Effect of Proton Pump Inhibitor on Esophageal Eosinophilia

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ABSTRACT

Objective: Differentiation between the common etiologies of dense esophageal eosinophilia such as gastroesophageal reflux disease (GERD) and eosinophilic esophagitis can be difficult. We hypothesized that histologic features may provide diagnostic clues concerning the etiology of esophageal eosinophilia.

Methods: We performed a retrospective chart review of 204 children with the diagnosis of esophagitis characterized by ≥15 eosinophils (eos) per high-power field (HPF) in at least 1 biopsy. We then restricted our analysis to subjects who had received at least 8 weeks of only proton pump inhibitors (PPIs) followed by endoscopy and who had a clinicopathologic response to this treatment. Symptoms, endoscopic findings, and pathologic descriptions were reviewed and an eosinophil peroxidase (EPX) index was determined to assess for degranulation/eosinophil activation.

Results: Of the 204 identified charts, 7 subjects identified met the inclusion criteria. Five of these 7 patients showed a clinicopathologic response to PPIs after their follow-up endoscopy, (mean peak eosinophil count: 92 vs 5 eos/HPF, and EPX index: 39.2 vs 14.6, pre- and posttreatment, respectively). Two patients experienced initial resolution of symptoms and esophageal eosinophilia with PPI therapy; however, within 17–23 months they redeveloped symptoms and esophageal eosinophilia while receiving PPI therapy at the time of a third endoscopy (mean peak eosinophil count: 40 vs 11 vs 36 eos/HPF, and EPX index: 44 vs 21 vs 36.5, pre-, post- and posttreatment, respectively). No clinicopathologic features or degranulation patterns differentiated subjects with GERD/PPI responsive esophageal eosinophilia from those who had transient response to PPI treatment.

Conclusions: No clinicopathologic features differentiated subjects who responded to PPI treatment. PPI treatment can be helpful to exclude GERD and PPI responsive esophageal eosinophilia but long-term follow-up is critical in the management of esophagitis.

Key Words: eosinophil, eosinophil peroxidase, gastroesophageal reflux disease, histopathology

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Esophageal eosinophilia is a histologic finding associated with gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE). Initial studies of children with GERD identified a distal eosinophilic infiltration of the squamous epithelium but the exact numbers and distribution defining GERD are not certain (1). Over the past decade, the diagnosis of EoE developed a new focus on how esophageal eosinophilia is defined and even more importantly, what mechanisms underlie the inflammatory process.

This new-found interest specifically concerns the role of proton pump inhibitor (PPI) treatments in determining etiologies. In this regard, PPI treatment has created a certain degree of clinical confusion and scientific controversy. PPIs can be costly and doses necessary to effectively treat eosinophilia are not certain. Increasing clinical experiences have also identified a subgroup of patients with esophageal eosinophilia who experience symptoms related to esophageal dysfunction and exhibit clinicopathologic responses to PPI treatment; when performed, pH impedance studies are normal. Whether this inflammation is related to GERD that has escaped technical detection or alternative mechanisms is not certain; however, a clinical descriptor, PPI responsive esophageal eosinophilia (PPIREE), has arisen to describe this patient population. To add further intrigue, a recent report described 4 patients who experienced an initial response to PPI treatment but subsequent clinicopathologic recurrence while receiving PPI treatment (2).

Thus, differentiation of inflammation associated with GERD, EoE, and PPIREE is not a straightforward task and no definitive clinical pathway to differentiate etiologies of esophageal eosinophilia has been identified. Because EoE is a chronic disease that is treated with lifelong use of diet restriction or topical corticosteroids, we have aggressively sought to differentiate between these conditions with a diagnostic trial of PPIs and/or use of pH monitoring probes.

To determine whether any feature may help to predict which patients will clinically and histologically respond to PPI treatment, we performed a retrospective analysis of children with esophagitis who had undergone pre- and post-PPI treatment endoscopies. We hypothesized those pediatric patients who demonstrated a clinicopathologic response to PPI treatment (ie, diagnosis of GERD or PPI responsive eosinophilia) would have distinct pathologic features.

