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## Proton Pump Inhibitor-Responsive Oesophageal Eosinophilia: An Entity Challenging Current Diagnostic Criteria for Eosinophilic Oesophagitis

Javier Molina-Infante<sup>1</sup>, Albert J. Bredenoord<sup>2</sup>, Etaire Cheng<sup>3</sup>, Evan S. Dellon<sup>4</sup>, Glenn T. Furuta<sup>5</sup>, Sandeep K. Gupta<sup>6</sup>, Ikuo Hirano<sup>7</sup>, David A. Katzka<sup>8</sup>, Fouad J. Moawad<sup>9</sup>, Marc E. Rothenberg<sup>10</sup>, Alain Schoepfer<sup>11</sup>, Stuart Spechler<sup>12</sup>, Ting Wen<sup>10</sup>, Alex Straumann<sup>13</sup>, and Alfredo J. Lucendo<sup>14</sup> From the PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS)

<sup>1</sup>Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain <sup>2</sup>Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, the Netherlands <sup>3</sup>Department of Pediatrics and Internal Medicine, Children's Health Children's Medical Center, and the University of Texas Southwestern Medical Center, Dallas, USA <sup>4</sup>Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA <sup>5</sup>Section of Pediatric Gastroenterology, Hepatology and Nutrition, Digestive Health Institute, Children's Hospital Colorado, Aurora, USA <sup>6</sup>Section of Pediatric Gastroenterology, Hepatology and Nutrition, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, USA <sup>7</sup>Department of Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, USA <sup>8</sup>Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, USA <sup>9</sup>Gastroenterology Service, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, USA <sup>10</sup>Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, USA <sup>11</sup>Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland <sup>12</sup>Department of Internal Medicine, VA North Texas Health Care System, and the University of Texas Southwestern Medical Center, Dallas, USA <sup>13</sup>Swiss EoE Research Network, Olten, Switzerland <sup>14</sup>Department of Gastroenterology, Hospital General de Tomelloso, Spain

### Abstract

Consensus diagnostic recommendations to distinguish gastro-oesophageal reflux disease (GORD) from eosinophilic oesophagitis (EoE) by response to a trial of proton pump inhibitors (PPI) unexpectedly uncovered an entity called “PPI-responsive oesophageal eosinophilia” (PPI-REE). PPI-REE refers to patients with clinical and histologic features of EoE that remit with PPI treatment. Recent and evolving evidence, mostly from adults, shows that PPI-REE and EoE patients at baseline are clinically, endoscopically and histologically indistinguishable, and have

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Corresponding author: Javier Molina-Infante, M.D. Department of Gastroenterology, Hospital San Pedro de Alcantara., C/ Pablo Naranjo s/n 10003 Caceres, Spain, Phone: 0034927621544 Fax: 0034927621545, xavi\_molina@hotmail.com.

#### COMPETING INTERESTS

Drs. Glenn T. Furuta, David A. Katzka, Fouad J. Moawad, Ting Wen, Alfredo J. Lucendo: no conflict of interest to declare.

significant overlap in terms of features of Th2 immune-mediated inflammation and gene expression. Furthermore, PPI therapy restores oesophageal mucosal integrity, reduces Th2 inflammation and reverses the abnormal gene expression signature in PPI-REE patients, similar to the effects of topical steroids in EoE patients. Additionally, recent series have reported that EoE patients responsive to diet/topical steroids may also achieve remission on PPI therapy. This mounting evidence supports the concept that PPI-REE represents a continuum of the same immunologic mechanisms that underlie EoE. Accordingly, it seems counterintuitive to differentiate PPI-REE from EoE based on a differential response to PPI therapy when their phenotypic, molecular, mechanistic, and therapeutic features cannot be reliably distinguished. For patients with symptoms and histologic features of EoE, it is reasonable to consider PPI therapy not as a diagnostic test, but as a therapeutic agent. Due to its safety profile, ease of administration and high response rates (up to 50%), PPI can be considered a first-line treatment, before diet and topical steroids. The reasons why some EoE patients respond to PPI, while others do not, remain to be elucidated.

