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# Causes, evaluation, and consequences of eosinophilic esophagitis

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**This paper presents commentaries on whether eosinophilic esophagitis is a food allergy; inflammation in the context of eosinophilic esophagitis; whether eosinophilic esophagitis a cause of noncardiac chest pain; the role of endoscopy in the evaluation of eosinophilic esophagitis; and whether response to proton pump inhibitor therapy can distinguish eosinophilic esophagitis from gastroesophageal reflux disease.**

**Keywords:** eosinophilic esophagitis; food allergies; noncardiac chest pain; GERD; PPI

## Concise summaries

- A link between food allergies and eosinophilic esophagitis (EoE) has been established through a series of clinical studies implicating foods as disease triggers, and a limited number of translational studies suggest this link. However, identification of these foods by standard allergy testing remains difficult. Esophageal intraepithelial mast cells, eosinophils, and T lymphocytes are increased in number; many of these are activated. Both $CD4^+$ (T-helper) and $CD8^+$ (T-suppressor) subsets are increased in the esophageal epithelium, with maintenance of $CD8^+$ predominant over $CD4^+$ cells. In the peripheral circulation, patients with EoE were found to have an increased percentage of $CD4^+$ cells expressing IL-5 compared with nonatopic controls.
- EoE is characterized by an unique gene expression profile resulting in a characteristic transcriptome, which do not vary with the gender of patients or their allergic background. Inflammation in EoE involves all cell types taking part in the immune system, which are needed to develop an inflammatory response against antigenic components of the diet that make contact with the inner esophageal surface. The inflammation goes deep into all layers of the esophageal wall, promoting fibrous remodeling, originating smooth muscle disturbances, and giving increased risk to tissue damage and perforations, by acting through eosinophils' cytoplasmatic cytotoxic granule proteins.
- Chest pain has been described in a number of adult patients with EoE. Most patients tend to be males and may have either a normal or abnormal endoscopy. Endoscopic biopsies should thus be obtained in patients with noncardiac chest pain (NCCP), particularly if they are males, whether endoscopy is normal or abnormal.
- Regarding the diagnosis of EoE, a great variety of endoscopic findings have been described in the literature, including an apparently normal esophagus in up to 25% of cases. The capacity of the endoscopic technology narrow-banding imaging (NBI) to increase the reliability of endoscopic features has been assayed: several endoscopists analyzed images obtained from EoE patients before and after using NBI in order to identify three characteristic features: furrows, rings, and plaques. Only rings and furrows were correctly identified. The utility of endoscopy for treating EoE was

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demonstrated in two different situations: food impaction and endoscopic dilation developed in cases of esophageal stenosis. Endoscopy has also a role in the monitoring of patients, which aims to prevent progressive esophageal dysfunction and detect complications from therapy.

- In some patients, it can be difficult to distinguish EOE from gastroesophageal reflux disease (GERD). The relationship between these two esophageal disorders can be quite complex, and one might contribute to the pathogenesis of the other. Data suggest that the pathogenesis of EoE starts with a genetically susceptible individual, for whom some food allergen activates the immune system by binding to mast cells and antigen-presenting cells that, in this genetically susceptible person, induces a Th2 response with the production of Th2 cytokines like IL-5. IL-5 activates eosinophils that reside in the bone marrow. The effect of proton pump inhibitors (PPIs) on reducing Th2 cytokine–stimulated eotaxin-3 production is entirely independent of any effect on gastric acid secretion, and a response to PPI therapy cannot distinguish EoE from GERD.

## 1. Is eosinophilic esophagitis a food allergy?

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EoE is defined as a chronic immune/antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation of the esophageal mucosa.[1] A link between food allergies and EoE has been established through a series of clinical studies implicating foods as disease triggers and a limited number of translational studies suggesting this link.