METHODS

Subject Selection

A retrospective chart review was performed of patients who were evaluated in the Digestive Health Institute, Section of Pediatric Gastroenterology, Hepatology, and Nutrition at Children's Hospital Colorado from 2000 to 2011who had received a diagnosis of esophagitis and had undergone at least 2 esophagogastroduodenoscopy (EGD) procedures to assess the mucosa before and after PPI treatment ($1-2\,mg\cdot kg^{-1}\cdot day^{-1}$) for at least 8 weeks. Esophagitis was defined as >15 eosinophils (eos) per high-power field (HPF) in at least 1 biopsy (distal, middle, or proximal) specimen as described

previously (3,4). Subjects were excluded from this analysis if they had incomplete treatment records, dietary modifications, and/or initiation of topical steroid therapy (budesonide, fluticasone, ciclesonide) between first and second endoscopy or had gastrostomy tubes placed for elemental diet as a treatment (5–7). Medical records were reviewed and clinical features recorded to include presenting symptoms, history of allergic diseases, and endoscopic findings such as linear ridging, edema, ulcerations, microabscesses, furrows, and esophageal stricture.

Patients were classified as PPI responders if after PPI treatment their second mucosal biopsy showed $\leq$15 eos/HPF, and PPI nonresponders if they continued to have inflammation with $>$15 eos/HPF. PPI responders received a diagnosis of GERD or PPIREE. Non-PPI responders received a diagnosis of EoE.

Histologic Assessment and Staining

All of the esophageal tissue sections were assessed independently by a pathologist (K.C.) and 2 other research investigators (S.S., J.M.). Reactive changes (rete peg elongation, basal cell hyperplasia), eosinophil number (mean of 15 HPF and peak number counted in single most densely inflamed HPF at $\times$40 magnification-field size 0.26 mm^2, data presented as mean $\pm$ range), eosinophil degranulation, superficial layering of eosinophils, and presence of microabscesses were measured as previously described (8–11). Tissues were assessed for intercellular edema, lamina propria fibrosis, and presence of additional immune cells. Immunostaining was completed with an eosinophil peroxidase (EPX) antibody as previously described. (12) Briefly, each section underwent staining with a monoclonal antibody for EPX (hybridoma MM25–82.2.1; Mayo Clinic Arizona, Scottsdale). Slides were assessed for eosinophil patchiness, degranulation, and intact eosinophils to determine an EPX index. The present study was approved by the institutional review board at the University of Colorado (COMIRB 07–0888).

RESULTS

Subject Identification

In the present study, we sought to determine the effect of PPI treatment alone on patients with dense esophageal eosinophilia and determine whether any histologic features helped discriminate between these clinical responses. Screening of pathology and medical records identified 204 subjects with a diagnosis of esophagitis who had at least 2 EGDs performed. Primary indications for EGDs included regurgitation, feeding difficulties, dysphagia, vomiting, heartburn, failure to thrive, abdominal pain, and foreign body impaction. The majority of subjects (169) were excluded because they received a diagnosis of EoE and undergone a variety of treatments in addition to PPI treatment before their second endoscopy (Fig. 1).

Of the remaining 35 patients, who had undergone at least 2 EGDs and received only PPI treatment, 27 (77%) did not have resolution of symptoms or esophageal eosinophilia (PPI nonresponders), and thus received a diagnosis of EoE. Resolution of esophageal eosinophilia was determined by $<$15 eos/HPF in their follow-up biopsies. The final 8 patients (23%) showed resolution of symptoms and esophageal inflammation after PPI treatment (PPI responders). One of these patients was excluded because of unavailable biopsies for EPX analysis. These PPI-responsive patients received a diagnosis of either GERD or PPIREE because no pH studies were performed to differentiate them. Five of these patients continued with PPI treatment and remained asymptomatic after an average of 8 months of follow-up. Two of the remaining patients continued receiving PPI treatment and underwent a third endoscopy because of recurrence of symptoms 17 and 23 months after their second endoscopy. Both of these patients demonstrated dense eosinophilia with mean peak eosinophil counts of 52 and 21 eos/HPF and EPX indices of 40 and 33 at the time of their first and third EGD, respectively. These subjects were treated with dietary elimination and topical corticosteroids and experienced clinical remission. Consistent with a previous report, these 2 subjects had a transient response to PPI and were ultimately given a diagnosis of EoE (2). Through the rest of the present study, we will refer to PPI responders as having either GERD or PPIREE and these transient PPI responders as having EoE. The 27 patients who were PPI nonresponders were clinically defined as having EoE and their histologic findings before and after PPI are presented in Table 1. These patients had a mean peak eosinophil count 43 $\pm$ 22 eos/HPF at the time of their first biopsy and after PPI therapy had a mean peak eosinophil count 62 $\pm$ 36 eos/HPF.

