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Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference

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BACKGROUND & 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 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 used online communications, teleconferences, and a face-to-face meeting to review the literature and clinical experiences. **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 approximately 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: Diagnosis; Eosinophilic Esophagitis; Esophageal Eosinophilia; Proton Pump Inhibitor.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Clinical experiences and research studies have raised questions regarding the use of proton pump inhibitors (PPIs) as a part of the diagnostic strategy for eosinophilic esophagitis (EoE).

NEW FINDINGS

Substantial evidence has documented that PPIs reduce esophageal eosinophilia in children, adolescents and adults, with several mechanisms explaining the treatment effect. An updated diagnostic algorithm for EoE was developed, with removal of the PPI trial requirement.

LIMITATIONS

Consensus conference relying on previously published data.

IMPACT

PPIs are better classified as a treatment for esophageal eosinophilia due to EoE than as a diagnostic criterion, and the new algorithm will impact how EoE is now diagnosed.

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 clinicopathologic condition that was immune or antigen driven and was characterized clinically by symptoms of esophageal dysfunction and histologically by ≥15 eosinophils per high power field (eos/hpf), with expert consensus determining that 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 believed to be mutually exclusive.

***Authors share co-first authorship; § Authors share co-senior authorship.**

Abbreviations used in this paper: **AGREE, A Working Group on PPI-REE; EoE, eosinophilic esophagitis; eos/hps, eosinophils per high-power field; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; PPI-REE, proton pump inhibitor–responsive esophageal eosinophilia.**

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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 before PPI treatment, suggesting that distinguishing these entities with a medication trial is artificial and that 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 criterion 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.

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 $\geq$ 15 eos/hpf responded to treatment with high-dose PPIs 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 $\geq$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 believed to be 2 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; and 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 (before a PPI trial) of both EoE and PPI-REE and found no conclusive factors could distinguish the 2 conditions.[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 2 conditions (and distinct from GERD), with normalization after topical steroid treatment or dietary elimination, although some differences existed.[20,21] In addition, case reports of PPI-REE patients showed 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 as 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 the facts that it potentially reduces the number of endoscopies required, helps address concomitant GERD, and provides a stepwise approach for EoE diagnosis. In favor of eliminating the use of a PPI trial was the fact that it permits the ability to discuss a range of therapies (eg, 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). 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 1 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 that there were no relevant omissions. Although a formal quality assessment was not performed, limitations of the evidence (eg, retrospective design, small sample size, nonstandardized 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 and 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 in which clinical presentations of GERD and EoE overlap (particularly an issue in pediatrics), were discussed on a series of teleconferences and e-mail discussions to establish uniform agreement before the final submission. This process included all co-authors, who each confirmed agreement with the consensus. Health benefits, adverse effects, and risks of findings were discussed as a part of these proceedings. The document was not externally reviewed before submission. A procedure for updating recommendations is provided.

Clarity of Presentation. The criteria provided are specific because 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

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 $\sim$60 eos/mm^2) on esophageal biopsy and defined *confirmed EoE* as symptoms of esophageal dysfunction and at least 15 eos/hpf (or $\sim$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 (nonspecific vs dysphagia-predominant symptoms).[31] Full results are presented in online in the Supplementary Material 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% (Supplementary Figure 1*A*). In a meta-analysis by Lucendo and colleagues, the pooled histologic response to PPI treatment in children with $\geq$15 eos/hpf was 54% (95% confidence interval, 38–70), although heterogeneity was high ($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% (Supplementary Figure 1*B*). The meta-analysis by Lucendo et al reported a pooled histologic response rate of 50% (95% CI, 40–59) for PPI use in adults, although 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 and

heterogeneous study designs; it was not possible to determine the role of overlapping GERD in most 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 (Supplementary 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 (see Supplementary Material 1 for a full discussion). 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 believed to be the same disease in children and adults[33] and any age cutoff would be arbitrary, the criteria were crafted to be applicable to all ages. Second, there was a focus on removing the PPI trial 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 nonresponse 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 $\geq$15 eos/hpf ($\sim$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 before any treatment, whereas patients with heartburn or vomiting may have other testing or medical treatment (eg, 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.

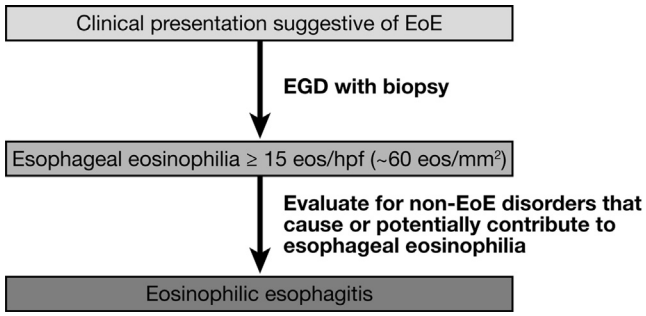

Figure 1. Updated EoE diagnostic algorithm.

