Proton pump inhibitor-responsive esophageal eosinophilia: still a valid diagnosis?

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Purpose of review
To update rapidly evolving concepts regarding the controversial entity of 'proton pump inhibitor (PPI)-responsive esophageal eosinophilia,' referring to patients with clinical, endoscopic and histologic features of eosinophilic esophagitis (EoE) who achieve remission on PPI therapy.

Recent findings
Up to half of pediatric and adult patients with typical EoE symptoms and histology achieve clinicopathologic remission on PPI therapy, irrespective of whether esophageal pH monitoring demonstrates abnormal acid reflux. In patients with clinical and histologic features of EoE, genotypic and phenotypic features of PPI responders and nonresponders are virtually indistinguishable, and different from those of patients with gastroesophageal reflux disease. In PPI responders, PPIs effects on esophageal Th2 inflammation and gene expression are similar to those of topical steroids in PPI nonresponders. These therapies, along with diets, recently have been shown to be potentially interchangeable in two small series.

Summary
Proton pump inhibitor-responsive esophageal eosinophilia is an inappropriate disease descriptor, arbitrarily based on a response to a single drug, and should be abandoned. Patients who have esophageal eosinophilia and esophageal symptoms that resolve with PPI therapy have phenotypic, molecular, mechanistic, and therapeutic features indistinguishable from similar patients who do not respond to PPIs. These patients with PPI responsiveness should be considered within the spectrum of EoE.

Keywords
eosinophilic esophagitis, esophageal eosinophilia, gastroesophageal reflux disease, proton pump inhibitor

INTRODUCTION

In the first consensus guidelines for the diagnosis and management of eosinophilic esophagitis (EoE) published in 2007, EoE diagnostic criteria included symptoms of esophageal dysfunction, esophageal eosinophilic infiltration [defined by ≥15 eosinophils per high power field (eos/HPF)], and either absence of response to proton-pump inhibitor (PPI) therapy or normal esophageal acid exposure on pH monitoring [1]. These guidelines suggested that symptomatic patients with esophageal eosinophilia who responded to PPIs or had abnormal acid reflux suffered from gastroesophageal reflux disease (GERD), not EoE. This dichotomous diagnostic criterion assumed that GERD and EoE were mutually exclusive disorder. However, this assumption was counterintuitive, since both diseases commonly affect young males, so the likelihood of their coexistence was *a priori* high.

In 2011, the first prospective series systematically evaluating PPI therapy in patients who had esophageal eosinophilia with EoE symptoms showed that up to 50% responded to PPIs [2]. Furthermore, clinical, endoscopic and histologic features were indistinguishable among the PPI responders and nonresponders. In disagreement with the 2007 consensus guidelines, the investigators found considerable overlap between GERD (determined by esophageal pH monitoring) and EoE. Among patients with abnormal acid reflux by pH

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KEY POINTS

- Response to PPI therapy was judged to rule out EoE in the diagnostic criteria for EoE in guidelines published in 2007, 2011, and 2013.
- In patients with symptoms and histologic signs of EoE, evolving research has demonstrated that phenotypic, molecular, mechanistic, and therapeutic features do not reliably distinguish between PPI responders and nonresponders.
- Updated position papers and upcoming guidelines have included responders to PPI therapy within the spectrum of EoE, abandoning the term PPI-responsive esophageal eosinophilia.

monitoring, 20% did not respond to PPI therapy. Conversely, 33% of patients with normal esophageal pH monitoring results responded to PPIs. This study led to significant changes in subsequent EoE diagnostic guidelines [3,4], and esophageal pH monitoring was eliminated as a negative diagnostic criterion for EoE [3]. Nevertheless, a response to PPI therapy was still considered sufficient to rule out EoE in 2011 [3] and 2013 [4], even though evidence was mounting that PPI responders had virtually the same clinical, endoscopic, histologic, and molecular features as EoE patients who did not respond to PPIs [5,6].