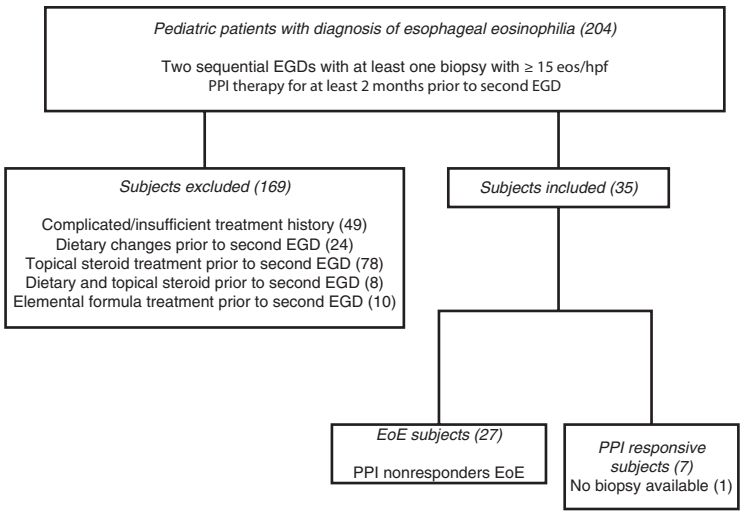

FIGURE 1. Flow diagram of included and excluded subjects.

Clinical Features of Subjects With GERD/PPIREE and EoE

When comparing GERD/PPIREE (5) with EoE (2), no clinical differences were identified in ethnicity, presenting symptom, history of atopic diseases, or initial endoscopic findings (Table 2). Symptoms of dysphagia, coughing, or abdominal pain were not specific to either patients with GERD/PPIREE or EoE. No specific endoscopic findings differentiated GERD/PPIREE from EoE (Table 2).

Histologic Features of the Untreated Esophageal Mucosa of Subjects With GERD/PPIREE and EoE

GERD/PPIREE had a higher pretreatment peak eosinophil counts compared with EoE peak eosinophil counts, which are shown in Table 3. Additional features of epithelial inflammation, including eosinophil degranulation, eosinophil microabscesses, superficial layering of eosinophils, intercellular epithelial edema, lamina propria fibrosis, presence of other immune cells, and reactive changes including basal cell hyperplasia and rete peg elongation were present in both GERD/PPIREE and EoE tissues and did not display any significant differences. Total EPX indices as well as examination of subcategories within the EPX index scoring paradigm (patchiness, degranulation, eosinophil number) were not different between GERD/PPIREE and EoE (Table 3).

Features of Transient PPI Responders

Evaluation of the 2 subjects who had recurrence of symptoms and esophageal eosinophilia while continuing PPI treatment did not reveal any distinguishing clinicopathologic features. At the time of their third endoscopy, no differences were seen in comparison to their initial presenting symptoms (abdominal pain, vomiting, and coughing), degree of eosinophilia (35 vs 52 and 45 vs 21 for first and third endoscopy, respectively for each subject), or EPX index (48 vs 40 and 40 vs 33 for first and third endoscopy, respectively for each subject).

DISCUSSION

Because of complexities surrounding use of PPI treatment to determine the etiology of esophageal eosinophilia, we performed a retrospective study covering a time span of 11 years that documented the mucosal response to PPI treatment in well-defined children with dense esophageal eosinophilia. The goal of our study was to determine whether any of these features could help to guide clinical practice in distinguishing between these emerging patient populations. Our search yielded a small number of subjects who did not identify key clinical or histologic features that suggested nonresponsiveness or responsiveness to PPIs but 3 key clinical observations were made. First, 77% (27/35) of patients with dense esophageal eosinophilia showed no clinicopathologic response to PPI supporting the lack of effect of PPIs on esophageal inflammation in EoE (3). Second, PPI treatment reduced dense esophageal eosinophilia in 23% (8/35) of patients treated, thus supporting the concept that dense eosinophilic inflammation may be PP responsive (13) and that the use of PPI is helpful as a diagnostic test for EoE. Third, a transient PPI response was found in 6% (2/35) of children with dense esophageal eosinophilia, thus emphasizing the importance of close follow-up of patients with esophagitis (2). Taken together, these findings support the utility of PPIs in the evaluation of dense esophageal eosinophilia but also indicate that patients with esophagitis should have long-term follow-up.