### Keywords

eosinophilic oesophagitis; proton pump inhibitors; proton pump inhibitor-responsive oesophageal eosinophilia; gastro-oesophageal reflux disease

## 1. HISTORICAL BACKGROUND AND DEFINITIONS

Eosinophilic oesophagitis (EoE) and gastro-oesophageal reflux disease (GORD) are the most prevalent chronic oesophageal inflammatory conditions in children and adults in the western world.[1] Whereas the first is an allergen-driven disease, [2] the latter develops as a consequence of pathologic exposure of the oesophageal mucosa to acid predominant gastric contents.[1] Distinguishing both disorders is important because of their different aetiopathogenesis, natural history, and monitoring.[2] However, a rigid distinction between EoE and GORD is difficult due to overlapping clinical and histological features, not to mention their frequent coexistence and potential partially shared pathogenic pathways.[3] The presence of heartburn and marked oesophageal eosinophilia, for instance, might be fairly common in both entities.[3,4] In pediatric patients, this differentiation is even more complex due to a wider spectrum of clinical manifestations, difficulties in expressing symptoms and subtle or absent endoscopic abnormalities.[5]

In order to solve this diagnostic conundrum, the first consensus recommendations for diagnosis and management of EoE were published in 2007.[6] These guidelines advocated a diagnosis of EoE in patients with symptomatic oesophageal eosinophilia (> 15 eosinophils per high power field (eos/HPF)) showing either lack of response to proton pump inhibitor (PPI) therapy or a normal acid exposure on oesophageal pH monitoring. Accordingly, a diagnosis of GORD was recommended for those patients who were either responders to PPI therapy or had objective evidence of pathological oesophageal acid exposure. This distinction was based on the assumption that only GORD, as an acid-related disorder, could respond to the acid suppressive effect of PPIs. As such, these guidelines equated GORD with symptomatic and histological response to PPI therapy. Far from fulfilling the expectation of distinguishing GORD from EoE, the recommended PPI trial unexpectedly

uncovered a third intriguing category of patients, apparently sharing features of EoE and GORD.[4]

Updated consensus recommendations in 2011 [2] included changes to these findings: 1) the description of a novel phenotype, PPI-responsive oesophageal eosinophilia (PPI-REE), referring to patients with features of EoE who achieve clinical and histological remission on PPI therapy 2) response to PPI therapy in patients with PPI-REE was not necessarily considered a manifestation of GORD, 3) the retraction of recommending oesophageal pH monitoring as a diagnostic criterion, due to its low accuracy to predict response to PPI.[4] Nonetheless, support for a PPI trial was maintained as a diagnostic criterion, since PPI-REE and EoE were still considered separate clinical entities as they showed a different response to the PPI trial.[2]

At this stage, it is crucial to ascertain the accurate location of PPI-REE within the spectrum between EoE and GORD, the therapeutic mechanisms leading to responsiveness to PPI therapy in patients with suspected EoE and whether the response to a PPI trial has any validity as a means of excluding EoE.

## 2. DIFFERENCES AND SIMILARITIES BETWEEN GORD, PPI-REE AND EOE

The need to distinguish among GORD, EoE and PPI-REE in clinical practice, pharmaceutical trials and research studies has led to careful investigations to distinguish these entities. The results of these studies are summarized in Table 1.

### 2.1. Symptoms

In adults, the clinical presentations of GORD and EoE are typically distinct.[3] GORD patients present with heartburn, regurgitation and bitter/sour taste of gastric content. Dysphagia as a dominant symptom is rare in GORD, unless a peptic stricture is present. GORD symptoms are exacerbated after consumption of large meals, rapid eating, acidic foods, alcohol, obesity, tobacco, and body position changes. In contrast, EoE adult patients present predominantly with intermittent dysphagia during consumption of solid foods, commonly associated with food impactions. While heartburn and chest pain may be present in EoE, they are characteristically not the dominant complaints reported by adult patients and if present, usually accompany dysphagia. Available studies have identified that demographics, atopic history and clinical manifestations do not reliably discriminate EoE from PPI-REE.[4,7–11] Paediatric presentations of EoE are more heterogeneous and include abdominal pain, nausea, reflux-like symptoms not responsive to acid suppression, feeding difficulties, and growth failure. It remains unclear if this difference in symptom profile reflects inadequate symptom reporting by young children, initial symptoms related to inflammation prior to onset of oesophageal remodelling or in part functional symptoms caused by comorbid conditions, such as irritable bowel syndrome. Along the same lines, it is unclear if adults with EoE only develop dysphagia after an initial period of paediatric type symptoms.[5]

## 2.2. Endoscopic features

Most GORD patients have a normal appearance to the oesophageal mucosa on endoscopy, whereas erosive oesophagitis or Barrett's oesophagus are identified in the minority.[3] Endoscopically, nearly all adult EoE patients demonstrate one or more characteristic features of loss of vascular markings, rings, white exudates, longitudinal furrows, narrow caliber oesophagus and strictures, whereas some children may have a visually normal mucosa.[11,12] Reflecting the natural history of oesophageal remodelling, rings and strictures are common in adults but rare findings in children with EoE.[5] Typical EoE endoscopic signs are useful in distinguishing GORD from EoE, but not PPI-REE from EoE [4,7–8,10–11].

