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Distinguishing GERD from eosinophilic oesophagitis: concepts and controversies

Leila Kia[#] and Ikuo Hirano[#]

Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, 676 North Saint Clair, Suite 1400, Chicago, IL 60611, USA (L.K., I.H.).

[#] These authors contributed equally to this work.

Abstract

Over the past three decades, the detection of oesophageal mucosal eosinophils has transitioned from a biomarker of GERD to a diagnostic criterion for eosinophilic oesophagitis (EoE). In GERD, oesophageal eosinophils are considered part of the chronic inflammatory response to acid reflux, whereas the marked eosinophilia in EoE is viewed as a central feature of the immune response to ingested food and/or environmental antigen stimulation. Descriptions of a considerable subset of patients with symptomatic, endoscopic and histological findings of EoE that resolve with PPI therapy has led to confusion and controversy regarding the distinction of EoE from GERD. Study findings indicate that PPI-responsive oesophageal eosinophilia (PPI-REE) more closely resembles EoE than GERD, both from a clinical and immunological aspect. Although responsiveness to PPI therapy should not be utilized to exclude EoE, PPI therapy is effective at reducing oesophageal eosinophilia in ~40% of patients, and PPI therapy is both a safe and practical initial step in the management of patients with oesophageal eosinophilia. Ongoing studies elucidating the mechanism behind PPI-REE will improve our understanding and management of EoE. In this Review, the mechanisms and evidence that underlie the controversy in the distinction between GERD and EoE are evaluated.

Introduction

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated, clinicopathological disease defined by symptoms of oesophageal dysfunction, eosinophilic inflammation localized to the oesophagus, and exclusion of other recognized causes of oesophageal eosinophilia, including GERD.^{1,2} Despite this seemingly straightforward definition from the latest consensus recommendations,^{1,2} distinguishing EoE from GERD can be complicated, challenging and confusing. Symptoms of heartburn, chest pain and dysphagia are recognized manifestations of both disorders, as is the presence of oesophageal eosinophilia.^{3–5} The prevalence of GERD in the general population (~20%) is sufficiently high enough to make coexistence of GERD with EoE inevitable.⁶ Intensifying the disease delineation, a subset of

Correspondence to: I.H. i-hirano@northwestern.edu.

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patients with typical features of EoE and absence of indicators of GERD (heartburn, erosive oesophagitis and abnormal pH testing) respond clinically and histologically to PPI therapy. Our understanding of the complex interplay between GERD and EoE has evolved over the past decade, and making distinctions between the two conditions is important for management. The aim of this Review is to evaluate the mechanisms and evidence behind this controversy in the distinction between GERD and EoE.

Historical perspective

The presence of intraepithelial oesophageal eosinophils was initially viewed as an important biomarker for the diagnosis of GERD^{7,8} (Figure 1). This understanding was largely based upon findings from a paediatric study that correlated the presence of intraepithelial oesophageal eosinophils with delayed acid clearance on prolonged pH monitoring.⁴ The eosinophilia was generally mild (<10 eosinophils per high power field, eos/hpf), concentrated in the distal oesophagus,⁹ and was thought to occur in part due to stimulation of local production of eosinophil-attracting substances such as platelet-activating factor, eotaxin-1, eotaxin-2, eotaxin-3 and macrophage inflammatory protein 1 α by refluxed gastric contents into the oesophagus.¹⁰

EoE was first characterized as an entity distinct from GERD in 1993 by Attwood and colleagues¹¹ who observed increased intraepithelial oesophageal eosinophils (>20 eos/hpf, mean of 56 eos/hpf) and squamous epithelial hyperplasia in 12 adults with dysphagia in the absence of GERD (that is, with normal findings on endoscopy and 24 h pH testing). They compared this group to a cohort of 90 patients with GERD based on increased distal oesophageal acid exposure on pH testing whose biopsies revealed minimal intraepithelial oesophageal eosinophils (mean of 1 eos/hpf). The patients with “dense” intraepithelial oesophageal infiltrate with dysphagia but without GERD were proposed to have a “distinct clinicopathologic syndrome”.¹¹ A year later, Straumann *et al.*¹² reported a series of 10 adults in Switzerland with dysphagia and intraepithelial oesophageal eosinophils, further characterizing this entity with the first description of endoscopic abnormalities in patients with “idiopathic eosinophilic oesophagitis”.