PPIs have been helpful to differentiate mucosal inflammation associated with EoE from other causes. In 2 retrospective series of subjects with dense esophageal eosinophilia ($\geq$15 eos/HPF), >40% of subjects responded histologically to PPI and no demographic, presenting symptoms, pH study, endoscopic, or histologic findings differentiated PPI responders from nonresponders (14,15). In a prospective series of 35 adults with dysphagia and dense esophageal eosinophilia (35–165 eos/HPF), 50% had symptomatic and histologic remission with administration of PPI (16). Our results support these findings that further describe a population of patients presenting with dense esophageal eosinophilia who experience a successful response to PPI monotherapy. Our study identified that 23% of these pediatric patients have either GERD or PPIREE and support the utility of PPI as a part of the diagnostic paradigm for EoE (3,4). In addition, our study is consistent with previous works that have not

TABLE 1. PPI nonresponders—EoE histologic assessment

Patient	Peak eosinophil count pre/post	Degranulation	Reactive changes	Microabscess	Patient	Peak eosinophil count pre/post	Degranulation	Reactive changes	Microabscess
1	50/severe	Y/Y	Y/Y	Y/N	15	Moderate/40	N/N	Y/Y	N/N
2	15/60	N/Y	N/Y	N/Y	16	15/55	—/Y	—/Y	—/N
3	Moderate/moderate	Y/Y	Y/Y	N/N	17	50/15	Y/N	Y/Y	Y/N
4	40/40	Y/Y	Y/Y	N/N	18	20/60	N/Y	Y/Y	N/Y
5	30/57	Y/Y	Y/Y	N/N	19	60/23	Y/Y	Y/Y	Y/Y
6	Mild/150	N/Y	Y/Y	N/Y	20	58/48	Y/Y	Y/Y	Y/N
7	49/57	Y/Y	Y/Y	Y/N	21	44/100	Y/Y	Y/Y	N/N
8	Mild/15	N/N	N/N	N/N	22	100/100	—/—	—/—	—/—
9	80/35	Y/Y	N/Y	Y/Y	23	50/100	—/Y	—/Y	—/N
10	28/50	N/N	Y/Y	Y/Y	24	72/150	Y/Y	Y/Y	Y/Y
11	20/40	—/Y	—/Y	—/Y	25	Mild/30	—/Y	—/Y	——/N
12	40/80	—/Y	—/Y	—/Y	26	Moderate/95	—/Y	—/Y	—/Y
13	25/55	Y/Y	Y/Y	N/Y	27	35/37	—/Y	—/Y	—/N
14	20/50	Y/Y	Y/Y	Y/Y					

Reactive changes—basal epithelial hyperplasia, rete peg elongation. — = information not available; EoE = eosinophilic esophagitis; PPI = proton pump inhibitor.

TABLE 2. Demographics, clinical symptoms, and endoscopic findings in PPI-responsive patients

Patient no.	1	2	3	4	5	6	7	8
Diagnosis	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	EoE	EoE
Sex	M	F	F	M	M	M	M	M
Years	14	5	2	3	11	7	6	10
Ethnicity	W	W	A	W	W	W	W	W
Atopy	Y	Y	Y	Y	Y	N	Y	Y
Strictures	N	N	N	N	N	N	N	N
Family Hx	Y	N	N	Y	N	N	N	N
PPI dose/kg	1/kg	1/kg	2/kg	1.5/kg	1/kg	2/kg	2/kg, 1/kg*	2/kg, 2/kg*
Symptoms								
EGD 1	Heartburn, dysphagia	Foreign body impaction	Vomiting, diarrhea	Coughing	Vomiting	Vomiting, feeding difficulties	Abdominal pain	Vomiting, coughing
EGD 2	Heartburn, dysphagia	None	None	None	None	None	Abdominal pain, vomiting	Vomiting
EGD 3	NA	NA	NA	NA	NA	NA	Abdominal pain	Dysphagia
Endoscopic appearance								
EGD 1	Normal	Exudate, furrows	Exudate, linear ridging	Exudate	NA	NA	Exudate	Exudate
EGD 2	Normal	Normal	Normal	Normal	NA	Normal	Exudate, linear ridging	Normal
EGD 3	NA	NA	NA	NA	NA		Linear ridging	Exudate, linear ridging, furrows

A = Asian; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; Family Hx = history of same diagnosis in parent; GERD = gastroesophageal reflux disease; NA = not applicable; PPI = proton pump inhibitor; PPIREE = proton pump inhibitor responsive esophageal eosinophilia.