While history of immediate, IgE-mediated food allergy is present in ∼15% of patients with EoE, evidence for minor sensitization to multiple foods detected by skin-prick testing (SPT) and/or serum food-specific IgE levels is common.[1] Foods that test positive are not necessarily triggers in EoE patients. Clinical evidence for a food allergy in EoE comes from short-term dietary elimination trials resulting in disease remission, summarized in Table 1. The first such study was conducted by Kelly *et al.*,[2] who restricted the diet of 10 children with EoE to a hypoallergenic amino acid–based formula with resultant disease remission in 80% of the children after 6 weeks. When rechallenged with foods, patients' symptoms recurred following a median of two foods; milk, soy, wheat, peanut, and egg being common triggers despite negative SPT to these foods. Results from this study were later confirmed in other pediatric studies, with disease remission in >85% of children.

Studies in children and adults with EoE where dietary therapy was limited to avoidance of common food allergens (milk, egg, wheat, soy, nuts, and seafood) also demonstrated good results. The majority of patients improved after 6 weeks of dietary restriction, although standard SPT results were not predictive of the food triggers upon their reintroduction.[3,4] A test-directed dietary elimination therapy in children with EoE, consisting of avoidance of foods that tested positive by SPT and atopy patch testing (APT), resulted in symptom resolution in 69% of the patients after 6 weeks. The positive predictive value of these skin tests was highly variable for various foods, ranging from 30% to 90%.[5] In adults, data regarding the efficacy of this dietary regimen are limited.

The above studies demonstrate that foods are definite disease triggers in many patients with EoE. However, identification of these foods by standard allergy testing remains difficult.

Studies examining esophageal tissue and peripheral blood of patients with EoE demonstrate an allergic disease phenotype. Esophageal intraepithelial mast cells, eosinophils, and T lymphocytes are increased in number; many of which are activated. Both $CD4^+$ (T-helper) and $CD8^+$ (T-suppressor) subsets are increased in the esophageal epithelium, with maintenance of $CD8^+$ predominant over $CD4^+$ cells.[6] Despite $CD8^+$ predominance, the esophageal tissue in EoE patients displays an

**Table 1. Summary of dietary elimination trials in patients with EoE**

| Study | Patients | Dietary therapy type | Clinical response | Esophageal eosinophils/ HPF pretherapy | Esophageal eosinophils/ HPF posttherapy |
|---|---|---|---|---|---|
| [2] | 10 children | Amino acid-based formula ± 2 foods | 80% symptom resolution | 41 | 0.5 |
| Markowitz *et al.*, 2003 | 51 children | Amino acid-based formula + 1–2 foods | 96% symptom resolution | 34 | 1 |
| [3] | 35 children | Avoidance of common food allergens | 74% symptom improvement | 80 | 14 |
| [4] | 50 adults | Avoidance of common food allergens | 64% symptom resolution | 44 | 13 |
| [5] | 26 children | Avoidance of foods positive by SPT/APT | 69% symptom resolution | 56 | 8 |
| Simon *et al.*, 2006 | 6 adults | Avoidance of foods positive by SPT/IgE | 17% symptom improvement | Not reported | No change |

SPT, skin prick test; APT, atopy patch test; IgE, immunoglobulin E; HPF, high power field.

allergic cytokine profile, with increased tissue levels of interleukin (IL)-4, IL-5, and IL-13.[7] The extent of the contribution of esophageal T lymphocytes to this allergic phenotype in EoE has not yet been determined, however.

In the peripheral circulation, patients with EoE were found to have an increased percentage of $CD4^+$ cells expressing IL-5 compared to nonatopic controls. When stimulated with a nonspecific T cell stimulant, peripheral blood mononuclear cells (PBMCs) of EoE patients secrete more IL-13. Specific stimulation of these cells with milk, egg, soy, wheat, and peanut also results in secretion of more IL-5 and IL-13 compared to PBMCs of healthy controls, even in the absence of serum IgE levels to these foods.[8] The above studies are limited, however, by the fact that other concurrent allergic diseases are common in patients with EoE, which could have accounted for these responses. Comparison with allergic controls is needed to confirm these findings.