For these intriguing patients, who looked like EoE patients even though they did not have EoE according to the arbitrary consensus guidelines, the artificial term 'PPI-responsive esophageal eosinophilia' (PPI-REE) was coined. This disease descriptor was arbitrarily based on the response to a given drug, without considering the intrinsic characteristics of the condition. Thus, a dubious, provisional diagnostic category was created with the expectation that future research eventually would clarify the molecular and mechanistic basis of PPI-REE. Over the past 3 years (2014–2016), state-of-the-art research, mostly in adult patients, has confirmed that these patients are likely EoE patients. The evolving concepts on the diagnosis of these patients over the past decade are illustrated in Fig. 1. The aim of this review is to update knowledge on this controversial entity and, through our review of available data, we argue that the artificial and arbitrary term 'PPI-REE' should be discarded.

RESPONSE TO PROTON PUMP INHIBITOR THERAPY: QUITE COMMON, FREQUENTLY OVERLOOKED

A first systematic review with meta-analysis including 619 patients with suspected EoE (based on their symptoms and esophageal histology) recently has been published [7▪▪]. Up to 50% of children and adults with suspected EoE achieved both clinical and histologic remission with PPI therapy. Of note, the response to PPI therapy occurred irrespective of whether esophageal pH monitoring results were

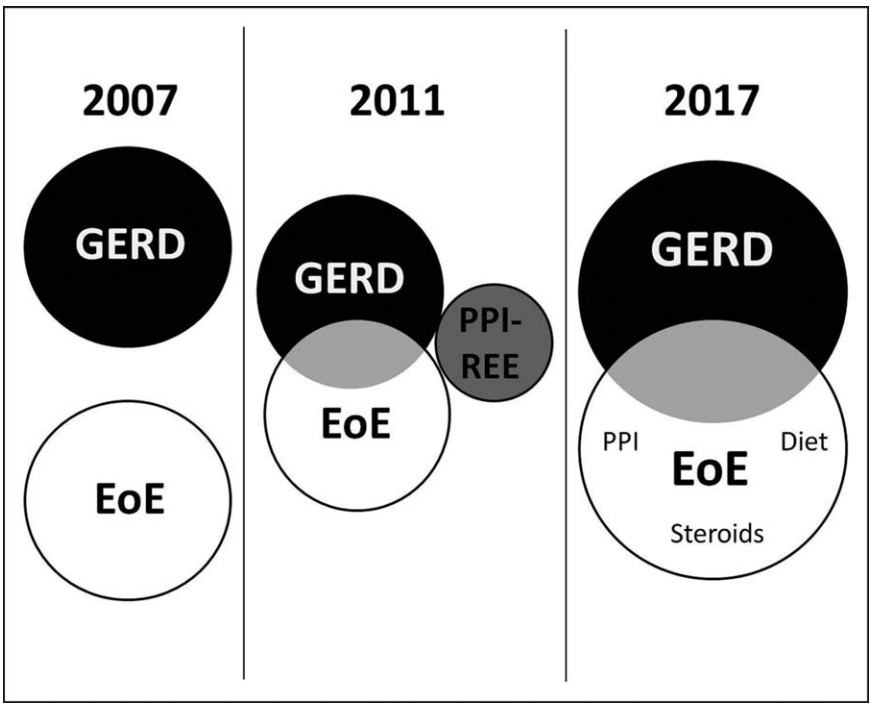

FIGURE 1. Evolving considerations on the relationship between GERD, EoE, and response to PPI therapy over the past decade. EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

normal or abnormal. These findings are entirely coincident with those of the first prospective series from 2011 [2]. EoE patients responsive to PPI therapy also have been reported in 2016 in reports from Korea [8,9], Japan [10], and Australia [11].

One of the most striking findings in recent literature is the lack of compliance with consensus guidelines published in 2007 [1], 2011 [3], and 2013 [4], specifically regarding the requirement for a failed trial of PPI therapy before making a diagnosis of EoE. A systematic review on studies evaluating the prevalence of EoE in adults between 2008 and 2015 [12▪] has shown that, contrary to the guideline recommendations [1,3,4], a PPI trial was not administered before making the diagnosis of EoE in 60% of studies. These important data likely underscore the confusing scenario created by arbitrary and, arguably, illogical guidelines.

