Published in final edited form as:

Gastroenterol Clin North Am. 2014 June ; 43(2): 243–256. doi:10.1016/j.gtc.2014.02.004.

Eosinophilic Esophagitis: Interactions with Gastroesophageal Reflux Disease

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Synopsis

Early authorities on eosinophilic esophagitis (EoE) deemed it crucial to distinguish this disorder from gastroesophageal reflux disease (GERD). However, it has become clear that GERD and EoE are not mutually exclusive disorders, and that their interactions can be complex. The notion that GERD and EoE can be distinguished by the response to PPI treatment is based on the assumption that gastric acid suppression is the only important therapeutic effect of PPIs, and therefore only GERD can respond to PPIs. This assumption appears to be incorrect for two major reasons. First, there are multiple mechanisms whereby PPI-induced acid reduction might benefit patients with EoE. Second, PPIs have acid-independent, anti-inflammatory effects that might be beneficial both for GERD and for EoE. Since the PPIs have multiple effects that might benefit both diseases, for patients who have esophageal symptoms and esophageal eosinophilia, we feel that a clinical and/or histological response to PPIs does not rule in GERD, and does not rule out EoE. However, we do recommend a trial of PPI therapy for patients with symptomatic esophageal eosinophilia, even if the diagnosis of EoE seems clear-cut.

Keywords

gastroesophageal reflux disease; eosinophilic esophagitis; proton pump inhibitors; PPI-responsive esophageal eosinophilia

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Introduction

Heartburn and dysphagia are frequent symptoms of both eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD), and esophageal biopsies in both disorders can show epithelial infiltration by eosinophils. Therefore, it can sometimes be difficult to distinguish EoE from GERD. EoE was not described as a distinct clinico-pathological disorder until 1993,¹ and confusion with GERD delayed appreciation that EoE was a burgeoning new esophageal ailment. Throughout the 1990s, pathologists and clinicians often attributed esophageal eosinophilia to GERD, and were either unaware of EoE or did not consider it seriously in the differential diagnosis.² It was not until well into the new millennium, when a number of reports had accumulated describing patients with esophageal symptoms and eosinophilia refractory to anti-reflux therapy, but responsive to elemental diets and steroids, that clinicians generally became aware that EoE was a *bona fide* new disorder distinct from GERD.^{3–6}

In 2007, a consensus report from the First International Gastrointestinal Eosinophil Research Subcommittee defined EoE as a primary clinicopathologic disorder of the esophagus characterized by esophageal and/or upper gastrointestinal symptoms, an esophageal biopsy showing ≥15 per high power field, and *the absence of pathological GERD* as evidenced by a normal esophageal pH monitoring study or lack of response to high-dose proton pump inhibitors (PPIs).⁷ This definition, which implied that EoE and GERD were mutually exclusive conditions, was formulated in an attempt to eliminate confusion between the two. However, other authorities soon challenged this definition, contending that the interactions between EoE and GERD could be complex, and that the notion of establishing a clear distinction between them was far too simplistic.⁸

A number of investigators chose simply to ignore the 2007 consensus definition and to include subjects with abnormal acid reflux in their series of patients with EoE.^{9–11} Others attempted to use clinical, endoscopic, histologic, and immunohistochemical features to distinguish GERD from EoE, with variable success.^{12–19} However, some of the histological and immunohistochemical differences described in those studies might have resulted merely from differences between GERD and EoE study subjects in their number of esophageal eosinophils rather than from differences in the disorders underlying the esophageal eosinophilia.²⁰ In 2011, another consensus group (with the benefit of information on EoE pathogenesis not available in 2007) proposed a conceptual definition for EoE as “a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.”²¹ This conceptual definition does not even mention GERD, and does not imply that GERD and EoE are mutually exclusive disorders.