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[34]) and for 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 biopsy specimens from 2 or more esophageal levels, targeting areas of apparent inflammation, are recommended to increase the diagnostic yield.[3,4,11,37–39] Gastric and duodenal biopsy specimens 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

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.
- $\geq$15 eos/hpf ($\sim$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

low yield in identifying other eosinophilic gastrointestinal disorders, they are routinely obtained in pediatric endoscopy and are 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 before 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, 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 biopsy results, 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 used or whether further evaluation without PPI therapy should be considered. Conversely, when patients receiving PPI treatment come to endoscopy, they may have endoscopic and biopsy findings consistent with EoE, but clinicians 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 "Evaluating for the Contribution of GERD" section). Hypereosinophilic syndrome, non-EoE eosinophilic gastrointestinal disorders, 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]

Table 3. Conditions Associated With Esophageal Eosinophilia

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- 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 (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 syndrome, severe atopy metabolic wasting syndrome)

EoE is finally diagnosed after evaluation shows that there are no other causes 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 be 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 and who has an endoscopy showing subtle edema and biopsy results showing 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 (Supplementary Material 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 1 single criterion 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 before a definitive diagnosis of EoE.[51,52]

Available studies examining the distinction between GERD and EoE (Supplementary Material 3) are limited by study design, absence of comprehensive testing modalities, and the lack of a criterion standard to define either condition. Furthermore, the high background prevalence of GERD

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 nonwhite 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 (eg, vonoprazan or H_2 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 their relationship to treatment responses such as PPI therapy

(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, because preliminary studies have been promising,[17,54–58] as have been some symptom 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 article 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, because of 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, because 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 (eg, dietary elimination or a topical steroids) to optimally treat both conditions, although there are few data on combination therapy. Finally, treatment decisions must be made with the understanding that most 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 because 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, 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 nonresponsive, PPI responsive, or PPI naïve. 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 challenges 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 subpopulations of EoE to study for drug and other therapeutic development, 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 2 decades spanning clinical presentation, epidemiology, genetics, pathogenesis, treatment, and outcomes. With such a rapid evolution of knowledge, diagnostic criteria must also evolve. Although EoE and GERD were first believed 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 subtype 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 ta 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

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.07.009.

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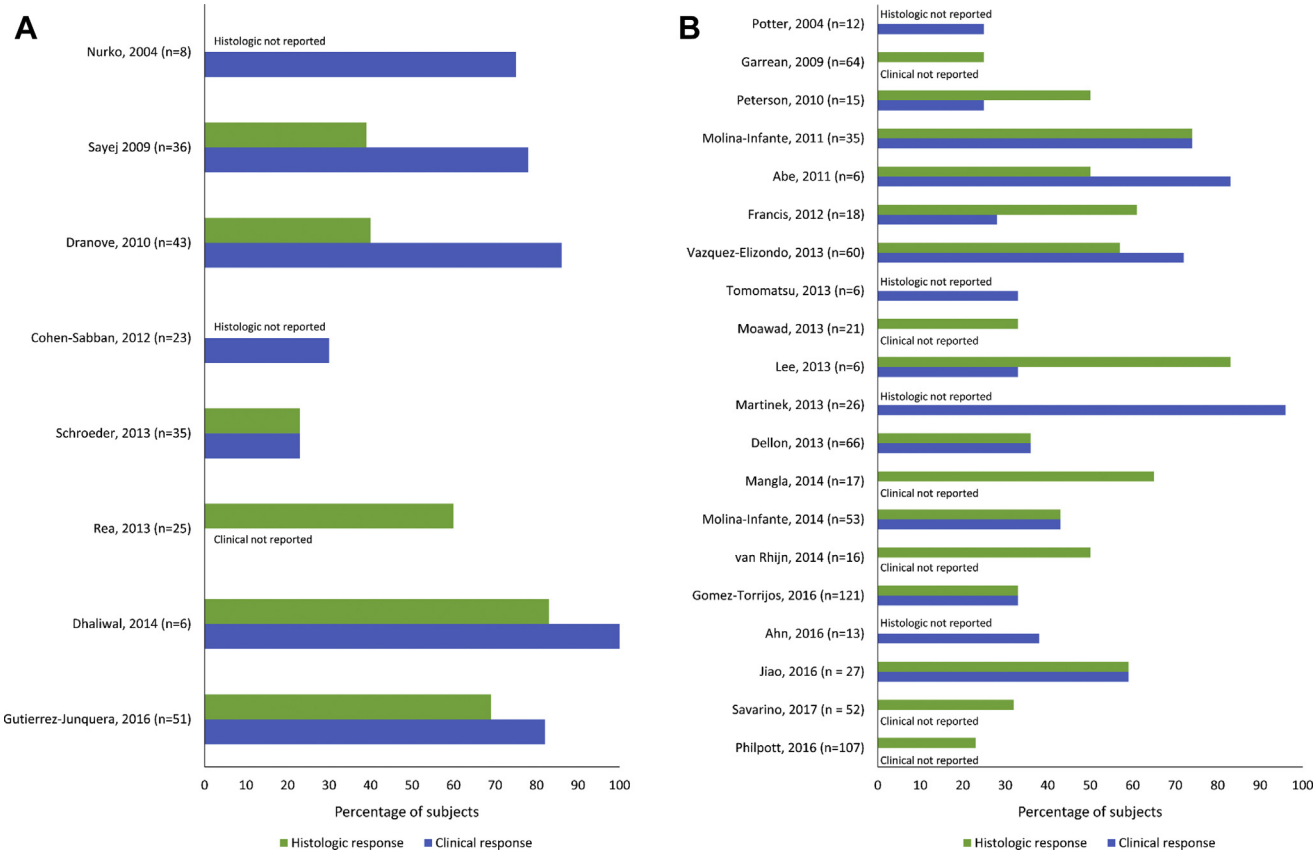
Supplementary Material 1