* PPI dose/kg at time of 3rd EGD.

TABLE 3. Histologic assessment of PPI-responsive patients and EPX score

Patient	1	2	3	4	5	6	7	8
Diagnosis	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	GERD/PPIREE	EoE	EoE
PPI treatment	Pre/post	Pre/post	Pre/post	Pre/post	Pre/post	Pre/post	Pre/post/post	Pre/post/post
Eosinophil count (mean)	43/0	54/1	114/0	29/1	5/7	22/0	19/2/30	27/5/11
Eosinophil count (peak)	84/0	108/5	176/0	73/4	17/16	40/0	35/8/52	45/14/21
Degranulation	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N/Y	Y/Y/Y
Microabscesses	N/N	N/N	Y/N	Y/N	N/N	N/N	Y/N/Y	Y/N/N
Superficial layering	Y/N	N/N	Y/N	Y/N	N/N	N/N	Y/N/Y	Y/N/N
Edema	Y/N	Y/N	Y/N	Y/Y	Y/N	N/N	Y/N/Y	Y/Y/Y
Lamina propria present	N/Y	Y/Y	Y/Y	Y/Y	Y/N	—/—	N/Y/Y	Y/Y/Y
Fibrosis	—/N	N/N	Y/N	Y/Y	N/—	—/—	—/N/Y	Y/Y/Y
Reactive changes	Y/N	Y/N	Y/N	Y/N	Y/Y	—/—	Y/Y/Y	Y/Y/Y
Other immune cells	Y/Y	Y/Y	Y/Y	Y/Y	Y/N	—/—	Y/N/Y	Y/Y/Y
EPX analysis								
Patchiness score	8/0	8/2	8/0	4/0	4/2	—/—	8/0/8	8/6/4
Degranulation score	10/0	2/4	8/4	6/4	4/6	—/—	8/0/8	8/8/8
Total EPX scored	50/0	42/22	48/17	24/9	32/25	—/—	48/0/40	40/42/33

— = not available; EoE = eosinophilic esophagitis; EPX = eosinophil peroxidase; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor; PPIREE = proton pump inhibitor responsive esophageal eosinophilia.

identified clinical or histologic pathognomonic findings that distinguish EoE, GERD, and PPIREE (17–23).

The third finding imports the need for close clinical follow-up of patients with recurrent or new symptoms of reflux or dysphagia. Overlap symptoms in GERD and EoE often make it difficult to make a clear diagnosis at the time of presentation and the natural history of EoE continues to be investigated. Our results further characterize an emerging group of patients with transient response to PPI treatment. Dohil et al (2) described 4 children who had an initial endoscopy revealing esophageal eosinophilia, a second endoscopy after 2 months of PPI that documented histologic remission, and a third endoscopy showing recurrence of eosinophilia. Patients were asymptomatic at the time of the second endoscopy and had recurrence of symptoms at the time of the third. Our patients described here experienced the same transient response. Potential explanations for this clinical course include lack of compliance with PPI treatment, missed detection of mucosal inflammation at the time of the second endoscopy, variation in allergenic exposures at the time of the second endoscopy, decreased responses with tapered or low-dose PPI, and diminished effect of PPIs over time. Another possible explanation is that these transient PPI responders may initially present with GERD and later develop EoE. The interaction between GERD and EoE is complex and esophageal eosinophilia from GERD may cause changes in the esophageal epithelium that predispose to the development of EoE at a later time (24). The diagnosis of EoE rests on the identification of appropriate clinicopathologic features and the elimination of other causes of esophageal eosinophilia. The best way to exclude GERD as an etiology for this inflammation remains uncertain. pH monitoring of the distal esophagus can be uncomfortable, costly, and may not capture clinically relevant reflux in a 24-hour period. Use of PPIs can be a diagnostic test but can be costly and compliance may be an issue. In addition, the optimal dose to treat esophageal eosinophilia, especially dense eosinophilic inflammation, is a source of fervent discussion. The emergence of PPIREE has identified another potential mechanism for PPIs anti-inflammatory effect, making one wonder whether PPIs also can target cytokine production. Kedika et al (25) reported that PPIs inhibited interleukin-6, interleukin-8, and tumor necrosis factor-α production from esophageal epithelial cells in vitro. Cheng et al (26) demonstrated the effect of omeprazole on eotaxin-3 production from esophageal epithelia in vitro also. Thus, these descriptions of transient clinicopathologic response to PPIs who eventually were found to have EoE add to the complexity of the use of PPIs.