## 2.3. Histologic findings

Histologic characteristics of GORD include basal cell hyperplasia, papillary elongation, dilated intra cellular spaces and a paucity of intraepithelial inflammatory cells. [13] Eosinophils may be present in GORD but typically are in low numbers (< 10 eos/hpf), although we lack prospective studies defining numbers and extent and numbers of eosinophilia observed in GORD. Histologic features of EoE include all of the above GORD features with the addition of a marked, eosinophil-predominant, cellular infiltration of the mucosa. Superficial squamous epithelial distribution, eosinophil degranulation, eosinophil microabscesses and lamina propria fibrosis are also commonly identified in EoE, but not in GORD. Mast cells have been recognized in the mucosa of both GERD and EoE patients. [14,15]. Multiple studies have noted that these histologic features are found in both EoE and PPI-REE. These include evidence of superficial distribution of epithelial eosinophils, eosinophil degranulation and microabscess formation, [4,7,8,11], basophil infiltration[10] and the expression of major basic protein and tryptase.[15] Interestingly, a lower rate of response to PPI therapy has been reported in patients with more severe histologic findings including either 15 eos/HPF at 3 levels of biopsies[16] or increasing degrees of oesophageal eosinophilia.[4]

## 2.4. Molecular and genetic features

GORD promotes a pro-inflammatory response characterized by innate immunity with over-expression of cytokines, such as interleukin (IL)-8 (CXCL8), CCL2 (monocyte chemoattractant protein 1 and CCL5 (RANTES) [17]. These cytokines and chemokines promote active recruitment of neutrophils and lymphocytes and sometimes a mild eosinophilic infiltration, normally < 5–10 eos/HPF. Unlike GORD, EoE is a chronic immunoallergic disorder characterized by an aberrant Th2 inflammatory response involving IL-5 and IL-13 and local production of CCL26 (eotaxin-3), a chemokine that specifically attracts eosinophils to the oesophageal mucosa. When activated, the eosinophils cause local tissue damage and recruit and/or activate other effector cells, such as mast cells, which have a role in oesophageal fibrotic remodelling. [18] By using whole-genome transcript expression profiling of esophageal tissue, a molecular EoE diagnostic panel (EDP) has been recently identified.[19] This panel is made of 94 EoE genes and accurately distinguishes patients with EoE from GERD or control subjects.[19]

Over the past years, an increasing number of papers have tried to further characterize PPI-REE. Baseline markers of eosinophilic inflammation in oesophageal tissue (e.g. eosinophil derived major basic protein and CCL26) have been shown to be increased in PPI-REE, similar to EoE. In addition, expression of mast cell signature genes (e.g. tryptase) [15], as well as expression of genes involved in type 2 (Th2) associated allergic inflammation (including CCL26, IL-5, IL-13, thymic stromal lymphopoietin (TSLP) and periostin (POSTN) [9,10,20,21] have demonstrated largely overlapping patterns between EoE and PPI-REE, although PPI-REE typically has more modest over-expression levels. One of the key findings in the past year is that PPI-REE, unlike GORD, has a transcriptome that nearly completely overlaps with the EoE transcriptome, including the hallmark EoE genes for eosinophil chemotaxis (*CCL26*), barrier molecules (desmoglein *DSG1*), tissue remodeling (*POSTN*), and mast cells (*CPA3*). [22] Overall, these findings suggest PPI-REE and EoE are alike and both associated with allergic inflammation (4). In addition, recent clinical studies have shown that PPI monotherapy in PPI-REE patients can almost completely reverse the Th2 signature of PPI-REE (CCL26, IL-5, IL-13, POSTN) [9,21,22] and concurrently induce a normalization of the mast cell genes (*CPA3*, *TPSAB2*), Th2 inflammation indicators (*TNFAIP6*, *ALOX15*), epithelial barrier genes (*DSG1*, *CDH26*, *FLG*), tissue fibrosis markers (e.g. *KRT13*), and IL-13/IL-4-induced genes (*POSTN*, *MUC4*) [22]. Since these effects are similar to those of topical steroids in EoE patients [9,23], these striking data pose the possibility that EoE and PPI-REE represent a common disorder.