Role of PPI Treatment of Esophageal Eosinophilia

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 (nonspecific vs dysphagia-predominant symptoms).[1]

PPI Treatment in Children. Most studies on severe (≥15 eos/hpf) pediatric esophageal eosinophilia had been conducted since 2006 and were largely retrospective or were case studies with varying PPI doses and duration of therapy,[2–8] although 2 more recent studies were prospective.[7,8] Although there were limited reports in children, there was evidence that PPIs could be used to treat esophageal eosinophilia when response was measured by histologic improvement; clinical responses were less frequently studied, and it was difficult to draw conclusions about symptom benefit with the current data. Overall, excluding the individual case series, histologic response rates ranged from 23% to 83%, and clinical response rates were 23%–82% (Supplementary Figure 1*A*).

Ngo et al reported a series of 3 patients, of whom 2 were younger than 18 years.[3] Both patients had esophageal eosinophilia that responded to a PPI (PPI dose between 1 and 2 mg/kg/d). In a retrospective study in 2009 by Sayej et al, 14 of 36 patients who had esophageal eosinophilia showed a significant response to PPI therapy (PPI dose varied).[4] That same year, Dranove et al conducted a retrospective study of 43 patients with esophageal eosinophilia who were treated with an average of 1 mg/kg/d of PPI therapy for an unknown duration.[2] Of these, histology improved in 17 from >15 eos/hpf to <5 eos/hpf, and only 41% had an abnormal pH probe result. In a 2013 prospective study, Rea et al found that 15 of 25 patients with severe esophageal eosinophilia responded to PPI (exact doses unknown).[7] Interestingly, 4 patients who underwent Nissen fundoplication continued to have normal esophageal histology results and no longer needed PPI therapy, indicating that some of the response could be due to reflux. Similarly, Gutierrez-Junquera et al. reported a prospective study of 51 patients who received up to 1 mg/kg twice daily of PPI therapy for 8 weeks[8]; 47% showed complete histologic resolution, and 22% had a partial histologic response. Fourteen patients were followed up for a year maintained on 1 mg/kg once daily of PPI therapy; 9 maintained a complete response, and 2 maintained a partial response.



Supplementary Figure 1. Summary of histologic and clinical response rates for PPI treatment of esophageal eosinophilia in studies with >5 subjects reported. (*A*) Studies in children. (*B*) Studies in adolescents/adults.

In a meta-analysis by Lucendo and colleagues assessing PPIs for treatment of symptomatic esophageal eosinophilia, the pooled histologic response to PPI treatment in children with ≥15 eos/hpf was 54% (95% confidence interval [CI], 38–70), although heterogeneity was high ($I^2 = 66\%$).[9] The clinical response was even higher (65%; 95% CI, 43–84), but so was the heterogeneity ($I^2 = 84\%$). Responses were similar regardless of PPI dosing. These results must be interpreted in the context of limitations in the literature. For example, the etiology of esophageal eosinophilia has not been well studied; in particular, the relation between allergen/immune-mediated vs acid/peptic-mediated mechanisms of eosinophilia remain unclear. Some patients with esophageal eosinophilia who responded to PPI therapy also improved after having a Nissen fundoplication,[7] whereas other patients who responded may or may not have had abnormal pH probe results.[2] The durability of the response to PPI therapy in children has also been questioned in some reports.[5,6]