In conclusion, EoE is triggered by foods in many patients. The mechanism of this dietary antigenic stimulation seems to be allergic in nature, as evidenced by dietary elimination trials resulting in disease remission, and a tissue and blood profile consistent with an allergic response. More research is needed to confirm and clarify the nature of this food allergy in EoE.

## 2. Inflammation in eosinophilic esophagitis

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EoE was firstly described around 20 years ago, and today represents a common esophageal disorder. The disease has been consensually defined as a chronic, immune/antigen-mediated esophageal disorder, characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation in biopsies.[1]

The most relevant histological finding in EoE is a dense infiltration by eosinophils in the esophageal mucosa, when stained with hematoxylin and eosin, but after immunohistochemistry, EoE is also characterized by the presence of antigen-presenting Langerhans' dendritic cells, a dense population of T lymphocytes (3/4 of them $CD8^+$), a very scarce number of B lymphocytes, and an increased density of mast cells compared to normal controls, showing mast trypstase- and IgE-positive staining.[9] Because of the presence of eosinophils, IL-5 expression, T lymphocytes, mast cells, and IgE-staining, a Th2-type immunologic reaction was implicated in the origin of the disease,[9] in a similar way to what happens in other respiratory and skin allergic disorders.

Under a molecular point of view, several studies have started to define the physiopathology of EoE by identifying potential genes involved in the origin of the disease. EoE is characterized by an unique gene expression profile resulting in a characteristic transcriptome, which does not vary with the gender of patients or their allergic background.[10] Among these genes, the potential role of eotaxins (a subfamily of eosinophil-selective chemoattractants) that interact with the same CCR-3 receptor primarily found on eosinophils has been analyzed.[11] Several data support the important role of eotaxin-3 in the molecular basis of EoE, since it was the most intensely upregulated gene. Patients with EoE also show higher eotaxin-3 plasmatic levels than control subjects, and the gene expression of *eotaxin-3* and its protein in esophageal tissue is directly and closely related to tissue eosinophil and mast-cell densities. Furthermore, a single nucleotide polymorphism in the 3′ untrans lated region of the *eotaxin-3* gene has been associated with disease susceptibility.[10]

Epithelial cells have also been involved in the origin of EoE: in fact, IL-13 (a Th2-type cytokine released by epithelial cells in EoE) and its gene expression appeared upregulated in patients compared to controls. IL-13 was able to induce eotaxin-3 gene expression, and reproduce the EoE-characteristic transcriptome. All these molecular changes reversed after steroid treatment.[12] In fact, eotaxin-3, together with major basic protein (MBP) has been recently found to be highly sensitive and specific for diagnosing EoE: immuno-staining against these two proteins demonstrated high sensitivity and specificity for diagnosing EoE patients, compared to GERD, even when not considering clinical symptoms and endoscopic appearance.[13]

Inflammatory changes in EoE patients can be reverted by using different therapeutic approaches, which include anti-inflammatory and immunosuppressant drugs (such as systemic and topical corticosteroids and thiopurines), and also after dietary modifications to decrease the antigenic content in the diet.[14]

Some important changes in the esophageal wall of EoE patients happen under the epithelial surface. From deep mucosal biopsies and patients who underwent esophagectomy after suffering from Boerhaave' syndrome because of EoE, we know that eosinophils permeate not only the epithelium, but also the lamina propria, submucosa, muscle layers, and even the neuronal plexus that controls the esophageal movements.

The eosinophil is a functionally complex cell, which participates in both regulatory and effector functions. Eosinophils synthesize and release several cytokines able to induce fibrous remodeling and subepithelial collagen deposition, including TGF-β and FGF-9,[15] contributing to the development of esophageal strictures and luminal narrowing, which are frequently found in adult EoE patients. MBP is also considered a strong agonist of M2-type muscarinic receptors, which govern the smooth muscle contraction. This contributes to esophageal dysmotility and dysphagia in EoE patients, together with the effect of several mediators released by mast cells over muscular fibers, including histamine and leukotrienes.

