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Summary of the updated international consensus diagnostic criteria for eosinophilic esophagitis: AGREE conference

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INTRODUCTION

EoE is a global health condition that has steadily increased over the last few decades and is now reported on all continents, with an estimated incidence of 4 per 100,000. Diagnostic Guidelines on eosinophilic esophagitis (EoE) were published in 2007 and updated in 2011.^{1, 2} EoE is defined as a clinicopathological condition that is likely immune or antigen driven, and characterized clinically by symptoms of esophageal dysfunction and histologically by ≥ 15 eosinophils per high power field (eos/hpf). In the initial guidelines, inflammation related to gastro-esophageal reflux disease (GERD) needed to be ruled out as an underlying cause and expert consensus determined that the best approach would be to use either high dose proton pump inhibitor (PPI) treatment or pH monitoring. EoE and GERD were felt to be mutually exclusive disorders where response to a PPI trial/pathologic pH exposure was consistent with GERD and non-response/normal pH monitoring confirmed

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EoE. However, multiple investigators observed that a large proportion of patients with clinical symptoms suggestive of EoE and esophageal eosinophilia ≥ 15 eos/hpf responded to treatment with high-dose PPI.³ Even in these reports, there is heterogeneity and inconsistency of the definition of high-dose PPI. Because of this, diagnostic guidelines published in 2011, 2013, and 2014 defined a new condition termed PPI-responsive esophageal eosinophilia (PPI-REE).² Lack of response to a PPI trial confirmed the diagnosis of EoE, and response was suggestive of either GERD or PPI-REE.

An evolving body of research suggested that EoE and GERD were not mutually exclusive and instead had a complex relationship. In addition, multiple retrospective and prospective studies found that esophageal eosinophilia in patients with symptoms and endoscopic signs suggestive of EoE can respond to PPI therapy in both children and adult at a rate of 28-82% (summarized in Dellon et al, Gastroenterology paper)³. In a meta-analysis by Lucendo and colleagues assessing PPIs for treatment of symptomatic esophageal eosinophilia, the pooled histologic response to PPI was about 50% although heterogeneity was high ($I^2 = 66\%$).⁴ Therefore, it is estimated about 50% of the patients with esophageal eosinophilia respond to a PPI and those who do not respond to a PPI, almost all ($>90\%$) in children and adult respond to an elemental diet. However, how many patients who respond to a PPI also respond to diet is an unanswered and important question (Figure 1).

In addition, similar studies examined the clinical, endoscopic, and histologic features at baseline (prior to a PPI trial) of both EoE and PPI-REE cases, and found that few, if any, of these factors that could distinguish the two.^{5, 6} However, recent study found an increase in IgE-mediated food allergy in EoE population compared to PPI-REE.⁷ In addition, RNA expression profiles were largely similar between the two conditions (and distinct from GERD), though some differences were seen particularly related to a potassium channel in PPI-REE.^{8, 9} Finally, there are two case reports that some individuals respond to both diet and PPI.^{10, 11}

Potential non-acid mediated anti-inflammatory mechanisms of PPIs were identified.¹²⁻¹⁴ For example, PPIs inhibit the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule recognized by ligands on the eosinophil cell surface.¹⁵ PPIs also block IL-13 and IL-4 stimulated increase in eotaxin-3 mRNA expression and protein secretion,¹² via a STAT6 (signal transducer and activator of transcription 6) binding to the eotaxin-3 promoter.¹³ Finally, PPIs may improve the epithelial barrier function in the esophagus.^{16, 17}

Overall, these findings raised an important question of whether PPI-REE is a subset of EoE in both pediatric and adults. A new European EoE guideline, published in 2017,¹⁸ suggested that PPI-REE and EoE were on the same spectrum and that PPIs could be considered a treatment for EoE. To develop an international consensus, the AGREE (A working Group on ppi-REE) Conference was held on May 6, 2017 in Chicago IL. The full report is published in Gastroenterology and the following are highlights of the report.

New Diagnostic Criteria

EoE is suspected on a clinical basis with chronic symptoms of esophageal dysfunction (dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain, failure to thrive, among others). The updated diagnostic algorithm for EoE is shown in Figure 2, based on the diagnostic criteria listed in Table 1.

When endoscopy is performed, the esophagus should be examined for features of EoE (including esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow caliber esophagus, ideally quantified using the EoE Endoscopic Reference Score [EREFS])¹⁹ as well as alternative esophageal disorders. In all cases, including when the esophagus looks normal, esophageal biopsy specimens should be obtained with multiple biopsies from two or more esophageal levels.^{1, 2, 20} Gastric and duodenal biopsies should be obtained as clinically indicated by symptoms.