Although the initial descriptions of EoE were in adults, early investigations into the pathogenesis were from paediatric centres. A paediatric study identified an inverse correlation between the degree of oesophageal eosinophilia and reflux severity as determined by pH testing. A cut-off of 20 eos/hpf was associated with normal reflux testing (acid exposure time <4.2% of the time on 24 h testing), whereas <5 eos/hpf correlated with abnormal testing.^{13–15} A second series evaluated the treatment response to reflux therapy (H₂ receptor antagonist and prokinetic agent) among children with at least 1 eos/hpf, and found that a threshold of >7 eos/hpf was predictive of reflux treatment failure.¹⁶ A third paediatric series of patients with so-called refractory GERD who had failed prior medical and surgical treatments directed at GERD found that treatment with an elemental formula resulted in marked reduction in intraepithelial oesophageal eosinophils and improvement in symptomatology, introducing the concept that a food-protein-induced, allergic mechanism was responsible for the pathogenesis of EoE.¹⁷

Besides highlighting differences in the degree of oesophageal eosinophilia between GERD and EoE, pathologists identified additional histological distinctions. Eosinophilic microabscesses, surface layering and sloughing of squamous cells and eosinophils, and eosinophil degranulation, although not entirely specific for EoE, were consistent with the diagnosis of EoE in the appropriate clinical setting (Figure 2).¹⁸ Less specific to EoE, but still indicative, was the finding of pronounced basal cell hypertrophy, lengthening of the lamina propria papillae, an increase in numbers of intraepithelial lymphocytes and mast cells, and intercellular oedema.^{9,18,19} Although several of these changes were also found in GERD, the combination of findings was thought to be suggestive of EoE. Pathologists also pointed to the distribution of oesophageal eosinophilia as indicative of underlying disease state, with distal eosinophilia a characteristic of GERD and diffuse oesophageal eosinophilia in EoE. Studies identified subepithelial or lamina propria fibrosis in a high proportion of children and adults with EoE, a feature not typically found in GERD.^{2,13}

As EoE became increasingly recognized over the past two decades, it became apparent that the clinical pheno-type of the 'typical' patients with EoE differed markedly from that of the patients with GERD, particularly in adult cohorts. Patients with EoE tended to be young (median age 30–40 years), atopic males, presenting with solid food dysphagia and food impactions with endoscopic findings of oesophageal rings, furrows, white exudates and oedema^{2,12,20–22} (Table 1, Figure 3). These findings are in contrast to the typical patient with GERD who is middle-aged, male and who classically presents with heartburn and regurgitation readily responsive to a variety of over-the-counter, acid-suppressant therapies.²³ Although most patients with GERD have normal findings using endoscopy,⁴ relevant findings of erosive oesophagitis, Barrett metaplasia and hiatal hernia are distinct from the endoscopic features of EoE.

Despite the 'textbook' separation of diseases, an overlap in symptom presentation is recognized. Heartburn and noncardiac chest pain have been reported in 30–60% and 8–44% of patients with EoE, respectively.^{24,25} Clinical distinction of EoE from GERD is highly problematic in children in whom symptoms are less discrete with a high degree of overlap with GERD. Paediatric presentations of both GERD and EoE include vomiting, failure to thrive, abdominal pain and food aversion.^{1,26} Furthermore, up to one-third of children with EoE might have a normal appearance to the oesophageal mucosa on endoscopy in contrast to less than one-tenth of adults.^{1,27,28}