Proposed Mechanisms Underlying an Association between Esophageal Eosinophilia and GERD

Four major mechanisms might explain an association between esophageal eosinophilia and GERD: 1) GERD causes esophageal eosinophilia in the absence of EoE, 2) GERD and EoE

coexist but are unrelated, 3) EoE contributes to or causes GERD, 4) GERD contributes to or causes EoE.⁸

GERD causes esophageal eosinophilia in the absence of EoE

Since 1982, it has been appreciated that esophageal eosinophilia can be a manifestation of GERD.²² This eosinophilia is usually mild, with <7 eosinophils per high power field, and may occur because refluxed gastric juice stimulates the esophagus to produce substances that attract eosinophils. In cultures of human esophageal microvascular endothelial cells, acid exposure has been shown to induce the expression of VCAM-1, an adhesion molecule recognized by ligands on the eosinophil cell surface.^{23, 24} Studies using a preparation of human esophageal mucosa have found that acid stimulates the release of platelet activating factor (PAF), a phospholipid that can attract and activate eosinophils.²⁵ Esophageal squamous epithelial cells in culture secrete IL-8 when they are exposed to acidified bile salts,^{26, 27} and HET-1A esophageal epithelial cells exposed to acid show upregulation of eotaxin-1, eotaxin-2, eotaxin-3 and macrophage inflammatory protein (MIP)-1 α .²⁸ Eotaxins and MIP-1 α bind eosinophil chemokine receptors (CCR3 and CCR1, respectively) that play a key role in eosinophil chemotaxis.²⁹ In patients with reflux esophagitis, furthermore, esophageal mucosal biopsy specimens show elevated levels of eosinophil chemoattractants such as IL-8 and RANTES.³⁰ It is not known which, if any, of these factors underlie the esophageal eosinophilia of GERD.

GERD and EoE coexist but are unrelated

Since approximately 20% of adults in Western countries have GERD,^{31, 32} it would be expected that, by chance alone, 20% of Western adults with EoE should have GERD. This might not be the case if GERD were to protect the esophagus from EoE but, presently, there is no evidence for such a protective effect. Indeed, some studies have suggested that pathological acid reflux is inordinately common in EoE.^{11, 33} For example, 24-hour esophageal pH monitoring revealed abnormal acid reflux in 10 (42%) of 24 adults with EoE in one study,³³ and in 14 (56%) of 25 in another.¹¹ Some studies have suggested that, unlike in adults, abnormal acid reflux is uncommon in pediatric patients with EoE.^{34–36} However, the accuracy of esophageal pH monitoring as a test for GERD in children is not well established.³⁷ Further confounding interpretation of reports on the frequency of GERD in EoE is inconsistency among investigators regarding the criteria used to define EoE. According to the 2007 consensus statement, the frequency of abnormal acid reflux in EoE should be 0% since, by the 2007 definition, an abnormal esophageal pH monitoring study would preclude the diagnosis.⁷ The 2011 consensus definition has no such preclusion.²¹

EoE contributes to or causes GERD

Eosinophils produce a number of substances that might contribute to GERD by promoting gastroesophageal reflux and by impairing the ability of the esophagus to clear itself of noxious refluxed material. For example, eosinophils produce vasoactive intestinal peptide and PAF, which can reduce lower esophageal sphincter pressure and thereby predispose to reflux.^{38, 39} Eosinophils also secrete IL-6, a cytokine that weakens esophageal muscle contraction. This weak muscle contraction might impair peristalsis and delay esophageal acid clearance.^{40, 41} Furthermore, esophageal eosinophils can induce tissue remodeling with

subepithelial fibrosis, and such fibrosis also conceivably might contribute to GERD by interfering with lower esophageal sphincter function and peristalsis.⁴²

In addition to secreting substances that can promote reflux and delay esophageal acid clearance, eosinophils also produce cytotoxic substances that might render the esophageal epithelium more permeable and susceptible to injury by refluxed gastric material.^{43–46} For example, major basic protein has been shown to disrupt barrier function in monolayers of human colonic carcinoma cells.⁴⁶ Eosinophil infiltration of the bronchial mucosa of asthmatic patients is associated with damage to cellular tight junctions and dilation of the intercellular spaces.⁴⁷ Similar changes are found in the esophageal mucosa of patients with GERD, presumably as the result of acid-peptic damage to tight junctions. This tight junction damage increases mucosal permeability, which enables acid and other noxious molecules to reach nociceptors located deep in the epithelium, and these nociceptors might convey the sensation of heartburn.⁴⁸ Perhaps increased mucosal permeability caused by cytotoxic eosinophil products underlies the hypersensitivity to esophageal acid perfusion that has been described in patients with EoE.⁴⁹