As effector cells, eosinophils participate in the host defense against helminthes and parasites through the production and degranulation of cytotoxic proteins, including MBP, eosinophil-derived neurotoxin (EDN), eosinophilic cationic protein (ECP) and eosinophilic peroxidase (EPO). This fact relates to the increased fragility seen in the esophageal walls of patients with EoE, in which a high frequency of tears and perforations have been described after endoscopic procedures or even spontaneously.[16]

Available evidence concerning the role played by mast cells alongside eosinophils in the inflammatory infiltrate of EoE supports the idea that their function could be of considerable importance in the physiopathology. Furthermore, interaction between both cell types could be feasible, and it is suggested that this interaction could act as a feedback loop that increases the inflammatory response.

In conclusion, inflammation in EoE involves all cell types taking part in the immune system, which are needed to develop an inflammatory response against antigenic components of the diet that make contact with the inner esophageal surface.

The inflammation goes deep into all layers of the esophageal wall, promoting fibrous remodeling, originating smooth muscle disturbances, and giving increased risk to tissue damage and perforations, by acting through eosinophils' cytoplasmatic cytotoxic granule proteins.

## 3. Is eosinophilic esophagitis a cause of noncardiac chest pain?[1,17–24]

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EoE is a chronic, immune/antigen-mediated esophageal disease characterized symptomatically by esophageal dysfunction and histologically by eosinophil-predominant inflammation.[1] EoE is an emerging worldwide disease. Estimates of the prevalence indicate that it affects between 40 and 55 individuals per 100,000 inhabitants in Western countries;[17,18] this compares with similar figures for the prevalence noted in Crohn's disease.

The clinical presentation of EoE varies according to age. Neonates and infants may present with food refusal. Children may complain of heartburn, vomiting and abdominal pain. With increasing age, dysphagia and food impaction may occur more often.[19] In a review of the literature, Sgouros *et al.* examined the clinical presentation of EoE in adults. They found 24 studies with 325 patients (male/female ratio: 3/1). Presenting symptoms included dysphagia (93%), food impaction (62%), and heartburn (23.6%).[20]

Chest pain occurring in EoE was originally described by Dobbins *et al.* in 1977[22] and Landres *et al.* in 1978.[23] Since those two original reports, chest pain has been described in a number of adult patients with EoE.[23] At our center, we observed a number of patients with NCCP and EoE. These observations led us to investigate the prevalence of eosinophilic infilitration in patients presenting with NCCP. We hypothesized that eosinophillic infiltration of the esophagus causes chest pain.

During a 2-year span we completed a retrospective study of consecutive patients with NCCP referred for esophago-gastro-duodenoscopy (EGD).[24] Patients were entered in the study if they had chest pain as the dominant complaint that led to EGD. All patients had prior cardiac testing to exclude cardiac sources of chest pain. Those with dysphagia as the main symptom for endoscopy were excluded. Esophageal biopsies were obtained from the distal (5 cm above the gastro-esophageal junction (GEJ), upper (5 cm below the crico-pharyngeal area), and middle esophagus (10 cm above the GEJ). Histological results were grouped as: normal = 0–5 eosinophils/hpf, indeterminate = 6–20 eosinophils/hpf, and eosinophilic esophagitis $=\geq$21 eosinophils/hpf. A total of 171 patients were enrolled in the study. We found that 14% had esophageal eosinophilic infiltration (8% with indeterminate counts and 6% with $\geq$21 eosinophils/hpf). A normal eosinophilc count (0–5 eosinophils/hpf) was noted for 86% of the patients. Using currently accepted histological criteria for the diagnosis of EoE ($\geq$ 15 eosinophils/hpf)[1] 20 patients (12%) had EoE. Compared with normals, those with abnormal esophageal eosinophilic infiltration were more likely to be male (71% vs. 34%, $P = 0.001$), have allergies (29% vs. 12%, $P = 0.050$), have current GER symptoms (42% vs. 18%, $P = 0.013$), and exhibit rings (54% vs. 22%, $P = 0.002$), furrows (21% vs. 1%, $P < 0.001$), and abnormal EoE findings on endoscopy (67% vs. 32%, $P = 0.001$). Of the 24 abnormal patients, 23 (96%) were either male or had rings, furrows, or white specs. A normal endoscopy was observed in 18 patients (33%) with abnormal eosinophilc infiltration.