The lack of well conducted studies evaluating the rate of response to PPI therapy in children with EoE is remarkable, since pediatricians have often taken the lead in conducting EoE studies on topical steroid therapy [13,14], empiric diets [15,16], and even on PPI therapy before 2011 [17,18]. One of the most important contributions of 2016 is the first prospective series evaluating response to systematic PPI therapy in children with suspected EoE [19▪▪]. Among 51 such children, 35 (68%) achieved histological remission (defined by <15 eos/HPF) with PPIs, whereas complete symptomatic remission was accomplished in 24 (47%). As in earlier studies, esophageal pH monitoring results did not adequately predict the response to PPI therapy. As recently reported with other therapeutic modalities like topical steroids and diet, this important study underscores that EoE is likely the same disease in children and adults.

MOLECULAR AND GENETIC BASIS UNDERLYING RESPONSE TO PROTON PUMP INHIBITOR THERAPY

A response to PPI therapy was assumed to establish the diagnosis of GERD in 2007 [1], and was still out of the EoE spectrum in 2011[3] and 2013[4]. Nevertheless, the phenotypic expression of PPI responders and nonresponders (including clinical, endoscopic, esophageal pH monitoring, and histologic features) is virtually indistinguishable [2,5,6,7▪▪,10,11,17,18,19▪▪]. Hence, it would be important to characterize the molecular and genetic basis of patients with suspected EoE who respond to PPIs. EoE is well known to be 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 esophageal mucosa. When activated, the eosinophils cause local tissue damage and recruit and/or activate other effector cells, such as mast cells, which are key modulators of esophageal fibrous remodeling [20]. Moreover, a molecular EoE diagnostic panel has been recently developed by using whole-genome transcript expression profiling of esophageal tissue [21]. This panel comprises 94 EoE genes and accurately distinguishes patients with EoE from GERD and control subjects [21]. Regarding the molecular basis, baseline expression of markers of eosinophilic inflammation (eosinophil derived major basic protein and CCL26), and genes modulating mast cell signature or involved in type 2 (Th2) associated allergic inflammation (including CCL26, IL-5, IL-13, thymic stromal lymphopoietin and periostin (POSTN)) in esophageal tissue have demonstrated largely overlapping patterns between nonresponders and responders to PPI therapy [5,22,23]. A first milestone study from the United States [24] and a very recent study from Japan [25▪▪] have demonstrated that, unlike GERD patients, responders to PPI therapy have a transcriptome that nearly completely overlaps with that in nonresponders to PPIs, including the hallmark EoE genes for eosinophil chemotaxis (*CCL26*), barrier molecules (desmoglein *DSG1*), tissue remodeling (*POSTN*), and mast cells (*CPA3*). Recent genome wide association studies in EoE have identified two replicated susceptibility loci at 2p23 and 5q22, regions that encode the epithelial gene products *CAPN14* and *TSLP* [26–28]. Susceptibility loci were equally present in PPI responders and nonresponders, reinforcing the idea that both groups of patients, independent of PPI stratification, share a similar molecular and genetic etiology.

Moreover, recent clinical studies have shown that PPI monotherapy in PPI-REE patients can almost completely reverse the Th2 signature (CCL26, IL-5, IL-13, POSTN) [5,23,24] while concurrently inducing normalization of 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*) [24]. These effects are similar to those of topical steroids [29,30] or anti-IL-13 biological drugs in EoE patients [31]. Finally, two recent series have described EoE patients who initially responded to diet and topical steroid therapy and who were later found to respond to PPI therapy, and vice versa [32,33▪]. Therefore, PPI therapy has similar clinical, histologic, molecular, and genetic effects in PPI-responto those shown for conventional EoE therapies (eg, diet and steroids).

