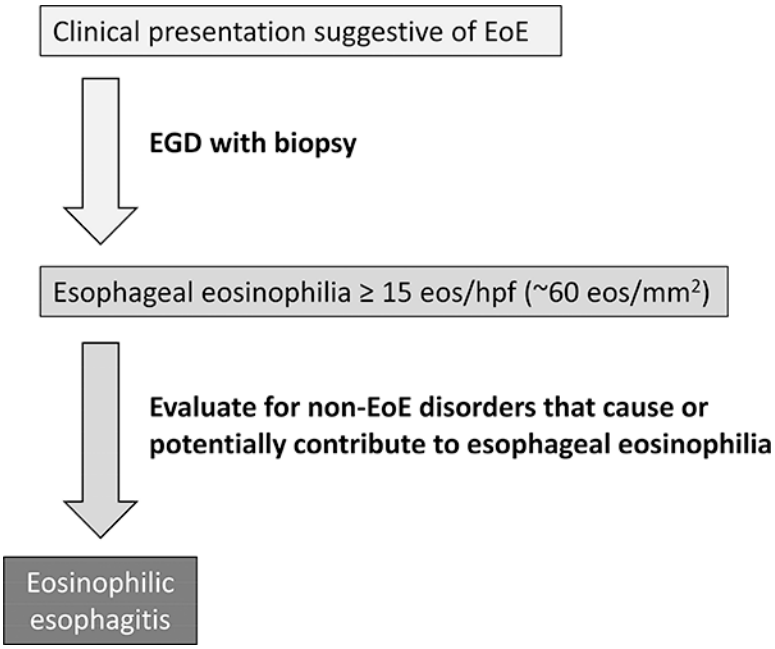

Figure 1.
Updated EoE diagnostic algorithm.

Table 1:

Rationale for changing the EoE diagnostic criteria and removing the PPI trial

Rationale	Comment
Similarities between EoE and PPI-REE	EoE and PPI-REE share similar clinical, endoscopic, histologic, immunologic, and molecular features prior to PPI treatment, suggesting that distinguishing these entities with a medication trial is artificial, and the PPIs are better positioned as a treatment for EoE.
EoE and GERD are not necessarily mutually exclusive	An initial rationale for the PPI trial was to distinguish EoE from GERD, but it is now known that these conditions have a complex relationship and are not necessarily mutually exclusive.
Lack of a gold standard for GERD diagnosis	Without a definitive method for defining GERD, no single test (including a PPI trial) can exclude the presence of GERD.
Novel mechanisms of action of PPIs to explain response of eosinophilia	Mechanisms that support PPIs as a treatment for EoE and esophageal eosinophilia include acid-independent anti-inflammatory/anti-eosinophil activity and reversal of epithelial permeability.
Observation that PPI-REE could also respond to classic EoE treatments	Patients with PPI-REE can also have a response to dietary elimination or topical steroid therapy, further blurring the line between EoE and PPI-REE.
Concern about using a treatment response to define a disease	Few diseases are primarily defined by response to treatment, and doing so limits potential treatment options for patients with EoE and esophageal eosinophilia.

Table 2:

EoE diagnostic criteria

- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion for EoE
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe-paper mucosa should increase suspicion for EoE
- ≥15 eos/hpf (~60 eos/mm^2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Table 3:

Conditions associated with esophageal eosinophilia

• Eosinophilic esophagitis
• Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
• Gastroesophageal reflux disease
• Achalasia and other disorders of esophageal dysmotility
• Hypereosinophilic syndrome
• Crohn’s disease with esophageal involvement
• Infections (fungal, viral)
• Connective tissue disorders
• Hypermobility syndromes
• Autoimmune disorders and vasculitides
• Dermatologic conditions with esophageal involvement (i.e. pemphigus)
• Drug hypersensitivity reactions
• Pill esophagitis
• Graft vs host disease
• Mendelian disorders (Marfan Syndrome Type II, Hyper-IgE Syndrome, PTEN Hamartoma Tumor Syndrome, Netherton’s Syndrome, Severe Atopy Metabolic Wasting Syndrome)

Table 4:

Future research directions related to PPIs and esophageal eosinophilia

Research category	Research topic
Basic research	• Interaction between GERD and EoE in animal models • Elucidation of mechanism of PPIs including anti-inflammatory effects in vitro and in vivo • Genetics of EoE as a function of PPI responsiveness • Transcriptome that distinguishes EoE as a function of PPI responsiveness
Clinical/translational research	• Comparison of PPIs with topical steroids and dietary elimination in treatment-naïve EoE patients • Comparative effectiveness of PPIs vs topical steroids or dietary elimination therapy • Assessment of efficacy of topical steroid and dietary elimination treatment in PPI-responders • Determination of optimal short- and long-term PPI dosing, as well as safety of these chronic PPI dosing regimens ° Assess in the context of the CPY2C19 genotype ° Assess in non-white populations • Determination of efficacy of PPIs on symptom response using validated instruments ° Assess whether symptom and histologic responses are concordant ° Assess for differences in histologic responses in different levels of the esophagus • Phenotypic and mechanistic distinctions between GERD-related epithelial barrier-induced eosinophilia vs non-GERD atopic esophagitis with eosinophils • Assessment of the role of other non-PPI acid suppressive drugs (e.g. vonoprazan or H2 blockers) • Assessment of the role of PPI therapy in combination with either topical steroids or dietary elimination in partial responders to PPIs • Characterization of the natural history of esophageal eosinophilia related to: ° Esophageal remodeling and fibrosis ° Loss of PPI response ° Recurrence of eosinophilia after stopping PPI ° Risk of neoplasia and malignancy • Characterization of the natural history of esophageal eosinophilia in the absence of symptoms of esophageal dysfunction • Implications of a prior PPI-REE diagnosis • Determination of predictors of PPI response, including molecular and genetic determinants • Determining role of environmental factors in EoE, particularly related to PPI-responsiveness. • Identifying EoE disease endotypes and its relationship to treatment responses such as PPI therapy.