In summary, in NCCP, one in 16 patients may have abnormal eosinophilc infiltration. Most patients tend to be males and may have either a normal or abnormal endoscopy. Endoscopic biopsies should be obtained in patients with NCCP, particularly if they are males, whether endoscopy is normal or abnormal.

## 4. What is the role of endoscopy in the evaluation of eosinophilic esophagitis?

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The past few years have witnessed a progressive rise in diagnosed cases of EoE, which has become the most common cause of dysphagia in young patients. In spite of this, EoE remains underdiagnosed in many settings, especially because endoscopic findings are usually much harder to detect than those observed in esophageal growths or erosive disorders. At the same time, research efforts aimed at providing efficient therapy for this chronic illness has also intensified. Unfortunately, no treatment strategies have been commonly accepted to date, making adequate management of these patients somewhat controversial.[25] The role of endoscopy in the evaluation of EoE stretches from diagnosis, mainly allowing the procurement of esophageal biopsies, to therapy, having also a role in the follow-up of these patients.

Regarding the diagnosis of EoE, a great variety of endoscopic findings have been described in the literature, including an apparently normal esophagus in up to 25% of cases, which suggests that changes in this organ's appearance may be subtle enough to be overlooked by an endoscopist unaccustomed to EoE. Esophageal biopsies are considered to be essential for diagnosing EoE; no available alternative method exists. Previous research showed that 100% diagnostic sensitivity can be achieved when at least five endoscopic biopsy samples are obtained[26] and no significant differences exist in eosinophil counts between upper and lower esophageal thirds. The pathology report should include not only the count of eosinophils, but also some EoE-associated histopathological features, including microabscesses, basal cell hyperplasia, and intercellular edema.

Before settling on a diagnosis of EoE, eosinophilic gastroenteritis should be ruled out, by taking endoscopic biopsies from the gastric and small bowel mucosa, especially if symptoms related to these sections are present. Finally, repeating biopsies after treatment with PPIs is a good method to exclude GERD as a cause of esophageal eosinophilia.

EoE is a polymorphic disorder, and a varied range of endoscopic findings has been provided, including longitudinal mucosal furrows, whitish exudates, and esophageal rings. Some cases can present esophageal stenosis, which blocks the pass of the endoscope, and others show tears and mucosal rents. The utility of endoscopic findings for diagnosing EoE have been addressed by several investigators: Prasad *et al.* gave a diagnosis of EoE to 15% of patients who prospectively underwent endoscopy because of nonobstructive dysphagia: only 38% of EoE patients showed typical endoscopic features, and around 10% of EoE patients exhibited a normal esophagus.[27] A more recent study by Mackenzie *et al.* found similar results: 12% of patients presenting dysphagia received a diagnosis of EoE, but only 34% of them presented typical EoE-associated findings in endoscopy.[28] So we can conclude that the reliability of endoscopy alone in diagnosing EoE is really low, not surpassing 40%.

The capacity of the endoscopic technology NBI to increase the reliability of endoscopic features has been also assayed: several endoscopists analyzed images obtained from EoE patients before and after using NBI in order to identify three characteristic features: furrows, rings, and plaques. Only rings and furrows were correctly identified, but recognition did not improve after NBI.[29] A novel classification and grading system for EoE-associated endoscopic features has been recently proposed; further prospective studies should validate proposed nomenclature and severity scores for its real utility in EoE patients.[30]

With regard to the utility of endoscopy for treating EoE, this technique was demonstrated to be useful in two different situations.[25] First, food impaction constitutes an emergency that should be rapidly resolved by food bolus removal. In fact, food impaction is the symptom that most frequently leads to EoE diagnosis in adult patients. Around one out of three EoE patients will require food bolus removal,[31] which can be done by both endoscopists and otolaryngologists (these last using rigid esophagoscopes). Second, endoscopic dilation can develop in the case of esophageal stenosis. We should take into account that reductions in esophageal caliber can be caused by both fibrosis in the organ's wall or inflammation-induced esophageal dysmotility.