PROTON PUMP INHIBITOR-REE? LET'S CALL A SPADE A SPADE

All the aforementioned data provide no rational basis for making a distinction between patients with symptomatic esophageal eosinophilia based solely on their different response to a single drug. It seems counterintuitive to differentiate responders and nonresponders to PPI therapy when their phenotypic, molecular, mechanistic, and therapeutic features are virtually identical. As such, the requirement to provide a distinct name among indistinguishable patients for the subgroup that responds to PPIs is questionable, at the very least [34]. If there is no azathioprine-responsive inflammatory bowel disease (we call it Crohn's disease), short beta agonists-responsive bronchial eosinophilia (we call it asthma) or budesonide-responsive colonic lymphocytosis (we call it microscopic colitis), why should we continue to distinguish PPI-REE from EoE?

A recent international consensus position paper endorsed by pediatricians, allergists, immunologists and adult gastroenterologists, has recently supported this concept of abandoning the artificial term 'PPI-responsive esophageal eosinophilia,' [35▪▪]. Contrary to 2011 guidelines, a response to PPI cannot be considered a diagnostic exclusion criterion for EoE anymore, since PPI therapy is now deemed to be a potential therapeutic agent for all patients with clinical, endoscopic and histologic features of EoE. All these changes in diagnostic criteria, relying on clinical and histologic features of EoE rather than its response to a medication, have been included in the soon to be published, first evidence-based guidelines on the diagnosis and management of EoE in children and adults [36▪▪]. These updated diagnostic criteria for EoE are displayed in Table 1.

MAINTENANCE PROTON PUMP INHIBITOR THERAPY

Until recently, the sustained efficacy of PPI therapy in initial responders to PPIs was limited to two retrospective series comprising six pediatric patients with recurrence of esophageal eosinophilia and symptoms while on maintenance PPI therapy [37,38]. A first long-term follow-up, multicenter study in 2015 including 75 adult patients demonstrated that all patients who temporarily discontinued PPI therapy had symptom and/or histological relapse [39▪]. The majority of patients (73%) maintained histological remission after at least 1 year on PPIs with the dosage tapered to the minimum effective clinical dose [39▪]. A *CYP2C19* rapid metabolizer genotype and allergic rhinitis were independent predictors of loss of PPI responsiveness. Among relapsers, most regained histological remission after dose escalation, suggesting that some patients continue to require maintenance high-dose PPI treatment [39▪]. Another recent prospective series has confirmed these findings with a step-down approach (80% of adult patients on sustained remission with tapering PPI doses) [40]. A first prospective study in children has also replicated these findings from adults studies, showing that 78% of PPI responders remain in clinico-pathologic remission at 1-year follow up on low maintenance PPI doses [19▪▪].

RESEARCH AGENDA FOR THE FUTURE

Type, doses, interval dosing and duration for acid suppressive drugs

An important recent breakthrough is the first series of four patients with suspected EoE unresponsive to PPI therapy, who achieved complete remission on vonoprazan [41▪]. Vonoprazan is a novel potassium-competitive acid blocker with a different mechanism of action than PPIs. Vonoprazan has a more potent and sustained acid suppressive effect and is less affected by *CYP2C19* polymorphisms than PPIs. The main criticism of this study relates to the adequacy of the PPI doses and interval dosing regimens (esomeprazole 20 mg daily), which raises concerns about underestimation of the response to PPI

Table 1. Updated diagnostic criteria for eosinophilic esophagitis in children and adults in 2017 [36▪▪]

(1) Clinic features: symptoms of esophageal dysfunction
Feeding difficulties, growth failure, abdominal pain, nausea, reflux-like symptoms in toddlers and younger children.
Dysphagia and/or food impaction in older children, adolescents, and adults
(2) Histologic features: esophageal eosinophil-predominant inflammation
Limited to the esophagus.
Detection of 15 eosinophils in at least one high power field.
(3) Other local/systemic causes of esophageal eosinophilia should be ruled out, including eosinophilic gastroenteritis, Crohn's disease, hypereosinophilic syndrome, parasites, drug hypersensitivity, achalasia, vasculitis, pemphigoid, connective tissue disorders, graft-versus-host disease.