Recent genome wide association studies (GWAS) in EoE have identified two replicated susceptibility loci at 2p23 and 5q22, regions that encode the epithelial gene products *CAPN14* and *TSLP*. [24–26] The presence of susceptibility loci was shown to not depend upon response to PPI, reinforcing the idea that esophageal eosinophilia, independent of PPI stratification, likely shares genetic etiology.

### 3. THE EFFICACY OF PPI THERAPY IN PATIENTS WITH SUSPECTED EOE

The evidence for PPIs inducing either clinical or histologic disease remission in patients with suspected EoE was initially reported by one case series and three retrospective studies published between 2005 and 2009. [16,27–29] The case series reported clinico-histological response in all 3 patients, [27] whereas a 50–86% clinical response and a 40% histologic response was reported in the retrospective cohorts. [16,28,29] In the first large prospective study in adults with clinical, endoscopic and histological features of EoE, an 8 week course of PPI therapy led to complete response in 50% of cases. [4] Of note, response to PPI was observed in 80% of patients with endoscopic evidence of GORD or abnormal pH monitoring, but also in 33% of those with a normal pH study. [4]

Two randomized controlled trials comparing PPIs to topical steroids in patients with an EoE phenotype reported a similar efficacy (33%) for PPI therapy. [30,31] The latter trial demonstrated a response to PPI in 100% and 18% of patients with a pathological and normal pH study, respectively. [31] In three recent prospective studies, 35% to 47% of adult and pediatric patients achieved histologic remission (defined by < 5 eos/HPF) on PPI therapy. [15,32,33] Of note, response to PPI therapy increased up to 50% [30], 57% [32] and 68% [33] when histological remission was redefined as < 15 eos/HPF.

A recent systematic review with meta-analysis, including 33 studies with 619 patients with suspected EoE, revealed that PPIs achieved histological remission (defined by  $< 15$  eos/HPF) in 51% (95% CI, 42.2%–58.7%) and symptomatic improvement in 61% (95% CI, 48.38% – 72.2%) of cases.[34] No significant differences were noted in patients' age, study design and type of PPI assessed. However, a trend towards increased efficacy was observed when PPIs were administered twice daily compared to once daily, and among patients with increased oesophageal acid exposure on pH monitoring. Noteworthy, a significant publication bias in favor of studies reporting histologic responses to PPI therapy was observed in this meta-analysis.

The sustained efficacy of PPIs in children has been evaluated in two retrospective small series and a recent prospective study, with most patients (78.6%) remaining in clinicopathological remission at one-year follow up while on maintenance PPI therapy. [33,35–36]. As for adults, the first long-term follow-up multicentre study including 75 PPI-REE patients demonstrated that the majority of patients (73%) maintained histological remission 1 year after tapering dosage to the lowest effective clinical dose.[37] Among relapsers, most regained histological remission with dose escalation, suggesting some patients with PPI-REE continue to require high-dose maintenance PPI. Allergic rhinoconjunctivitis and a CYP2C19 rapid metabolizer genotype predicted long-term relapse, hinting at the influence of pharmacogenomic and environmental factors on the long-term efficacy of PPI therapy.

#### 4. POTENTIAL MODE OF ACTION OF PPI IN EOE

It is widely appreciated that PPI block gastric acid secretion, and this antisecretory effect is assumed to underlie their great efficacy in treating GORD. However, PPI do not prevent the reflux of non-acidic material, and up to 20% of GORD patients have symptoms that are refractory to PPI. It is less well known that PPI have anti-inflammatory actions (independent of antisecretory effects) that also might contribute to healing oesophagitis.[38] PPI have anti-oxidant properties, inhibit immune cell functions, decrease adhesion molecule expression by endothelial cells, and reduce inflammatory cytokine expression by epithelial cells.[39] PPI also have anti-inflammatory effects that might be especially pertinent to the allergen-driven eosinophilia of EoE.