GERD contributes to or causes EoE

While increased mucosal permeability caused by eosinophilia might contribute to GERD, it is also possible that increased esophageal mucosal permeability caused by GERD predisposes to the development of EoE. The normal esophageal mucosa is highly impermeable to large molecules like food allergens,⁵⁰ which typically have a molecular weight between 3 and 90 kD.⁵¹ For example, Tobey *et al.* found that the normal rabbit esophagus was virtually impermeable to epidermal growth factor, a peptide with a molecular weight of 6 kD, and to dextrans with a molecular weight of 4 kD.⁵⁰ After exposure to acid and pepsin, however, the rabbit esophageal mucosa became permeable to epidermal growth factor and to dextrans as large as 20 kD. By increasing esophageal permeability, therefore, GERD could render the squamous epithelium permeable to allergens that might cause EoE.

As discussed above, GERD might contribute to esophageal eosinophilia by inducing the expression of eosinophil chemoattractants. Refluxed gastric material also can cause the release of mast cell products and other substances that attract non-eosinophil immune cells to the esophagus,^{26, 52} and it is conceivable that this immune response might contribute to the development of EoE. In addition, refluxed material can activate receptors that exacerbate EoE symptoms and inflammation. For example, reflux-induced activation of transient receptor potential cation channel, subfamily vanilloid member 1 (TRPV1) on esophageal neurons might contribute to the acid hypersensitivity that has been described in EoE patients,⁴⁹ and activated TRPV1 has been linked to the release of eosinophil chemoattractants (IL-8, PAF, eotaxin-1, eotaxin-2, eotaxin-3, and MIP-1 α) and other inflammatory mediators such as substance P and calcitonin gene-related peptide (CGRP).^{28, 53} Also, the proteinase-activated receptor 2 (PAR2) on esophageal epithelial cells can be activated by refluxed proteolytic enzymes to cause production of IL-8.^{54–57}

PPI-Responsive Esophageal Eosinophilia

Recent reports have described patients with a condition called “PPI-responsive esophageal eosinophilia” (PPI-REE).^{11, 21, 58–65} These patients have typical EoE symptoms and endoscopic abnormalities, no evidence of GERD by endoscopy or by esophageal pH/impedance monitoring, and nevertheless exhibit a clinical and histological response to PPI therapy. Studies in pediatric and adult patients with esophageal eosinophilia suggest that approximately 50% respond to PPIs,^{11, 58, 60–65} and that no clinical or endoscopic feature independently distinguishes PPI responders from non-responders.^{64, 65} In some pediatric patients initially found to have PPI-REE, Dohil *et al.* observed the subsequent reaccumulation of eosinophils and other inflammatory cells in the esophagus over a period of 3 to 12 months despite ongoing PPI treatment.⁵⁹ Thus, PPI-REE may be a transient condition. PPIs also might help to control esophageal symptoms, even if they do not cause resolution of esophageal eosinophilia. For example, Levine *et al.* found that PPI treatment of children with EoE failed to resolve their esophageal inflammation, but nevertheless resulted in long-term symptomatic improvement.⁶¹

It is possible that patients with PPI-REE simply have GERD that is not detected by conventional diagnostic tests, but that benefits from the acid-suppressive effects of PPIs. Alternatively, these patients may indeed have EoE or a related allergen-mediated process that responds to therapeutic effects of PPIs that are independent of gastric acid suppression (see below). Presently, the relative contributions of these acid-suppressive and acid-independent PPI actions are not clear.