therapy. This dose might suffice for mild reflux symptoms, but not for a chronic immuno-allergic disorder. All available guidelines recommend a minimum dose of 20–40 mg twice daily for a minimum of 8 weeks to adequately assess the response to PPI therapy [1,3,4,36▪▪]. In this regard, a case report has recently described a patient who achieved histologic improvement but no remission after a 2-month course of PPI therapy (dexlansoprazole 60 mg once daily), and who finally achieved remission after four months on the same drug in the same dose [42]. This study suggests the existence of a subset of slow responders to PPIs who may need more than 2 months for complete resolution. Undoubtedly, more studies on this issue and on vonoprazan are warranted.

Potential interactions between gastroesophageal reflux disease and eosinophilic esophagitis

Presently, EoE is defined as an immune/antigen-driven disease, and no allergic disease has been shown to respond completely to acid suppressive drugs. Some recent studies have advocated the importance of GERD as a potential trigger for EoE that responds to PPIs [41▪,43,44]. GERD and EoE, triggering Th1-mediated and Th2-mediated immune response, respectively, are not mutually exclusive disorders anymore [34]. Extrapolating data from studies on asthma, Fig. 2 summarizes potential mechanisms of interactions between Th1 and Th2 inflammatory responses [45].

Mechanisms involved in response of eosinophilic esophagitis to proton pump inhibitor therapy

The most accepted hypotheses for the mechanism whereby PPIs are beneficial in EoE include their direct acid suppressive effects or their anti-inflammatory effects that are independent of acid suppression [44]. PPI therapy has recently been shown to down-regulate Th2 allergic esophageal inflammation [5,23,24] but it is not certain whether this is a direct (primary anti-inflammatory effect) or indirect (primary acid inhibition leading to secondary inflammation healing) effect.

As for acid suppression, it is important to note that GERD has been historically deemed to develop