In EoE, eosinophils accumulate in the oesophagus when allergens induce production of Th2 cytokines like IL-4 and IL-13, which stimulate oesophageal secretion of CCL26 (eotaxin-3). [18] Omeprazole, in concentrations achieved in blood with conventional dosing, inhibits Th2 cytokine-stimulated eotaxin-3 secretion in isolated oesophageal epithelial cells by blocking binding of the transcription factor STAT6 to the eotaxin-3 promoter.[40,41] Lansoprazole exhibits similar actions, suggesting that this inhibition of Th2 cytokine-stimulated eotaxin-3 secretion is a PPI drug class effect.[41] In one study of children with oesophageal eosinophilia, PPI treatment significantly decreased eotaxin-3 protein expression by epithelial cells in the proximal but not distal esophagus.[42] In three recent studies primarily in adult PPI-REE patients, [9,21,22] PPI reduced oesophageal expression of eotaxin-3, IL-5, and mast cell density, suggesting that PPIs down-regulate Th2-mediated events. Moreover, gene transcriptome analyses of oesophageal biopsies from adult and

pediatric PPI-REE patients have shown a pronounced and specific effect of PPI on reducing expression of genes related to allergic inflammation.[22] Impaired oesophageal mucosal barrier function, likely mediated by reduced expression of desmoglein-1, is a common feature of EoE, and PPIs have been shown to restore mucosal barrier function and improve desmoglein-1 expression in patients with PPI-REE.[21,22,43]

All of the therapeutic effects of PPIs on oesophageal inflammation, gene expression and mucosal integrity in PPI-REE patients are similar to the responses seen with topical steroid therapy in EoE patients.[9,44] Collectively, these data support a trial of PPI for virtually any patient with oesophageal eosinophilia, regardless of the underlying mechanism. [45]. If eosinophilia is caused solely by GORD and is not antigen-driven, then PPI antisecretory effects can improve eosinophilia by limiting acid reflux. If oesophageal eosinophilia is solely antigen-driven, anti-inflammatory PPI effects might improve eosinophilia by attenuating Th2-associated responses. If GORD causes or exacerbates an antigen-driven oesophageal eosinophilia, both the antisecretory and anti-inflammatory effects of PPI might combine to ameliorate the condition. Finally, hypersensitivity to acid in the oesophagus has been reported in EoE patients.[46] During perfusion of the oesophagus with acid, EoE patients felt the burning sensation evoked by the acid earlier than those with concomitant reflux or the healthy volunteers.[46] This phenomenon might explain why PPI-mediated acid suppression may improve symptoms in some EoE patients, despite the absence of histologic remission on PPI therapy.[4,9,16,28,47–49]

## 5. PPI-REE: IS IT GORD OR IS IT EoE?

The above mentioned data all point in the same direction suggesting that PPI-REE and EoE are indistinguishable except that PPI have a more robust effect on PPI-REE patients than EoE patients. Subjects with EoE and PPI-REE have similar symptoms, demographics, endoscopic findings, histology and response to other treatments besides PPI. Most striking perhaps is that the transcriptome of EoE and PPI-REE largely overlaps. Furthermore, recent data reveal that EoE patients responsive to diet and topical steroid therapy were eventually found to respond to PPI therapy as well, providing further data that an allergic inflammatory cause is important in PPI-REE.[50,51].

All of these data provide no rational basis to make a distinction between patients with symptomatic esophageal eosinophilia based on a different response to PPI therapy. At the present time, phenotypic, molecular, mechanistic, and therapeutic features cannot be reliably distinguish EoE from PPI-REE. As such, the requirement of a distinct name among indistinguishable patients for the sub-group responding to PPI is questionable.[52]. We therefore propose not to include the responsiveness to a given drug as a diagnostic criterion and, consequently, avoiding the term PPI-REE for those subjects that have an EoE phenotype with both histological and clinical response to PPI therapy. Given all of the above mentioned arguments, we suggest viewing the PPI trial not as a diagnostic tool for EoE, but rather as a potential therapy in all patients with clinical, endoscopic and histological features suitable for EoE.

## 6. REAPPRAISAL OF THE PPI-TRIAL AS A DIAGNOSTIC TOOL AND POSITION OF PPI IN THE TREATMENT OF EOE

Currently, either swallowed topical steroids or dietary elimination are considered appropriate first-line therapeutic options after the diagnosis of EoE is established [53,54], but these modalities have limitations and neither is universally effective [55,56]. Therefore, it is important to consider where PPI might fit in the treatment algorithm for EoE. Respecting their favourable safety profile, the simplicity of administration of the compounds and high response rates, [34] PPI could be considered as first line therapy for patients with EoE. Use of PPI would therefore, instead of deciphering which patients do not have EoE, will likely identify a substantial proportion of EoE patients who achieve remission on PPI therapy and will not need topical steroid or dietary therapy. As with topical steroid use, it is important to note that this represents off-label use of these medications.