The most important aspect related to endoscopic treatment of EoE patients is the risk of complications: flexible endoscopy should be used to remove an impacted food bolus, since a 20% rate of perforation has been reported when using a rigid esophagoscope.[31] Regarding endoscopic dilation, this technique has been considered risky, since a high rate of complications, including chest paint and perforation, occurred in up to 5% of reports.[32] However, recent literature has reported a lower rate of severe complications after EoE dilation, perforation occurring in 1% of patients.[33,34] Identified potential risk factors for complication include long evolution of dysphagia, high density of esonophils,[35] younger patients with stenosis in the upper or middle esophagus, or repeated procedures.[33] The use of bougies instead of hydro-pneumatic balloons has been also related to an increased risk.[34] In EoE patients that present stenosis in spite of steroid or dietary treatment, endoscopic dilations should be done gently, preferably after using other treatment modalities to reduce or eliminate inflammation, by experienced endoscopists if possible, and using smaller calibers that used in other types of esophageal strictures. Some authors prefer balloons instead of bougies, this decision depending on the explorer's experience.

Finally, endoscopy also has a role in the monitoring of EoE patients, which aims to prevent progressive esophageal dysfunction and detect complications from therapy. Commonly accepted monitoring for EoE has not been provided, but repeated upper endoscopies can be performed to evaluate the efficacy of a newly introduced treatment. Endoscopy with biopsies should be carried out at least 4 weeks after starting the new therapy to allow changes in the inflammatory infiltration. Patients presenting worsening or new symptoms should also be endoscopically evaluated. In the case of asymptomatic patients, it could be useful to carry out an exam every 2 or 3 years, in order to prevent progressive disease.[32]

As a conclusion, endoscopy is today essential in the management of patients with EoE. Endoscopic findings are not sensitive or specific enough for diagnosing EoE, so biopsies should always be taken if a suspicion exists, even when the esophagus appears normal. In the case of food bolus impaction, flexible scopes should be preferred, and if dilation is needed, it should be done when inflammation had been controlled.

## 5. Does a response to PPI therapy distinguish EoE from GERD?

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### *Introduction*

EoE is a chronic, immune-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation.[1] EoE appears to be a new disorder, recognized widely only within the past decade, and its frequency is increasing rapidly in both adults and children. Adults with EoE usually complain of dysphagia, and often have a history of emergency room visits for food impactions. Other symptoms of EoE include heartburn, chest pain, and epigastric pain. Esophageal biopsies typically demonstrate $\geq$15 intraepithelial eosinophils/hpf and basal zone hyperplasia.[1] However, these same clinical and histologic features can be found in patients with GERD and, in some patients, it can be difficult to distinguish EoE from GERD. The relationship between these two esophageal disorders can be quite complex, and one might contribute to the pathogenesis of the other.[36]

**Table 2. Potential anti-inflammatory effects of proton pump inhibitors**

| |
|---|
| Antioxidants |
| Inhibitory effects on neutrophil function |
| Decreased cytokine production by endothelial and epithelial cells |
| Decreased adhesion molecule production by endothelial and epithelial cells |
| Decreased IL-13 and IL-4-stimulated eotaxin-3 production in esophageal squamous epithelial cells |

Further blurring the distinction between EoE and GERD are recent data demonstrating that most patients who have upper gastrointestinal symptoms with esophageal eosinophilia exhibit a symptomatic response to therapy with PPIs.[1]