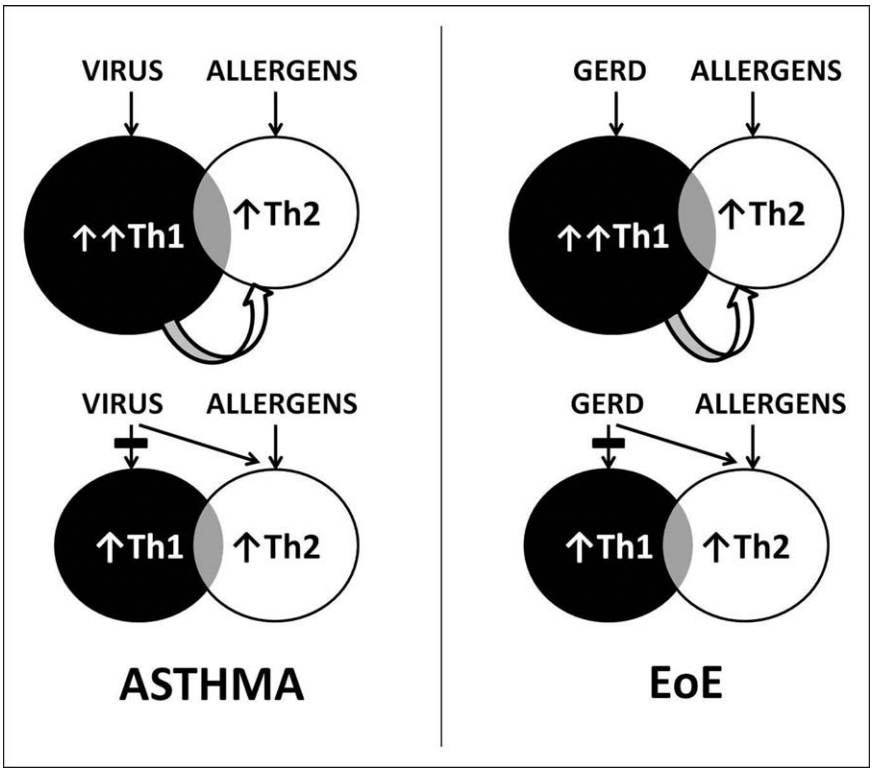

FIGURE 2. Interactions between GERD (Th1 immune response) and EoE (Th2 immune response). Extrapolation from development of immune response in asthma [45]: overexpression of Th1 activity and epithelial integrity impairment may promote subsequent recruitment of Th2 cells, providing a setting for enhanced allergen responsiveness (top figures). Alternatively, nonallergen-driven local production of Th1 cytokines (eg, viruses in airway tract, GERD in esophagus) may be redirected to production of Th2 cytokines (bottom figures). EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

as a chemical injury starting at the epithelial surface. The acid-induced death of surface cells is assumed to stimulate hyperplasia of papillae and basal cells, provoking an inflammatory Th1 cascade, mainly made up of granulocytes and lymphocytes. If GERD is assumed to be the event that triggers EoE in patients who respond to PPIs, and PPIs are thought to act solely through gastric acid suppression, then it is crucial to appreciate that these PPI responders do not have just conventional GERD. As mentioned, EoE patient who respond to PPI therapy (ie, PPI-REE – a term we prefer not to use) exhibit the same genetic and molecular Th2 features as EoE patients who do not respond to PPIs [35▪▪]. Of note, an alternative concept for GERD pathogenesis recently has been proposed based on an earlier study in a murine model [46] and later confirmed in a study in humans [47▪▪]. The authors demonstrated that refluxed gastric material did not appear to damage esophageal epithelial cells directly, but stimulated them to secrete cytokines that attracted immune cells, which ultimately damaged the mucosa. In other words, GERD might be a cytokine-mediated disease rather than a chemical injury-mediated disease. This revolutionary new concept opens up a number of hypotheses to explain responsiveness to acid suppressive drugs, including PPIs and vonoprazan. Might there be an 'allergic' form GERD, in which gastroesophageal reflux incites a conventional Th1 response that triggers Th2 inflammation in a subset of atopic patients? (See Fig. 2) In the first study to demonstrate esophageal anti-inflammatory effects of PPI therapy, esophageal squamous cells from EoE patients and from GERD patients both exhibited a similar increase in the expression of the eosinophil chemoattractant eotaxin-3 when they were stimulated with a Th2 cytokine (IL-4), suggesting that the esophagus of GERD patients might be driven to a Th2 inflammatory cascade given the appropriate stimulus [48].

Regarding anti-inflammatory effects, omeprazole, in concentrations *in vitro* equivalent to those achieved in blood with conventional dosing, inhibits Th2 cytokine-stimulated eotaxin-3 secretion in isolated esophageal epithelial cells by blocking binding of the transcription factor STAT6 to the eotaxin-3 promoter [48]. Anti-inflammatory effects of PPIs have been demonstrated only in studies using EoE cells *in vitro*. While omeprazole *in vitro* is present in the culture media for up to 48 h, the short half-life for PPI drugs (1–2 h active) makes it unclear if a sustained anti-inflammatory effect is maintained *in vivo*. Nevertheless, recent studies showing PPIs downregulating effects of eotaxin-3 in murine asthma [49] and chronic rhinosinusitis with nasal polyps, both *in vitro* and *in vivo* [50▪], corroborate that PPIs might have anti-inflammatory effects unrelated to acid suppression. Further studies evaluating these novel anti-inflammatory effects of PPIs are definitely warranted.

CONCLUSION

PPI-REE is an inappropriate disease descriptor, arbitrarily based on a response to a single drug, and should be abandoned. Unlike typical GERD patients, patients who have esophageal eosinophilia and esophageal symptoms that resolve with PPI therapy have phenotypic, molecular, mechanistic, and therapeutic features indistinguishable from similar patients who do not respond to PPIs. These patients with PPI responsiveness should be considered within the spectrum of EoE.

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Conflicts of interest

This manuscript has been seen, reviewed, and approved by all contributing authors. The authors have no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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