Because the definition of EoE in children has included nonresponse to PPI therapy, there are no data that compare PPIs as the primary treatment of children with dietary elimination or topical steroids. Most of the data in children/adolescents were based on using diet or topical steroids only after PPI therapy had already failed.[1] The available evidence shows that the optimal dose of PPI therapy to induce remission of severe esophageal eosinophilia is up to 1 mg/kg twice a day (although some studies have shown a response with less than this dose), with a maximum of 30 mg twice a day of lansoprazole and 40 mg twice a day of omeprazole, for approximately 8 weeks.

PPI Treatment in Adolescent and Adults. There was substantial evidence that PPIs can be used to treat esophageal eosinophilia in adolescents and adults with suspected EoE when the response was measured by histologic improvement. The studies that provide this evidence include case reports/series and retrospective studies,[3,10–20] prospective investigations,[21–31] and randomized clinical trials.[32,33] The reported rates for histologic response to PPI treatment in these studies ranged from 23% to 83% (Supplementary Figure 1*B*). The meta-analysis by Lucendo et al reported a pooled histologic response rate of 50% (95% CI, 40–59) for PPI use in adults, although there was substantial heterogeneity ($I^2 = 70\%$).[9] Overall, the interpretation of the data is limited by a number of small studies with retrospective designs, lack of what would be termed an *adequate* PPI trial with twice daily dosing for at least 8 weeks,[34,35] lack of a consistent definition of *histologic response,* few data on PPI response in non-White predominant populations, and lack of randomized clinical trials incorporating all of these features.

When examining the set of prospective studies alone,[21–33] the range of histologic responses to PPI was 23%–74%, and in the meta-analysis the pooled rate was 53% (95% CI, 44–61; $I^2 = 53\%$).[9] Complicating the interpretation is the fact that 4 different histologic thresholds were used to define response (<5 eos/hpf,[26,31] <7 eos/hpf,[33] ≤10 eos/hpf,[21] and <15 eos/hpf[23–25,27,29,30,32]), and 2 studies did not specify a histologic response threshold.[22,28] When examining the prospective studies that used high-dose or twice daily PPI treatment,[21–24,26–31] we found that the range of histologic responses was also 23%274% and the pooled rate was 56% (95% CI, 46–66; $I^2 = 60\%$).[9]

There were 2 clinical trials that randomized patients with suspected EoE to receive either a PPI or a topical steroid.[32,33] In the study by Peterson et al,[32] 15 subjects were randomized to receive esomeprazole 40 mg daily, and 15 were randomized to swallowed fluticasone 440 μg twice daily, both for an 8-week course; 12 and 13 subjects in each group, respectively, completed treatment. Six patients (50%) in the esomeprazole arm and 4 patients (31%) in the fluticasone arm achieved the ≤15 eos/hpf histologic endpoint ($P = .28$). In the study by Moawad et al, the same treatment arms and dosages were used, with 21 subjects in each arm.[33] A total of 7 patients (33%) in the esomeprazole arm and 4 patients (19%) in the fluticasone arm achieved the ≤15 eos/hpf histologic endpoint ($P = .48$). These rates of PPI response are lower than the pooled rates described for the high-dose PPI treatments and are also lower than the pooled rates reported for once daily PPI use (50%; 95% CI, 29–54).[9]

Although the evidence would suggest that PPIs have a beneficial impact on symptoms in patients with suspected EoE, there are a number of limitations to consider. Symptom or clinical response rates ranged from 25% to 96% in the referenced studies, but most studies did not report or quantify a specific response threshold. In addition, part of the symptomatic improvement could be due to typical reflux symptoms that respond to acid inhibition, or even acid hypersensitivity, in EoE despite lack of documented GERD.[36] In a meta-analysis, the pooled clinical response rate in adults is higher than the histologic response rate (56%; 95% CI, 41–70), but with a high degree of heterogeneity ($I^2 = 78\%$).[9] It is difficult to interpret these data. No studies measured symptoms or quality of life using a validated EoE metric, and most studies reported a general or overall symptom improvement, which is difficult to compare between studies. Although some studies showed histologic/symptomatic concordance,[37,38] others showed absence of symptoms in some patients despite recurrent eosinophilia when the PPI dose was lowered.[30,39] This lack of rigor in symptom measurement, coupled with the heterogeneity already discussed, makes understanding the impact of PPIs on symptoms of suspected EoE a priority for future research (see "Future Research Directions" in the main body of the paper).