### *PPI-responsive esophageal eosinophilia*

Increasingly recognized is a fascinating subgroup of patients who have symptoms and histologic findings typical of EoE, no evidence of GERD by endoscopy and pH monitoring, and yet exhibit a symptomatic and histological response to PPIs.[1] This condition is called *PPI-responsive esophageal eosinophilia*.[1] It has been thought that, since the only important effect of PPIs is to decrease gastric acid production, only an acid–peptic condition like GERD can respond to PPI therapy. However, PPIs appear to do far more than just inhibit gastric acid production. Recent studies have demonstrated a number of potential anti-inflammatory effects of PPIs. For example, PPIs have antioxidant properties and inhibitory effects on neutrophil function that could decrease inflammation. PPIs decrease cytokine production by endothelial and epithelial cells, and they decrease adhesion-molecule production by endothelial cells and neutrophils[37] (Table 2). In patients with esophageal eosinophilia who respond to PPI therapy, it is very possible that some of these anti-inflammatory effects contribute to the clinical response. Therefore, a clinical response to PPIs should no longer be regarded as proof of an underlying acid–peptic disease.

### *Why do eosinophils home to the esophagus in EoE?*

EoE is caused by a food allergy, but why do eosinophils home exclusively to the esophagus as a result of food allergy? Food passes rapidly through the esophagus, but, in EoE, the esophagus

sustains the allergic injury, while the mouth, the stomach, and the intestines are spared. Using an RNA microarray, Blanchard *et al.* examined RNA from esophageal biopsy specimens taken from six control subjects and 13 pediatric patients with EoE.[10] They found a unique EoE transcriptome in which 230 genes were downregulated and 344 genes were upregulated in the EoE patients.[10] The most dramatic upregulation involved the eotaxin-3 gene, which was increased by more than 50-fold, and eotaxin-3 is a potent chemoattractant for eosinophils.[10]

### *Proposed model of EoE pathogenesis*

Every day, we ingest millions of antigens that have the potential to evoke an immune response. If one of these antigens gets the attention of an antigen-presenting cell, and that cell presents the antigen appropriately, then it is possible to activate the immune system, and this can stimulate the differentiation of naive $CD4^+$ T cells into Th1 cells that secrete TNF-β and IFN-γ, or into Th2 cells that secrete cytokines like IL-4, IL-5, and IL-13. Overproduction of these Th2 cells is characteristic of a number of allergic disorders, and that appears to include EoE. Data suggest that the pathogenesis of EoE starts with a genetically susceptible individual, for whom some food allergen activates the immune system by binding to mast cells and antigen-presenting cells that, in this genetically susceptible person, induces a Th2 response with the production of Th2 cytokines like IL-5. IL-5 activates eosinophils that reside in the bone marrow. Meanwhile, the surrounding Th2 cells, mast cells, and eosinophils themselves release IL-13 and IL-4, which stimulate the production of eotaxin-3 by the esophageal epithelial cells. Eotaxin-3 is a potent chemoattractant that causes activated eosinophils to home to the esophagus, where they cause esophageal epithelial injury from their degranulation products.

### *Omeprazole blocks eotaxin-3 expression by esophageal squamous cells from EoE patients*

Our group recently reported the effects of the Th2 cytokines IL-13 and IL-4 on eotaxin-3 production in esophageal squamous cells from patients with EoE, and the effects of omeprazole on that expression of eotaxin-3.[38] We established novel, telomerase-immortalized EoE cell lines (EoE1-T and EoE2-T) from endoscopic biopsies of esophageal squamous mucosa obtained from patients with EoE. Unstimulated, these cells secrete very little eotaxin-3. When treated with IL-13 or IL-4, their production of eotaxin-3 mRNA and protein increases dramatically.[38] Treatment with omeprazole (50 μM) suppressed the Th2 cytokine–stimulated mRNA expression and protein secretion of exotaxin-3 in both EoE cell lines.[38] Remember, these are squamous cells growing in a culture dish. There are no parietal cells and no acid in this system. This PPI effect on reducing Th2 cytokine-stimulated eotaxin-3 production is entirely independent of any effect on gastric acid secretion. Therefore, the answer to the question "Does a response to PPI therapy distinguish EoE from GERD?" is no!

## Conflicts of interest

The authors declare no conflicts of interest.

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