On the basis of observations and studies showing this apparent distinction between GERD and EoE, the initial consensus report sponsored by the American Gastroenterological Association Institute and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition defined EoE in 2007 as a clinico pathological disorder characterized by oesophageal symptoms, biopsies showing >15 eos/hpf and the absence of pathological GERD as shown by normal pH testing or lack of response to high-dose PPI treatment.²⁹ This definition implied that GERD and EoE were mutually exclusive conditions: patients with GERD respond to PPI therapy and patients with EoE are best treated with either steroids or elimination diet therapy. Furthermore, patients with typical EoE features and histopathology who also had GERD (defined by erosive oesophagitis or

abnormal pH testing) would be excluded from the diagnosis of EoE. The realm of EoE seemed straightforward at that point in time (Figure 1).

Interactions between EoE and GERD

Over the past decade, a debate has ensued regarding the clinical significance of oesophageal eosinophilia in the distinction of GERD from EoE. The substantial overlap in symptoms and identification of oesophageal eosinophilia in both entities makes the clinical separation challenging. More objective diagnostic testing would seem to be the remedy. Unfortunately, ambulatory pH testing, whilst widely used for the diagnosis of GERD, suffers from major limitations. As a biomarker of GERD, pH testing has limited sensitivity and specificity: abnormal acid exposure does not causally link a patient's problem with GERD, and a normal pH test is seen in as many as 25% of patients with documented erosive oesophagitis.³⁰ Owing to the high population prevalence of GERD, an individual patient might have eosinophilia and abnormal pH testing, but this finding does not prove that eosinophilia was caused by the increased oesophageal acid exposure.³¹ Furthermore, in our experience, pH testing is unfortunately a very unpopular test with patients due to associated discomfort. To elucidate these complex relationships, four scenarios to account for the interactions between oesophageal eosinophilia and GERD were proposed: eosinophilia is a marker of GERD (that is, GERD causes mild eosinophilia in the absence of EoE); GERD and EoE coexist but are unrelated; EoE contributes to or causes GERD; and GERD contributes to or causes EoE.^{10,20,32}

Eosinophilia as a marker of GERD

Mild eosinophilia in biopsy samples as a marker of GERD was the prevailing notion in the 1970s and 1980s until the studies by Attwood and Straumann and colleagues challenged this concept.^{11,12} Prior to this advance, the belief was that acid exposure caused oesophageal injury resulting in chronic inflammation that included the presence of oesophageal mucosal eosinophils. Eosinophil recruitment to the oesophagus could occur via an increase in expression of adhesion molecules (such as vascular cell adhesion molecule) recognized by ligands on eosinophils, the release of chemokines that attracted eosinophils, including platelet-activating factor, IL-8, eotaxin-1, eotaxin-2, eotaxin-3 and CC-chemokine ligand 3 (also known as macrophage inflammatory protein 1 α), and an increase in blood flow, enhancing delivery of eosinophils.^{33–38} However, the role of these adhesion molecules and chemokines outside of experimental models in the pathogenesis of GERD is not clear, and their specificity to GERD has not been established. In fact, many of these factors can also be seen in EoE, particularly eotaxin-3, which has been identified as a highly expressed biomarker of EoE.^{39,40} Moreover, a study has indicated that dense oesophageal eosinophilia was distinctly uncommon in patients with GERD.¹¹

GERD and EoE coexist but are unrelated

Owing to the high prevalence of GERD in the general population (~20% in Western countries), it would be expected that, by chance alone, a large number of patients with EoE should have GERD as well (unless GERD were to protect the oesophagus from EoE).⁴¹ With this concept in mind, studies reporting heartburn as a common symptom of EoE have

to be interpreted with caution, as this finding might reflect the frequency of heartburn that would be expected in the general population.³² On the other hand, studies utilizing 24 h pH monitoring have shown increased oesophageal acid exposure in 25–50% of patients with EoE.^{2,42} These data indicate a higher frequency of pathological acid reflux in the EoE population than expected in the general population, and supports the notion of an important interaction between GERD and EoE.