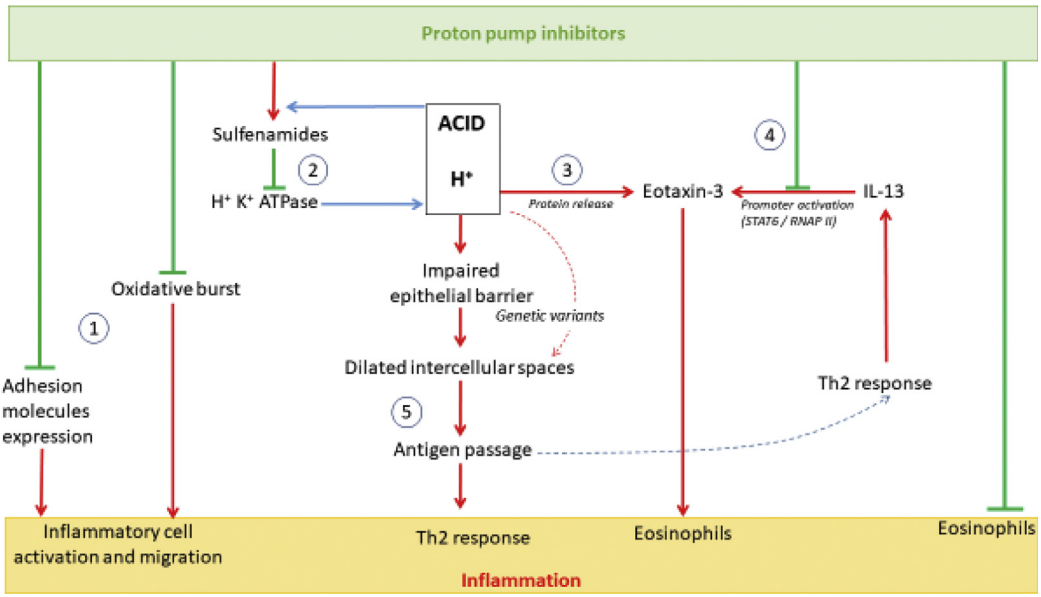
Similar to in children, there is currently little published evidence examining the use of PPIs as a primary (or first-line) treatment in adolescents and adults with confirmed EoE. Nevertheless, there is substantial clinical experience with using a PPI before treating with either a topical steroid or dietary elimination. In fact, most randomized controlled trials of topical steroid treatment in EoE required nonresponse to a PPI, as did many of the large studies of dietary elimination in EoE.[1] Therefore, current response rates for topical steroids and dietary elimination must be assessed in the context that the patients under study were PPI nonresponders.

Potential Mechanisms of PPI Response. The notion that resolution of symptomatic esophageal eosinophilia with PPI therapy established a diagnosis of GERD and excluded a diagnosis of EoE was based on the following assumptions: (1) gastric acid inhibition is the only important effect of PPIs, and (2) acid reflux does not contribute to antigen-mediated esophageal eosinophilia; therefore, (3) GERD is the only esophageal disease that can respond to PPIs. Recent data suggest that all 3 of these assumptions may be flawed[40–42] and that several mechanisms may underlie PPI response (see Supplementary Figures 2 and 3).

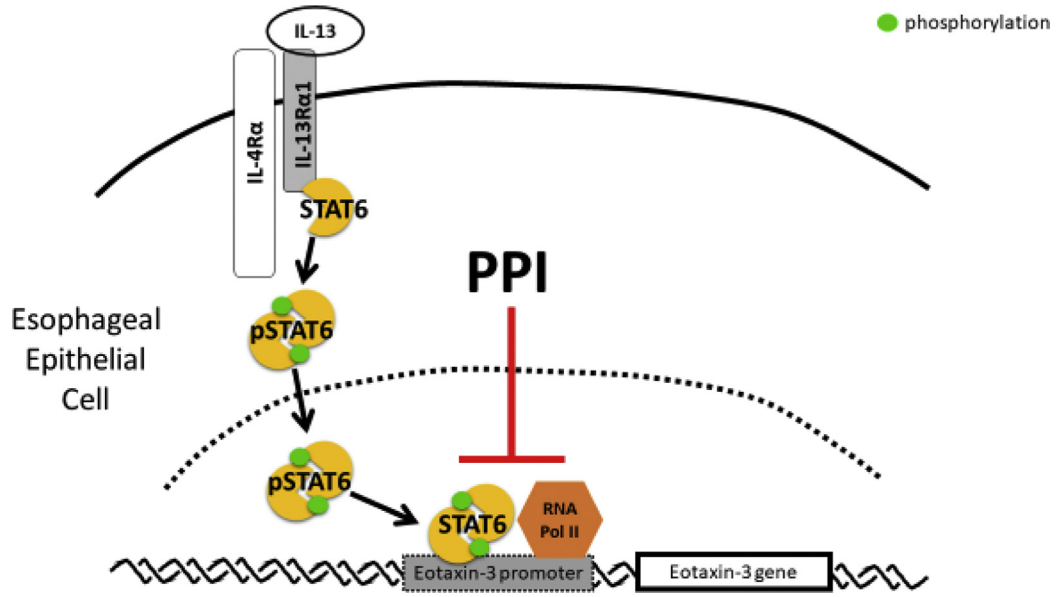
Anti-inflammatory Effects of PPIs Unrelated to Gastric Acid Suppression That Might Reduce Esophageal Eosinophilia. PPIs have a number of antioxidant properties that potentially could benefit both antigen-driven and acid-mediated esophageal inflammation.[43–46] PPIs are prodrugs that require an acidic environment for activation. In the acid-secreting mucosa of the stomach, the PPI prodrugs are converted into sulfenamides that bind to and inhibit parietal cell H^+-K^+ adenosine triphosphatases (ATPases) (proton pumps). Some inflammatory cells and other nongastric cell types have vacuolar H^+-ATPases that pump acid into the extracellular space or into intracellular organelles like lysosomes.[47,48] In neutrophils and monocytes, PPIs can inhibit the oxidative burst, cell migration, and phagocytosis.[49–54] Eosinophils also have vacuolar H^+-ATPases that might be influenced by PPI treatment[55] and also express the proton receptor GPR65.[56]