Potential Acid-Dependent Effects of PPIs in Esophageal Eosinophilia

PPIs target gastric $H^+/K^+-ATPase$, the “proton pump” of the parietal cells responsible for gastric acid secretion. In the acidic environment of functioning parietal cells, PPIs are acid-activated and covalently bind to cysteine residues on the $H^+/K^+-ATPase$, rendering the pumps inactive.⁶⁶ Without PPIs, the distal esophagus is exposed to refluxed acid for up to approximately 5% of the day in normal adults, and for 8% to 13% of the day in normal newborns and infants.^{67, 68} As discussed above, there are a number of mechanisms whereby acid reflux might contribute to esophageal eosinophilia and to esophageal infiltration by non-eosinophil immune cells. Thus, patients who have EoE and no evidence of GERD still might benefit from acid suppression to control their normal acid reflux.⁸ Additionally, patients with EoE can have hypersensitivity to acid-induced esophageal pain.⁴⁹ Therefore, PPIs might provide symptomatic relief even for patients with “normal” esophageal acid exposure.

Potential Acid-Independent, Anti-Inflammatory Effects of PPIs in Esophageal Eosinophilia

PPIs might benefit patients with esophageal eosinophilia through effects that are entirely independent of gastric acid suppression. Th2 cytokines such as IL-4 and IL-13, which can be overproduced in allergic disorders, stimulate esophageal epithelial cells to secrete the potent eosinophil chemoattractant eotaxin-3.^{69–72} This mechanism is thought to contribute

importantly to the esophageal eosinophilia of EoE. Two recent studies using esophageal epithelial cells in culture have shown that PPIs inhibit the Th2 cytokine-stimulated secretion of eotaxin-3.^{72, 73} This inhibition occurs with omeprazole in concentrations as low as 1 μ M, which are readily achieved in blood with conventional oral dosing, and with lansoprazole, suggesting a PPI drug class effect.^{74, 75} Mechanistically, the inhibitory effect of PPIs seem to involve chromatin remodeling of the eotaxin-3 promoter that blocks binding by its regulatory transcription factor STAT6, thereby reducing eotaxin-3 transcription.

The PPIs are pro-drugs that require acid activation to exert their anti-secretory and their anti-inflammatory effects.^{72, 73} This acid activation occurs readily in the acidic microenvironment of the functioning parietal cell, but it is not clear whether PPI acid activation can occur in the esophagus. Conceivably, gastroesophageal acid reflux might acidify the esophageal microenvironment sufficiently to achieve PPI acid activation. In addition, the Na⁺/H⁺ exchanger on esophageal epithelial cell membranes can extrude intracellular protons that accumulate in the setting of injury, thereby acidifying the microenvironment.⁷⁶ Eosinophils and neutrophils can also release protons from their exocytic granules and lysosomes into the microenvironment,^{77–79} and microenvironment acidification has been well documented in the setting of inflammation.^{80–82} Thus, there are a number of plausible mechanisms whereby PPIs might be activated in the diseased esophagus of EoE.

Other Anti-inflammatory Effects of PPI

A number of other potentially beneficial, acid-independent, anti-inflammatory effects of PPIs have been described (Table 1).⁸³ For example, PPIs have anti-oxidant properties including their ability to scavenge hydroxyl radicals, to increase the bioavailability of sulfhydryl compounds, and to induce heme oxygenase 1.^{84–88} PPIs can inhibit the oxidative burst, migration, and phagocytosis in neutrophils and monocytes.^{89–91} In epithelial cells and endothelial cells, PPIs can decrease expression of adhesion molecule and pro-inflammatory cytokines (e.g., IL-8, IL-6, tumor necrosis factor- α),^{83, 92, 93} and inhibit Th2 cytokine-driven STAT6 signaling.⁹⁴ These acid-independent, anti-inflammatory effects could potentially benefit esophageal inflammation caused by GERD as well as by EoE.

PPI Use Might Predispose to the Development of EoE

Although PPIs are used to treat esophageal eosinophilia, there are also intriguing data to suggest that PPIs might predispose to the development of celiac disease, food allergies, and EoE.^{95, 96} The human diet contains numerous proteins with the potential to evoke immunological responses. Digestion of these potential food allergens normally begins in the stomach through the action of pepsin proteinases in acidic gastric juice.^{95, 97} By raising the gastric pH to levels above 4 at which pepsin activity ceases, PPIs might enable food allergens to escape peptic digestion. In addition, PPIs have been shown to increase gastric mucosal permeability,^{98, 99} which might facilitate the absorption of undigested food allergens and their exposure to the immune cells that mediate allergy development. Also, gastric acid suppression by PPIs causes changes in the microbiome of the upper gastrointestinal tract that conceivably could alter mucosal immune responses.^{100, 101}