## 7. PROPOSAL FOR UPDATED DIAGNOSTIC CRITERIA FOR EOE

EoE represents a chronic, immune/antigen-mediated oesophageal disease, characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation. Eosinophilic inflammation is restricted to the oesophagus and other causes of local and systemic oesophageal eosinophilia should be excluded (Table 2).

After a diagnosis of EoE, clinical and histological features of EoE may respond in the majority of patients to treatment with PPI, topical steroids or elimination diets.

## 8. UNSOLVED ISSUES

### Can we positively state that PPI-REE is EoE?

No, we cannot. EoE is formally defined as an immune/antigen-mediated disease, but we currently lack evidence on the ultimate etiology of PPI-REE. Solid evidence corroborates it is a Th2-mediated disease with significant molecular overlap with EoE, but we do not know whether this immune response is triggered by reflux-mediated epithelial injury, food/airborne allergens or the combination of both factors.

In addition, a diagnosis of EoE in patients with no clinical or endoscopic features of EoE might be questionable, given the fact we know GORD patients might also have Th1 mediated oesophageal eosinophilia.[22] However, this subset of patients is likely to represent a minority of adult patients. A recent study performed a thorough subanalysis of 75 PPI-REE patients on long-term follow-up and 86% of patients had typical clinical and endoscopic features of EoE, with only one single patient showing a pure GORD phenotype. [37]. The bulk of evidence on PPI-REE comes from adult patients, so we need further prospective studies corroborating these findings in children as well. Based on the high population prevalence of GORD, it is inevitable that many patients with EoE will have co-existing GORD. In such cases or atypical clinical presentations, comprehensive consideration of the clinical criteria listed in Table 1, endoscopic features, ambulatory pH monitoring, and responsiveness to PPI therapy may have clinical utility in patient management.



Molecular biomarkers distinguishing EoE and PPI-REE would be helpful to distinguish between both entities. KCNJ2 has been recently identified as the only gene with significant differential expression between PPI-REE and EoE, showing a 72% sensitivity/specificity to predict PPI-REE at baseline.[22] KCNJ2 encodes a potassium channel which is abundant in gastrointestinal mucosa and colocalizes with the proton pump. Therefore, the authors proposed a potential interaction between this potassium channel and proton pump in the upper gastrointestinal epithelium to explain PPI-REE. A genome-wide approach currently underway may reveal alternative mechanisms that might differentiate the two entities.

**Considerations for pediatric patients**—A distinction between EoE and GORD may be especially complex in children, where EoE symptoms tend to overlap more substantially with GORD (feeding difficulties, regurgitation, heartburn) and endoscopic findings are not so prototypical as in adults. Concerns about endoscopic procedures in children often lead to treatment with PPI before any diagnostic procedures are completed. A symptomatic response to PPI will lead to most paediatricians considering a diagnosis of GORD, but a diagnosis of PPI-REE might be missed since a biopsy was not obtained. Furthermore, a significant dissociation between esophageal symptoms and inflammation has been reported in EoE, so a clinical response to PPI therapy does not necessarily rule out EoE. [4,9,16,28,47–49] Unfortunately, EoE is a clinico-histological entity requiring objective confirmation of histological abnormalities for diagnosis and for remission after therapeutic interventions.

Performing an additional baseline endoscopy off PPI therapy raises concerns for practitioners, parents and patients, but it is critical to remember that normal endoscopic and histologic esophageal features on PPI therapy in children with suspected EoE could create a lack of diagnostic clarity as well as short and long term therapeutic uncertainty. For instance, children with GORD, PPI-REE, functional dyspepsia or recurrent abdominal pain might have similar symptoms (regurgitation, vomiting, abdominal pain), experience a therapeutic or placebo related response to PPIs and exhibit normal endoscopic and histologic features on PPI therapy. Questions of the duration, dose and frequency of PPI treatment will remain unanswered. Overall, reconciling concerns about endoscopic procedures and anaesthesia with the current need of endoscopy for diagnosis and monitoring EoE will continue to be challenging in pediatric patients.

**Mechanisms underlying response to PPI therapy**—The precise mechanism(s) by which PPI accomplish their effects on oesophageal eosinophilia in EoE remains unclear. Anti-inflammatory effects of PPIs have been only proven in experimental studies.[40] While omeprazole *in vitro* is present in the culture media for up to 48 hours, the short half-life for PPI drugs (1–2 hours active) makes it unclear if a sustained anti-inflammatory effect is maintained *in vivo*. PPI therapy have recently shown their ability to down-regulate Th2 allergic oesophageal inflammation, [9,21,22] but it is not certain whether this is a direct (primary anti-inflammatory effect) or indirect (primary acid inhibition leads to secondary inflammation healing) effect.