EoE contributes to or causes GERD

Multiple mechanisms have been proposed by which EoE contributes to the development of GERD. These hypotheses are based on observations that eosinophils secrete a number of agents that can affect the function of oesophageal smooth muscle and the integrity of the mucosal barrier. Vasoactive intestinal peptide and platelet-activating factor are two such products that have been shown to induce relaxation of the lower oesophageal sphincter, possibly predisposing a patient to reflux.^{43,44} IL-6 has been shown to reduce oesophageal contractions in animal models, which might affect peristalsis and clearance of acid.⁴⁵ Other agents (such as eosinophil cationic protein, major basic protein and eosinophil peroxidase) secreted by eosinophils might have a direct cytotoxic effect on the mucosa, rendering the oesophageal epithelium more susceptible to caustic injury by refluxed gastric contents. Such damage might expose epithelial cells and nerves to further acid injury.^{46,47} Lastly, remodelling effects in EoE, manifested as fibrosis and increased thickness of the oesophageal wall, substantially increase oesophageal mural stiffness (reduced distensibility), as demonstrated by studies using the functional luminal imaging probe.^{48,49} Alterations in oesophageal function might contribute to increased acid exposure due to impaired clearance of refluxed contents.

GERD contributes to or causes EoE

Counter to the hypothesis of the previous section, it is possible that GERD could cause EoE. Dilatation of inter-cellular spaces of the oesophageal squamous epithelium is a well-described histopathological feature of GERD.^{50,51} Impairment of oesophageal mucosal integrity or increased mucosal permeability in GERD could allow for the penetration of swallowed allergens into the subepithelial space, which can then be accessed by antigen-presenting cells (dendritic cells or Langerhans cells) (Figure 4). Antigen presentation by dendritic cells to naive T cells is an important initial step in the development of allergic sensitization whereby T cells are transformed to antigen-specific type 2 T helper (T_H2) cells.⁵² In human and mouse models, thymic stromal lymphopoietin (TSLP) production from the oesophageal epithelium primes oesophageal mucosal basophils to secrete IL-4, which promotes the allergic sensitization process.^{52,53}

PPI-responsive oesophageal eosinophilia

Given the complex interactions between GERD and EoE, the overlap between their clinical presentations and limitations of pH testing, a therapeutic trial of PPI therapy was proposed as part of the diagnostic evaluation of patients with suspected EoE.²⁹ Owing to the presence of striking endoscopic features (rings, stricture and furrows) and typical absence of GERD symptoms, many gastroenterologists treating adults bypassed the PPI trial and initiated

primary therapy with steroids for patients with oesophageal eosinophilia. In 2006, Ngo *et al.*³ introduced the concept of PPI-responsive oesophageal eosinophilia (PPI-REE): that patients with an EoE phenotype—that is, endoscopically, histologically and clinically presenting similar to EoE—could completely respond to PPI therapy. Since then, many studies have tried to understand the underlying mechanisms, identify predictors of treatment response and distinguish whether PPI-REE is in fact a subtype of GERD, subtype of EoE, or perhaps an entity distinct from either GERD or EoE.

Clinical, endoscopic and histological evidence

Since the initial description of PPI-REE, there have been a number of studies evaluating clinical, endoscopic and histological outcomes to PPI therapy. A review of the literature by Molina-Infante *et al.*⁴² identified 10 publications that reassessed patients histologically and clinically after PPI therapy.^{42,54–60} Two were randomized control trials, one trial was randomized but uncontrolled, two were prospective cohort studies and the remaining five were retrospective. In their review, Molina-Infante *et al.*⁴² found that, after PPI therapy, clinical response was reported in 69% of patients, whereas histological remission (as in, improvements in the oesophagus, mainly in the eosinophil count, as noted on histological examination) was seen in 44%. In the subgroup of adults with PPI response, clinical response ranged from 25–80%, whereas histological response varied from 33–75%. The highest estimate of 75% from the prospective study by Molina-Infante *et al.*⁶⁰ included a cohort of unselected adults undergoing upper endoscopy.^{42,60} When restricting the cohort to those with an EoE phenotype, the PPI response fell to 50%. Histological response ranged from 23–40% in paediatric studies.^{55,57} Therefore, among patients with suspected EoE according to both clinical and pathological criteria, the estimated histological response to PPI ranged from 23–61%.