There is experimental and clinical evidence that PPI treatment can have immunological consequences. Untersmayr and her colleagues have shown that mice fed parvalbumin while treated with omeprazole develop parvalbumin-specific IgE antibodies,¹⁰² and that mice fed hazelnut extract while treated with omeprazole developed anaphylactogenic IgG1 antibodies and type I skin reactivity to hazelnut.¹⁰³ In one study of 152 allergy-free adults who were treated with acid suppressive medications for 3 months, 10% showed a rise in blood IgE antibody levels and 15% developed new, food-specific IgE antibodies.¹⁰⁴

PPIs were introduced into clinical practice in the United States in 1989, and the time course of their introduction and rising usage parallels the emergence and rising incidence of EoE. Although this association fits well with the hypothesis that PPIs play an etiological role in EoE, a plausible association does not establish cause and effect. Further studies on the role of PPIs in the development of EoE clearly are warranted. While it might seem paradoxical that a medication used to treat EoE also might cause EoE, there is no paradox because the proposed mechanisms are very different. A remote exposure to PPIs (e.g. in infancy or childhood) might trigger the food allergy that causes EoE, which might respond later to the anti-inflammatory effects of PPIs described above.

Conclusions

GERD and EoE are not mutually exclusive disorders, and their interactions can be complex. The notion that GERD and EoE can be distinguished by the response to PPI treatment is based on the assumption that gastric acid suppression is the only important therapeutic effect of PPIs, and therefore only GERD can respond to PPIs. This assumption appears to be incorrect for two major reasons. First, there are multiple mechanisms whereby PPI-induced acid reduction might benefit patients with EoE. Second, PPIs have acid-independent, anti-inflammatory effects that also might be beneficial both for GERD and for EoE. Since the PPIs have multiple effects that might benefit both diseases, for patients who have esophageal symptoms and esophageal eosinophilia, we feel that a clinical and/or histological response to PPIs does not rule in GERD, and does not rule out EoE. For these reasons, we recommend a trial of PPI therapy for patients with symptomatic esophageal eosinophilia, even if the diagnosis of EoE seems clear-cut.

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Key Points

- EoE and GERD are not mutually exclusive disorders, and their interactions can be complex.
- The notion that EoE and GERD can be distinguished by the response to PPI therapy has been challenged by the recognition of patients with PPI-responsive esophageal eosinophilia who exhibit a clinical and histological response to PPIs even though they have no evidence of GERD.
- In addition to inhibiting gastric acid production, PPIs have acid-independent, anti-inflammatory effects.
- Both the acid-inhibitory and the anti-inflammatory effects of PPIs might benefit patients with EoE as well as patients with GERD.
- For patients with esophageal symptoms and eosinophilia, we feel that a clinical and/or histological response to PPIs does not rule in GERD, and does not rule out EoE.

Table 1**Potential Mechanisms Underlying Beneficial PPI Effects in Esophageal Eosinophilia****Acid-Dependent Effects**

- Decrease acid-stimulated production of eosinophil chemoattractants by esophageal epithelial cells
- Decrease acid exposure that causes inflammatory cytokine production and esophageal damage
- Decrease acid exposure that causes increased esophageal permeability to potential allergens
- Decrease acid exposure that causes acid-induced pain

Acid-Independent, Anti-Inflammatory Effects**Effects on Epithelial Cells**

- Inhibition of Th2 cytokine-stimulated eotaxin-3 expression
- Decrease production of pro-inflammatory cytokines

Anti-Oxidant Effects

- Direct scavenging of reactive oxygen species
- Increase bioavailability of protective sulfhydryl compounds
- Increase protective heme oxygenase 1 expression

Effects on Inflammatory Cells (Neutrophils, Monocytes)

- Inhibition of oxidative burst
- Impair phagocytosis of micro-organisms
- Decrease expression of adhesion molecules
- Impair migration

Effects on Endothelial Cells

- Decrease expression of adhesion molecules
- Decrease production of pro-inflammatory cytokines