On the other hand, the role of GORD in PPI-REE is unclear. PPIs can reverse dilation of epithelial intercellular spaces and restore mucosal integrity in patients with GORD[57] and

PPI-REE[21,43] suggesting reflux may be the initial trigger in some PPI-REE patients. This hypothesis might be supported by a greater likelihood of GORD in PPI-REE patients[34]. However, the demonstration of pathological oesophageal acid exposure in PPI-REE patients does not prove a casual role for GORD, whereas lack of response to PPI does not necessarily rule out GORD as a primary trigger for EoE. It will be important to eventually determine if PPI-REE patients would also respond to other classes of anti-acid drugs such as Histamine Receptor 2 (H<sub>2</sub>R) antagonists, as it would be informative of the acid-suppressive effects as a primary driver of the PPI-REE designation. It is important to acknowledge that no complete response of another allergic disease with PPI therapy has been documented so far today.

**How do we define response to PPI therapy?**—The effect of PPI in patients with suspected EoE is not an all or none effect, but a gradient varying between no response, some response and near-complete or complete response. It should be emphasized that, currently, a diagnosis of EoE which responds to PPI therapy depends on subjective criteria for symptom response and on an arbitrary histological cut-off (15 eos/HPF) for histologic response. It is likely that PPI use will have at least some effect in most patients, suggesting that either the acid inhibitory and/or the anti-inflammatory effect of PPI may play a smaller or larger role in these patients.

**Adequate doses, dosing interval and duration of PPI therapy**—It is also necessary to determine the dose and duration of an adequate initial PPI trial. An 8 week course of any of the available agents at a regular dose twice daily (pantoprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg; all BID) or double dose once daily (omeprazole 40 mg, esomeprazole 40 mg) has been proposed as sufficient to assess a response to PPI therapy [2]. In young children, dosing should be weight-based as appropriate. However, evidence supporting the recommendations is poor and conflicting.[34] While there does not seem to be a relation between the medication dose and response rate in prospective studies, it is clear that any of the PPI agents can be effective when used at a “high daily dose” (Table 3). The first meta-analysis on this issue has recently suggested a non-statistically significant advantage of a twice daily administration, with no differences between drugs or doses [34]. Future prospective dose-ranging studies of PPIs in patients with esophageal eosinophilia would be helpful in providing more definitive dose and duration recommendations.

**Natural history and long-term prognosis of responders to PPI therapy**—The similarities between PPI-REE and EoE also raise the question of whether both disorders share a comparable pathogenesis and whether, if left unmanaged, PPI-REE can lead to reversal of oesophageal fibrosis. [58] Further studies should address this issue.

**Combination therapy: PPI plus steroid/diet therapy**—Another area of speculated use is in combined therapy with steroids, particularly for refractory patients. This would combine PPIs impeding antigen penetration of the esophageal mucosa through epithelial repair and steroids blunting the allergy based anti-inflammatory response. There is also data that PPIs inhibit different cytokines in EoE and GORD when compared to steroids, thus potentially and synergistically enhancing an anti-inflammatory response.[59]

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## Abbreviations

<b>EoE</b>	eosinophilic oesophagitis
<b>GORD</b>	gastro-oesophageal reflux disease
<b>HPF</b>	high power field
<b>PPI</b>	proton pump inhibitor
<b>PPI-REE</b>	PPI-responsive oesophageal eosinophilia