Some cell adhesion molecules have a major role in recruiting inflammatory cells to sites of inflammation. Lysosomal acidification influences the expression of adhesion molecules of the CD11/CD18 integrin family, and PPIs inhibit CD11b and CD18 expression in human neutrophils.[52,54] 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.[57] PPIs can also inhibit the expression of adhesion molecules by certain epithelial cells.[58]

A major mechanism thought to underlie the esophageal eosinophilia of EoE involves type 2 cytokine-stimulated secretion of eotaxin-3 by esophageal epithelial cells.[59] Using telomerase-immortalized esophageal squamous cell lines from patients with EoE and GERD, Cheng et al. showed that omeprazole blocked interleukin-13 and interleukin-4–stimulated increases in eotaxin-3 messenger RNA expression and protein secretion,[60] a process regulated through STAT6 (signal transducer and activator of transcription 6) and RNA polymerase II binding to the eotaxin-3 promoter[61] (see Supplementary Figure 3). Subsequent studies identified the fact that the impact of PPIs is not unique to omeprazole and that protons themselves increase the release of eotaxin-3 from esophageal epithelial cells.[62] In further support of these esophageal findings, various PPIs were shown to block T helper type 2 cytokine-stimulated eotaxin-3 secretion in a human bronchial and nasal epithelial cell line through a nongastric H^+-K^+-ATPase.[63]



Supplementary Figure 2. Anti-inflammatory effects of PPIs: PPIs may decrease esophageal eosinophilia in EoE. Different properties of PPI may explained the anti-inflammatory effect of PPI observed in PPI-RE patients: 1) PPIs can inhibit inflammatory functions such as oxidative burst, cell migration, and phagocytosis. PPIs also inhibit the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 recognized by ligands on the eosinophil cell surface. 2) Sulfenamides are the acid activated compounds derived from PPI. They inhibit parietal cell H^+-K^+ATPases (proton pumps) also expressed by inflammatory cells (including eosinophils). 3) Acidic milieu has been shown to increase eotaxin-3 release from esophageal epithelial cells. 4) PPI blocked IL-13 and IL-4 stimulated increase in eotaxin-3 mRNA expression and protein secretion through the signal transducer and activator of transcription 6 and RNA polymerase II binding to the eotaxin-3 promoter. 5) PPIs might reduce esophageal eosinophilia by restoring esophageal mucosal barrier integrity characterized in part by dilated intercellular spaces (DIS) which render the esophageal mucosa permeable to swallowed antigens linked to the Th2 response.



Supplementary Figure 3. Proposed Mechanism of PPI inhibition of Th2-cytokine-stimulated eotaxin-3 expression. Th2 cytokine, IL-13 (or IL-4), can stimulate eotaxin-3 expression via signal transducer and activator of transcription 6 (STAT6) signaling in esophageal epithelial cells. However, in the presence of a PPI such as omeprazole, binding of both STAT6 and RNA polymerase II (RNA Pol II) to the eotaxin-3 promoter is decreased, and transcription of eotaxin-3 mRNA is reduced.