To begin to address these issues, we wondered whether any clinicopathologic features could help to differentiate GERD/PPIREE from EoE before any PPI treatment was provided. We wondered whether eosinophil degranulation may provide a distinguishing pattern as suggested by past works (12). Degranulation is an indicator of eosinophil activation and others and our work suggests that it may only be present in EoE and not GERD (27). For instance, Mueller at al (28) found the correlation of eosinophil numbers with degree of eosinophil degranulation was a useful measure. Degranulation and eosinophil number were significantly higher in patients with EoE compared with GERD. Others have studied additional eosinophil granule proteins (eosinophil-derived neurotoxin [EDN], EPX) to histologically differentiate patients with EoE from those with GERD (28–30). In 1 study a significant increase in the EDN immunostaining was found in patients with EoE when compared with normal patients biopsies; however, there was no correlation in the degree of extracellular EDN to infiltrating eosinophil numbers (26). Our study did not find differences in EPX indices for patchiness or degranulation between our patients with GERD/PPIREE and EoE (pretreatment); however, our patients with

GERD/PPIREE had significantly denser esophageal eosinophilia compared with the above studies.

We address this specific question by identifying and analyzing a narrow subset of patients who had undergone successful PPI pre- and post-PPI treatment endoscopies without any other interventions and using a scoring system for eosinophilia that incorporated not only eosinophil number but also degranulation. Using EPX indices to measure degranulation, we were not able to identify a signature pattern that may indicate PPI responsiveness or not. EPX staining can therefore be a clinically useful test in differentiating etiologies of esophageal eosinophilia in patients with eosinophil counts <15 eos/HPF but may not be as valuable when eosinophil numbers are more dense.

Documentation of eosinophil degranulation remains an important tool to assess tissues affected by eosinophilic inflammation. Granule proteins can be measured in mucosal secretions as well as tissue sections. Within the gastrointestinal tract, measurements of eosinophil granule proteins in tissues and intestinal secretions from patients with eosinophilic gastroenteritis, inflammatory bowel diseases, and EoE have provided documentation of eosinophil activation. Recent works have also identified the fact that eosinophil degranulation may be a diagnostic feature of EoE; our previous work developed a scoring system that incorporated the number and distribution of eosinophils as well as the extent of degranulation to determine diagnostic thresholds for GERD and EoE. More important, the criterion standard for this test to determine a diagnostic threshold for GERD was based on GERD tissues that contained <15 eos/HPF. With increasing experience, it is clear that some patients with GERD, including at least 1 in our study, can have dense eosinophilia with numbers >15 and in some circumstances >100 eos/HPF (13). In our present study, all 5 PPI responder subjects had either >15 eos/HPF or an EPX index of >35, the ''diagnostic'' cutoff point for EoE. Whether these patients represent GERD with an exuberant mucosal response or PPIREE is not certain. Molecular analysis in the future may improve our understanding of this group.

Although our study is limited because of its retrospective nature and small sample size, we were able to cull these unique patient groups with a high degree of definition and certainty. Compliance to PPI treatment, doses prescribed, and concomitant use of unidentified treatments represent confounding variables that could have altered results. Another possible confounder is that allergenic exposures, whether seasonal, environmental, food, or others, could lead to a response, but based on close follow-up of these patients, that is unlikely. We did not perform EPX analysis on the 27 PPI nonresponder subjects, who were found to have EoE. Previous work has identified key histological patterns of degranulation in EoE and the further expense and time required would not add to our understanding. The small number of patients identified with transient response to PPI likely represents that rarity of phenomenon or subphenotype of EoE, but provides an important clue for clinicians.

Here we performed an 11-year retrospective study of mucosal response to PPI treatment. Although numbers of subjects are small, no specific clinical or endoscopic features distinguished GERD/PPIREE from EoE. Our results support use of PPIs as a diagnostic tool for EoE and therapeutic agent for dense esophageal eosinophilia. Also, the identification of the potential transient response to PPIs identifies the importance of long-term follow-up of patients.

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