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**Table 1**

Updated similarities and differences between GORD, PPI-REE and EoE

	<b>GORD</b>	<b>PPI-REE</b>	<b>EoE</b>
<b>Age</b>	Adults > Children	Children and young adults	Children and young adults
<b>Gender</b>	Male = Female	Male predominance	Male predominance
<b>Dominant symptom</b>	Heartburn, regurgitation	Dysphagia	Dysphagia
<b>Food impaction</b>	Uncommon	Common	Common
<b>Endoscopic findings</b>	Normal endoscopy (70–80%) Erosions, ulcers, strictures, Barrett's oesophagus, oesophageal adenocarcinoma	Normal endoscopy (<10%) Oedema, rings, exudates furrows, strictures, crêpe-paper oesophagus, narrow caliber oesophagus	Normal endoscopy (<10%) Oedema, rings, exudates, furrows, strictures, crêpe-paper oesophagus, narrow caliber oesophagus
<b>Histology and Inflammatory cells</b>	Usually < 5–10 eos/HPF Neutrophils, lymphocytes, low- grade eosinophilia	> 15 eos/HPF Eosinophils and mast cells	> 15 eos/HPF Eosinophils and mast cells
<b>Oesophageal acid exposure on pH monitoring</b>	Mostly positive	Positive and negative	Negative and positive
<b>Primary treatment</b>	Inhibitors of gastric acid secretion, including PPI, surgical fundoplication	PPI therapy, unclear whether other inhibitors of gastric acid secretion are effective	Topical steroids Elimination diet
<b>Aetiology</b>	Reflux of gastric contents	Unclear	Food/airborne allergens
<b>Type of immune response/ involved chemo/cytokines</b>	Th1 IL-8, MCP-1, RANTES	Th2 Eotaxin-3, IL-5, IL-13	Th2 Eotaxin-3, IL-5, IL-13
<b>EoE transcriptome panel</b>	Not expressed	Similar expression to EoE	Similar expression to PPI-REE
<b>Specific molecular effect of therapy</b>	-	PPI downregulate Th2 inflammation and normalize EoE gene expression	Topical steroids downregulate Th2 inflammation and normalize EoE gene expression

**Table 2**

## Proposal for Updated Diagnostic Criteria for EoE.

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<b>1</b>	<b>Symptoms of oesophageal dysfunction</b> (dysphagia/food impaction in adults; abdominal pain, nausea, reflux-like symptoms, feeding difficulties, growth failure, dysphagia in children)
<b>2</b>	<b>Baseline oesophageal eosinophil-predominant inflammation</b> (characteristically consisting of a peak value of $\geq 15$ eos/HPF) <b>limited to the oesophagus.</b>

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- Baseline endoscopy should be preferably performed off PPI therapy to better understand the patient profile in case of further response to PPI therapy.
- Other local and systemic causes of esophageal eosinophilia should be ruled out: eosinophilic gastroenteritis, Crohn's disease, hypereosinophilic syndrome, parasites, drug hypersensitivity, achalasia, vasculitis, pemphigoid, connective tissue disorders, graft-versus-host disease.
- Biopsies from the antrum and/or duodenum should be obtained in all children and in adults with gastrointestinal symptoms or endoscopic abnormalities
- A diagnosis of EoE in patients based solely on histology, without clinical and endoscopic features compatible with EoE, might be questionable
- Routine oesophageal pH monitoring is not recommended in the diagnostic work-up of EoE.
- A majority of EoE patients will achieve symptom response and histological remission ( $< 15$  eos/HPF) on PPI, topical steroid or dietary intervention

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**Table 3**

PPI doses and duration and response rates in prospective studies evaluating PPI-REE.

First author, year of publication	Drug, doses	Dosing interval	Duration	Histological remission rates after PPI therapy (definition)
Peterson KA, 2010 <sup>[30]</sup>	Esomeprazole 40 mg	Once daily	8 weeks	33% (< 5 eos/HPF) 50% (< 15 eos/HPF)
Molina-Infante J, 2011 <sup>[4]</sup>	Rabeprazole 20 mg	Twice daily	8 weeks	50% (< 15 eos/HPF)
Francis DL, 2012 <sup>[46]</sup>	Esomeprazole 40 mg	Twice daily	6 weeks	61% (average < 5 eos/HPF)
Moawad FJ, 2013 <sup>[31]</sup>	Esomeprazole 40 mg	Once daily	8 weeks	33% (< 7 eos/HPF)
Dellon ES, 2013 <sup>[7]</sup>	Any of the PPI drugs at 20–40 mg	Twice daily	8 weeks	36% (< 15 eos/HPF)
Vazquez-Elizondo G, 2013 <sup>[32]</sup>	Omeprazole 20 mg	Twice daily	8 weeks	25% (< 5 eos/HPF) 56% (< 15 eos/HPF)
Molina-Infante J, 2014 <sup>[9]</sup>	Omeprazole 40 mg	Twice daily	8 weeks	43% (< 15 eos/HPF)
Van Rhijn BD, 2014 <sup>[21]</sup>	Esomeprazole 40 mg	Twice daily	8 weeks	50% (< 15 eos/HPF)
Gutiérrez-Junquera C, 2015 <sup>[33]</sup>	Esomeprazole 1 mg/kg/dose	Twice daily	8 weeks	47% (< 5 eos/HPF) 68.6% (< 15 eos/HPF)