Gastric Acid-Inhibiting Effects of PPIs That Might Reduce Esophageal Eosinophilia. By impairing esophageal mucosal barrier integrity, GERD can render the esophageal mucosa permeable to swallowed antigens, which conceivably could contribute to the development of EoE. A number of studies have shown that esophageal acid exposure impairs esophageal mucosal integrity.[64–67] Acid reflux–induced impairment of mucosal integrity is manifested histologically by dilated intercellular spaces (DIS) and functionally by increased permeability to molecules as large as some peptide antigens.[64–66] DIS is a characteristic histologic feature of both erosive and nonerosive GERD, and in patients with GERD, PPI treatment can reverse DIS.[68] EoE genetic susceptibility is associated with genes that impair esophageal barrier function such as *FLG*, *DSG1*, *CAPN14*, and *SPINK5*, and genetic variability in these gene products may predispose the esophagus to increased acid sensitivity and/or responses.[69]

DIS and impaired mucosal integrity are also characteristic features of EoE.[70] The expression of intercellular adhesion molecules that maintain mucosal integrity is impaired in EoE patients,[71] who can exhibit increased esophageal mucosal permeability to molecules the size of some food allergens.[72] PPIs restore mucosal integrity and correct the abnormal mucosal permeability.[21] It is thus likely that in some EoE patients, acid reflux contributes to EoE by impairing mucosal integrity and enabling antigens to penetrate the esophageal mucosa and that PPIs work by reducing the secretion of the gastric acid that renders the esophageal mucosa permeable to food antigens. In support of acid reduction as the mechanism underlying the beneficial effect of PPIs in esophageal eosinophilia, vonoprazan (a potassium-competitive acid blocker that is a potent inhibitor of gastric acid secretion) reduced esophageal eosinophilia substantially in 3 of 4 EoE patients.[73] In support of the concept that increased mucosal permeability contributes to EoE, some non-GERD disorders that impair esophageal mucosal barrier function (eg, infectious esophagitis, caustic ingestion) have been associated with later development of EoE or esophageal eosinophilia.[74–77]

It is not clear which of the potential PPI effects discussed are responsible for resolution of esophageal eosinophilia. However, the data suggest at least 3 possible clinical scenarios. First, patients might have GERD as the sole cause of esophageal eosinophilia, and their GERD responds to PPI acid-inhibitory effects, PPI anti-inflammatory effects, or both. Second, patients might respond to anti-inflammatory effects of PPIs independent of the effect of PPIs on acid. A third possibility is that GERD is exacerbating or causing an antigen-driven esophageal eosinophilia. Such patients might respond to both the anti-secretory and anti-inflammatory effects of PPIs.

PPI Safety Considerations. There are no unique safety considerations for PPI use in children, adolescents, or adults with EoE for standard (US Food and Drug Administration–approved, daily) dosing regimens beyond those that are already recognized for non-EoE indications.[78] A full discussion of potential adverse effects, including the controversy surrounding recent reports, is beyond the scope of this article and has been fully discussed elsewhere.[78–81]

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Supplementary Materials 3

Potential Ways to Evaluate for the Contribution of GERD and Distinguish Between GERD and EoE in Patients With Esophageal Eosinophilia

The Sensitivity and Specificity of Diagnostic Tests for GERD. *GERD* is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[1] The lack of a criterion 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 results, 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.[2] Endoscopic features of GERD have a sensitivity of approximately 50% and specificity of 95%.[3] pH testing has a sensitivity of 65%–90%[4,5] and a high degree of specificity that varies based on the specific symptom being assessed. Histologic features of basal zone hyperplasia, papillary elongation, inflammatory cell infiltrate, and dilated intracellular spaces have widely varying reported sensitivities. Symptom response to PPI therapy is often used in clinical practice, with a reported sensitivity of 71%–78% and specificity of 44%–54%.[2,6]

The Utility of pH Testing for Esophageal Eosinophilia, PPI-REE, and EoE. Results of pH testing in patients with esophageal eosinophilia, PPI-REE, and EoE have raised more questions than answers regarding the potential role of GERD in these entities. The conclusions are largely based on retrospectively collected data from select patient cohorts with specific indications for reflux testing. Nevertheless, both pediatric and adult series support the concept that pH testing is more commonly normal in patients with levels of esophageal eosinophilia $>$ 20 eos/hpf.[7–9] Similarly, GERD defined by pH testing is associated with low-grade esophageal eosinophilia.[10] In a small number of series, however, abnormal pH testing has been seen with high-grade esophageal eosinophilia.[11] Furthermore, the data from studies focusing on patients with esophageal eosinophilia suggests that a histologic response to PPI is more common among patients with abnormal pH testing.