Available studies have failed to identify clinical, endoscopic or histological features that reliably predict which patients with oesophageal eosinophilia respond to PPI therapy.^{42,54} Sayej *et al.*,⁵⁵ however, did note that paediatric patients with ≥ 15 eos/hpf at distinct locations along the length of the oesophagus (distal, mid and proximal) were less likely to respond to PPI therapy. Similarly, the prospective study by Molina-Infante *et al.*⁶⁰ demonstrated a reduced response rate to PPI therapy with increasing degrees of oesophageal eosinophilia. Interestingly, symptomatic response to PPI therapy did not correlate with histological findings, which is an observation also noted in a study of adults.⁵⁶ Four studies to date have used pH monitoring in this group of patients.^{57–60} The largest studies showed a (histological) PPI response of 33% and 18%, respectively, in patients with normal pH studies, versus 82% and 100%, respectively, in those with abnormal pH studies.^{60,61} More patients with abnormal pH testing seem to respond to therapy, but if one-third of patients with normal testing also respond, it is hard to alter clinical practice on the basis of these observations.

An interesting clinical observation is the high percentage of clinical response to PPIs seen in patients who do not have histological response, suggesting the role of hypersensitivity in EoE. A study by Krarup *et al.*⁶² assessed response to infusions of acid into the oesophagus of healthy individuals versus patients with EoE. They found that patients with EoE

experienced pain earlier than those with concomitant GERD or healthy controls. This aspect, in addition to a placebo response, might in part explain why clinical remission with PPI therapy is seen in some patients in the absence of histological response.

Acid-dependent and acid-independent mechanisms

Numerous hypotheses have been proposed to explain PPI response in oesophageal eosinophilia. These hypotheses can broadly be separated into acid-dependent effects and anti-inflammatory (acid-independent) effects. Acid-dependent effects are based on the previously discussed concept that GERD might contribute to oesophageal eosinophilia, in that acid exposure reduces mucosal integrity that favours permeability to allergens.⁶³ Allergens are normally too large to penetrate the mucosal barrier, in the range of 3–90 kD. However, in rabbit models, when exposed to acid and pepsin, the oesophagus becomes permeable to particles as large as 20 kD.⁶³ Once these allergens enter the subepithelial space, via these dilated intercellular spaces, they can trigger a T_H2 immune response stimulating eotaxin-3 production and cytokine secretion, leading to recruitment of inflammatory cells and, ultimately, to further impairment of the mucosal barrier and the gross histological changes seen in EoE (Figure 4).⁴² Reversal of this mucosal barrier via an acid-suppressive PPI therapy could explain the therapeutic benefit observed in PPI-REE. This idea was evaluated by Van Rhijn *et al.*⁶⁴ who examined mucosal integrity in patients with suspected EoE and healthy controls by three methods: mucosal impedance; transit of fluorescein molecules across epithelial biopsy samples using Ussing chambers; and direct measurements on intercellular gaps in biopsy samples by electron microscopy. After an 8-week course of PPI therapy, oesophageal permeability improved in patients with PPI-REE, but not EoE.⁶⁴