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/mm²) on biopsy. There may be patients who enter the algorithm at this step, those who have abnormal biopsies, even if EoE was not a clinical consideration prior to the endoscopy and biopsy. A key point is that the presence of esophageal eosinophilia on histologic examination without further consideration of the clinical presentation is not diagnostic of EoE.

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. Often, patients who have symptoms that may be related to GERD or other acid related disorders are first treated with a PPI, and if they cannot stop this medication without a recurrence of symptoms, an EGD is performed while they are taking a PPI. Thus, a diagnosis of EoE cannot be definitively ruled out in patients who have an initial endoscopy for evaluation of symptoms suggestive of EoE but who are on a PPI and who 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 eventually decide whether ongoing long-term PPI therapy should be utilized or whether further evaluation off of PPI therapy should be considered. Conversely, patients on PPI treatment when they come to endoscopy 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/mm²) should be evaluated for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia. Hypereosinophilic syndrome, non-EoE EGIDs, Crohn's disease, infections, connective tissue disorders and drug hypersensitivity reactions (see Table 1) have been associated with esophageal eosinophilia but are uncommon or present with clinical features that readily distinguish them from EoE.² GERD continues to present a unique situation and is discussed in detail in the Gastroenterology paper. In some patients, it may be difficult to ascertain the precise contribution of GERD to esophageal eosinophilia, and clinical evaluation for GERD

could be undertaken in concordance with published GERD guidelines prior to a definitive diagnosis of EoE.²¹

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/mm²) on biopsy, and evaluation showing no significant other causes of symptoms and/or esophageal eosinophilia. We recommend that providers understand that the diagnostic criteria are and always have been uniform with respect to patient age, and that all providers involved in the diagnosis (allergist, gastroenterologist, pathologist and researchers) approach the patient with potential EoE without any age-based bias.

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.^{18, 22} 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 response rates in patients with esophageal eosinophilia, a PPI should be considered as a potential initial treatment (especially if it has not been used before), although steroids or dietary elimination may also be considered.^{4, 18} Due to the fact that single arm observational studies have found modest response rate to PPI in patients with esophageal eosinophilia. If diet or steroid therapy is used as a first line therapy and is determined to be ineffective on follow-up studies including endoscopy with biopsy, PPI therapy should be considered as there is a good chance that this will be successful. 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 almost entirely in the patient population that has failed to respond to PPI treatment previously.²²

Conclusion

The new proposed diagnostic criteria are an international collaboration of pediatric, adult gastroenterologist, allergist-immunologists, pathologists, and researchers. The new criteria allow some flexibility as the clinical presentation and treatments can vary for patients and provider. It allows for adult gastroenterologists to diagnose EoE without a PPI trial and also allows pediatrician to use PPIs to assess abdominal pain related to GERD without diagnosing EoE. It is important to note that these new guidelines are compatible with previous guidelines, in that patients previously diagnosed with EoE will still meet the new diagnostic criteria. For clinical trial participation, PPI trial is no longer mandatory. But, it might be some benefit for some clinical trials to examine and characterize appropriate patient cohorts for investigational medicines. Similar to previous guidelines, there will be a need for education of allergist-immunologist, gastroenterologists, pathologists, patients, and families on these new criteria. There are several obvious potential research and clinical questions that exist, in particular those about the comparative effectiveness of a PPI as a first

line therapy compared to other modalities such as diet and/or steroid, and if certain patient phenotypes are more responsive to one of these three potential first-line therapies. Finally, research is needed to better understand various phenotypes²³ that can be seen in EoE.

Like all things in medicine and science, new research may lead to changes in these recommendations as additional randomized clinical trials are done to answer these questions.

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Figure 1. Esophageal Eosinophilia Response

Potential response of subjects with esophageal eosinophilia. In average, 50% of patients will have improvement with high dose PPI. In the 50% of patients that do not respond to PPI, almost all (>90%) will have resolution of esophageal eosinophilia with an elemental diet. In the 50% of the patients that respond to PPI, the exact percentage that will respond to diet or swallowed steroids is unknown. This is not a proposed treatment pathway, but represents response to therapy for examining the role of antigen and diagnostic criteria.

Figure 2. Updated EoE diagnostic algorithm

New diagnostic algorithm. Figure reprinted with permission from Gastroenterology.³

Table 1

EoE diagnostic criteria³

<ul style="list-style-type: none">◦ 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/mm²) on esophageal biopsy◦ Eosinophilic should be isolated to the esophagus
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Other causes of EoE has been ruled out including but not limited to: 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; Dermatologic conditions with esophageal involvement (ie 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)