What Is the Utility of Endoscopy for Differentiating PPI-REE and EoE?. Studies reporting endoscopic findings in patients with PPI-REE and EoE identified endoscopic features of EoE (rings, furrows, exudate, stricture) more commonly in EoE than PPI-REE, but these did not persist after multivariable analysis.[12] Endoscopic features of hiatus hernia, reflux esophagitis, and Barrett's esophagus have been described in patients with both EoE and PPI-REE. Although the inclusion criteria in the reported studies were less restrictive than the studies reporting pH monitoring, most studies were again retrospective and did not use validated endoscopic scoring tools for either EoE or GERD.

Alternative Approaches That Might Distinguish EoE From GERD. *Histology.* A proportion of patients with severe GERD do show eosinophils in the mucosal inflammation, but usually in small numbers (1–3/hpf), and these resolve with PPI therapy.[13] Based on available data, neither histopathology nor distribution of inflammatory changes in esophageal biopsy specimens accurately predicts response to PPI therapy. Molina-Infante identified a GERD-like group of adults with lower-grade eosinophil counts (15–35 eos/hpf), with a high rate of clinical symptoms of GERD (35% heartburn as major complaint) and endoscopic GERD (60%), and pathologic pH monitoring in the remaining 40%.[14] Histologic response to PPIs was 100% in this subgroup compared with 50% among patients with a higher degree of eosinophilia and an EoE phenotype.

Collins et al have defined a recent system to evaluate EoE by histology, named the Eosinophilic Esophagitis Histology Scoring System (EoEHSS).[15] Based on a single study, the EoEHSS provided a more comprehensive examination of multiple histologic features of EoE and outperformed eosinophil density as a histologic activity measure. Further studies will determine if this system can discriminate EoE from PPI-REE and GERD.

Histology Biomarkers. Positive ALOX15 immunoexpression is more prevalent in EoE than in GERD and may prove to be a useful diagnostic marker in patients with discrepant biopsy findings between the proximal and distal esophagus.[16] Regulatory T cells in esophageal tissue are significantly more numerous in EoE compared with GERD.[17] More activated mast cells are present in the esophageal mucosa in patients with EoE vs GERD.[18–21] In addition, eotaxin-3 immunostaining is significantly higher in EoE compared with GERD.[21–23] Numbers of eosinophils and degranulation could be underestimated by hematoxylin and eosin staining, and eosinophil–major basic protein immunoreactivity is helpful to distinguish GERD and EoE.[21,22,24]

Mucosal Impedance. Recently, a minimally invasive device was developed to detect mucosal impedance as a measure of epithelial integrity during endoscopy. This device can measure alternation in esophageal epithelium due to GERD and EoE and is capable of distinguishing the 2 from each other and from normal epithelium with high confidence.[25] Mucosal impedance measurements correlate inversely with eosinophil counts (ie, lower impedance correlates with higher eosinophil counts).[26] Unlike GERD, for which the values are lower in the distal esophagus and recover in the mid and proximal regions, in EoE the values are low all along the esophagus.

Genetic Testing. A molecular diagnostic panel based on gene expression in mucosal biopsy samples distinguishes EoE and GERD.[27] A PPI-REE transcriptome study[28] and a recent genome-wide analysis[29] directly showed an overlapping transcriptome between EoE and PPI-REE. There is only a marginal difference between the 2 entities, with a gene for a potassium channel (Kir2.1, *KNJ2*) being potentially differentially expressed. Studies comparing the genetic signature of biopsy samples from patients with EoE, GERD, and PPI-REE that have similar numbers of intraepithelial eosinophils will be helpful to determine if the etiology of mucosal eosinophilia can be identified in biopsy samples containing $\geq$ 15 eos/hpf.

High-Resolution Manometry. Studies have identified early pan-esophageal pressurization and compartmentalized pressurization in 16%–48% of adult EoE patients and rarely in GERD control individuals.[30] Savarino and colleagues analyzed data on 35 EoE, 17 PPI-REE, and 27 GERD patients.[31] PPI-REE and GERD patients had similar frequency of heartburn/acid regurgitation symptoms and esophagitis that were statistically different from those of EoE patients. Manometric features of GERD including lower esophageal sphincter basal pressure and type 2–3 esophagogastric junction morphology were significantly more common in PPI-REE than EoE.

Challenges Created by the Background Prevalence of GERD. GERD is an extremely common disorder (prevalence, 10%–20% in the United States and Europe).[1] This high background prevalence confounds attempts to clearly differentiate EoE from GERD. Furthermore, the high background prevalence of GERD likely leads to an underestimation of the true prevalence of PPI-REE, although the magnitude of this underestimation is unclear. These data suggest that even in patients with dysphagia, GERD is many times more common than PPI-REE.

Supplementary References 3

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