From an acid-independent standpoint, PPIs might also have anti-inflammatory effects. Beyond restoring the mucosal barrier and disrupting entry of allergens that stimulate a T_H2-mediated immune response, PPIs themselves have been shown to directly inhibit the T_H2-stimulated secretion of eotaxin-3, which is a potent chemoattractant for eosinophils, by interfering with its regulatory transcription factor STAT6 (signal transducer and activator of transcription 6).^{39,40,65,66} These findings have been shown in an *in vitro* system of cultured oesophageal epithelial cells devoid of parietal cells, thus highlighting the acid-independent property of PPIs. Other acid-independent mechanisms for PPI response are antioxidant properties of PPIs and direct attenuating effects on inflammatory cells (neutrophils, monocytes or eosinophils).^{10,67–69} Interestingly, studies in animal and *in vitro* models of GERD have shown that acid reflux causes an initial inflammatory signal via lymphocytic infiltration of the oesophageal submucosa before its caustic effects (in the form of erosions), which appear after 4 weeks of acid exposure.³⁸ This finding suggests that reflux oesophagitis might have a dual inflammatory and caustic effect, which some have suggested could indicate that PPI-REE is an attenuated form of a GERD-induced aberrant inflammatory response in predisposed patients.⁴²

PPI response: issues as a diagnostic criterion

Using a PPI response for the diagnosis of EoE is problematic (Box 1). First and foremost, using response to a therapy as a diagnostic criterion is conceptually undesirable, especially

when the therapeutic intervention has limited sensitivity and specificity. The studies highlighted earlier have shown that the PPI response does not effectively confirm GERD nor exclude EoE. Second, practically speaking, the PPI trial adds expense and time to the diagnostic process by necessitating a second endoscopy with biopsy. Third, the studies to date have been inconsistent in describing length, type, dose and frequency of PPI dosing. No prospective trial identifying the optimal dose, duration, or frequency of PPI has been performed. Currently, PPI therapy is generally continued indefinitely, but dose reduction is often considered once a response has been achieved. Case reports of lost response with long-term use of PPI therapy support clinical and/or endoscopic follow-up for patients with PPI-REE.⁷⁰ The definition of response to PPI is unclear, as most patients demonstrate symptom improvement and reduction, but not normalization of oesophageal eosinophilia after PPI. Fourth, there is a hypothesis, though not well substantiated, that PPIs might in fact increase the propensity for food allergy. This hypothesis has been summarized in a review by Merwat *et al.*⁷¹ who noted an increase in PPI use concurrent with the rising prevalence of EoE. Experimental studies in mice have shown that acid suppression interferes with peptic food breakdown of ingested protein, leading to an increase in the presentation of antigens to the intestinal immune system and increased allergic sensitization.⁷¹

Similarities between PPI-REE and EoE

Fundamentally, determining whether PPI-REE is a subset of EoE or GERD might provide insights into the natural history and pathogenesis of EoE and better inform treatment decisions. From a mechanistic and biomarker profile, studies have provided growing evidence to support the concept that PPI-REE is a subset of EoE rather than GERD. Dellon *et al.*⁷² evaluated three known EoE inflammatory and mast cell biomarkers in oesophageal biopsy samples (eotaxin-3, tryptase and major basic protein) and found that they were accurate in differentiating EoE from controls (patients with GERD and/or dysphagia), but had similar levels of expression in EoE and PPI-REE samples. Another study found that baseline cytokine gene expression in patients with PPI-REE was indistinguishable from that in patients with EoE.⁷³ Notably, treatment with PPI was shown to downregulate eotaxin-3 and T_H2 cytokine gene expression in steroid-responsive patients with PPI-REE or EoE.⁷³ Finally, a third study evaluating an EoE diagnostic panel of 94 oesophageal genetic transcripts found that the majority of genetic markers were identical between PPI-REE and EoE, including expression of eotaxin-3, desmoglein-1, periostin and a mast cell marker.⁷⁴ In patients with PPI-REE, the altered inflammatory and allergic transcriptome, reversed after PPI therapy.⁷⁴ A cluster of 10 genes were identified whose expression differed between EoE and PPI-REE, in particular a gene encoding a potassium channel (*KCNJ2*) expressed in EoE. Interestingly, the specific potassium channel encoded by this gene co-localizes with the hydrogen-potassium ATPase–proton pump.⁷⁴ Taken together, these studies suggest that PPI-REE bears far greater similarity to the inflammatory or allergic pathogenesis of EoE than that of GERD, but that specific molecular differences might exist.

Current clinical guidelines

The past 25 years have witnessed major advances in the understanding of oesophageal eosinophilia in the context of GERD, EoE and PPI-REE. The inter-relationship between

these entities, however, remains complex.⁷⁵ At the present time, an adequate biomarker to distinguish these entities is lacking. Viewing a PPI response as a diagnostic criterion for EoE is overly simplistic and conceptually flawed (Box 1). Given the controversy, why is it recommended that patients with suspected EoE receive a therapeutic trial of PPI?

Historical precedents demonstrate the clinical relevance of differentiating GERD from EoE. Prior to the identification of EoE, patients with oesophageal eosinophilia unresponsive to antireflux medical therapy were diagnosed with so-called refractory GERD. Some of these patients were treated unsuccessfully with increased dosing of PPIs, repeated oesophageal dilations and fundoplications.^{28,76} After the identification of EoE and before the identification of PPI-REE, patients with high levels of oesophageal eosinophilia were commonly labelled with EoE and treated primarily with elimination diets or steroids. This approach withheld a safe, time-tested and effective therapy from the subset of such patients who might have responded to a PPI.

At the present time, a PPI trial remains a recommended strategy in the gastroenterology and allergy society guidelines for the management of patients with oesophageal eosinophilia who are clinically suspected of having EoE.^{1,2} Although problematic from a diagnostic standpoint, this approach is both practical and clinically effective (Box 2). PPIs are effective at improving oesophageal eosinophilia in 23–61% of patients with clinical and histological features of EoE.^{42,72–74} Ongoing research supports the concept that the benefit of PPIs might relate to antigen exposure via mucosal integrity induced by GERD or even a direct acid-independent anti-inflammatory effect. Translational studies point to more similarities than differences between EoE and PPI-REE. Regardless of the mechanism of action, PPIs have a long track record of safety. Currently, they are easier to administer than swallowed topical steroids or elimination diets. Alternative strategies to exclude potential contributions of GERD to a patient's presentation (such as ambulatory pH monitoring) are cumbersome and subject to both false-positive and false-negative results.³¹

Conclusions

Historical precedents and epidemiological considerations as well as complex immune and physiological interactions underlie the challenges and controversies in distinguishing GERD and EoE. Growing clinical and experimental evidence indicate that PPI-REE is, in most cases, a PPI-responsive form of EoE. Newly identified differences in gene expression between PPI-REE and EoE need further study. The benefits of PPI therapy in EoE might be due to improved mucosal integrity or direct anti-inflammatory effects. Ongoing studies elucidating the mechanism behind PPI-REE will improve our understanding and management of EoE.

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Key points

- Eosinophilic oesophagitis (EoE) is a chronic, immune and/or antigen-mediated, clinicopathological disease defined by symptoms of oesophageal dysfunction, oesophageal eosinophilic inflammation, and exclusion of other causes of oesophageal eosinophilia including GERD
- Potential interactions between GERD and EoE include eosinophilia as a component of chronic inflammation in GERD, coexistence of GERD and EoE, EoE causing GERD and GERD causing EoE
- A notable proportion (~40%) of patients with clinical, endoscopic and histological features of EoE demonstrate a clinical and histological response to PPI therapy, those with so-called PPI-responsive oesophageal eosinophilia
- Predictors of PPI response among patients with oesophageal eosinophilia and suspected EoE are presently lacking
- On the basis of current clinical and translational research, PPI-responsive oesophageal eosinophilia more closely resembles EoE than GERD
- Benefits of PPI therapy in EoE could be due to their ability to restore integrity of the oesophageal epithelium or direct anti-inflammatory effects

Box 1 | Problems with PPI response as an EoE diagnostic criterion

- Conceptual concern that a response to a therapy should not be utilized to define a disease
- A clinical and histological response to PPI therapy does not effectively exclude EoE or confirm GERD: PPI therapy might be directly or indirectly altering allergic and/or immune pathways involved in EoE; PPIs improve oesophageal epithelial barrier function, thereby potentially preventing oesophageal luminal antigen presentation for allergic sensitization
- A PPI trial adds expense and time to diagnostic process (that is, repeat endoscopy with biopsies after PPI therapy is necessary for the diagnosis of EoE)
- The duration (4, 6, 8 or 12 weeks), dose (single or double dose) and frequency (once daily vs twice daily) of PPI therapy have not been established
- Symptomatic improvement with PPI might not correlate with endoscopic and histological improvement

Abbreviation: EoE, eosinophilic oesophagitis.

Box 2 | Reasons for therapeutic trial of PPI in EoE

- Although PPIs do not reliably differentiate EoE from GERD, they effectively improve eosinophilic inflammation in 23–61% of patients with oesophageal eosinophilia and clinical features of EoE
- PPIs are safe and easier to administer than available formulations of topical corticosteroids and elimination diet therapies
- Alternative methods to exclude GERD (that is, pH monitoring) are cumbersome for patients and subject to both false-positive and false-negative results
- Growing translational research supports the concept that GERD might contribute to allergic and/or immune pathways involved in the pathogenesis of EoE
- In experimental systems, PPIs demonstrate anti-inflammatory properties independent of acid suppression

Abbreviation: EoE, eosinophilic oesophagitis.

Figure 1.

Historical aspects regarding the associations between oesophageal eosinophilia, GERD and EoE. Abbreviations: EoE, eosinophilic oesophagitis; PPI-REE, PPI-responsive oesophageal eosinophilia.

Figure 2.

Histopathology of EoE. Demonstrated findings include oesophageal mucosal eosinophilia with superficial distribution, eosinophilic microabscess formation (arrowhead), basal zone hyperplasia, dilated intercellular spaces (spongiosis) and lamina propria fibrosis (asterisk). None of these histological features appear to differentiate EoE from PPI-responsive oesophageal eosinophilia. Image courtesy of Dr Elizabeth Montgomery, Johns Hopkins School of Medicine. Abbreviation: EoE, eosinophilic oesophagitis.

Figure 3. Endoscopic features of EoE. Characteristic findings of EoE include rings (asterisk), longitudinal furrows (arrowhead), white exudates (arrow), and loss of vascular marking (oedema). Strictures and narrow calibre oesophagus are commonly identified in adults but not younger children with EoE. Abbreviation: EoE, eosinophilic oesophagitis.

Figure 4.

Proposed mechanism identifying the role of GERD in the pathogenesis of EoE. Oesophageal acid exposure results in epithelial barrier injury with widening of gaps between squamous epithelial cells. The impaired mucosal integrity allows for antigen exposure to Langerhans (dendritic) cells in the oesophageal mucosa resulting in sensitization with expansion of T_H2 cells and the recruitment of eosinophils. Activation of mast cells leads to the release of mediators involved in oesophageal remodelling. Abbreviations: EoE, eosinophilic oesophagitis; T_H2 cell, type 2 T helper cell.

Table 1

Distinguishing GERD from EoE

Factors	EoE	GERD
Dominant symptom	Dysphagia	Heartburn Regurgitation
Food impaction	Common	Uncommon
Gender	Male predominance	Male = female
Age	Children, young adults	Middle-age
Endoscopic findings	Oedema, rings, exudates furrows, strictures, crepe-paper oesophagus, narrow calibre oesophagus Normal findings on endoscopy (<10%)	Erosions, ulcers Barrett adenocarcinoma Strictures Normal findings on endoscopy (majority)
Ambulatory pH testing	Negative or positive	Positive
Histology	15 eos/hpf	<7 eos/hpf
Etiology	Immune-mediated or antigen-mediated response	Acid reflux
Primary treatment	Steroids Elimination diet PPI (?)	Antacid, H ₂ receptor blockers PPI

Abbreviations: EoE, eosinophilic oesophagitis; eos/hpf, eosinophils per high-power field.