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Eosinophilic Esophagitis: When to Suspect and Why to Treat with Proton Pump Inhibitors

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Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease driven by food allergens that manifests with symptoms of esophageal dysfunction and eosinophil-predominate esophageal inflammation. Since the early 1990s, the frequency of EoE has exploded for unclear reasons. Treatment of EoE with diet therapy or topical steroids, which are potent anti-inflammatory agents, makes sense for management of an allergic condition triggered by food antigens. Recent consensus guidelines now include proton pump inhibitor therapy as an alternative first-line treatment. This review will provide an overview of when to suspect and how to diagnosis EoE, concepts surrounding pathogenesis and increasing incidence of this newly recognized esophageal condition, and a discussion on why proton pump inhibitors are now being used as a first-line treatment strategy.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune- or antigen-mediated esophageal disorder characterized clinically by symptoms of esophageal dysfunction and histologically by the infiltration of eosinophils in the esophageal epithelium.[1] EoE was rarely recognized before the 1990s. Current epidemiologic data estimate that the prevalence of EoE is 50 to 100 cases per 100,000 individuals in the United States with a cost of diagnosing and treating this condition between 0.5 to1.4 billion dollars per year.[2,3] This is quite astounding for a disease that was essentially unknown just twenty years ago. Management of patients with EoE draws upon the expertise of providers in the areas of primary care, gastroenterology, allergy and immunology,

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and nutrition. The length of time that patients with EoE go undiagnosed and untreated significantly correlates with the risk of developing esophageal strictures, a major complication of EoE.[4] For primary care providers, suspicion of EoE and prompt referral to specialists are critical in the care of these patients. This review will provide an overview of when to suspect and how to diagnosis EoE, concepts surrounding pathogenesis and increasing incidence of this newly recognized esophageal condition, and a discussion on why proton pump inhibitors (PPIs) are being used as first-line agents to treat this antigen-mediated esophageal disorder.

When to Suspect and How to Diagnose EoE

EoE affects children and adults of all ages in all racial and ethnic groups, with reports of EoE from countries all around the world. EoE affects both sexes but males predominate by a factor of approximately 3 to 1. Providers should suspect EoE when patients present with symptoms of esophageal dysfunction. Esophageal dysphagia is reported by 60-100% of EoE patients and, in more than 25% of these patients, food impaction has occurred.[5] Patients often complain of chest pain, heartburn and upper abdominal pain. A history of atopic disease such as rhinitis, asthma, or atopic dermatitis is found in 50-60% of EoE patients.[6] In addition, a family history of EoE or dysphagia should further increase your clinical suspicion for EoE.[7] When endoscopy is performed, endoscopic signs of EoE are evaluated. Endoscopic features of EoE are described using the EoE endoscopic reference score, EREFS, which stands for exudates, rings, edema, furrows, and strictures.[8] However, none these features are specific for EoE and the esophagus can appear totally normal in approximately 5-10% of cases. An esophageal biopsy showing at least 15 eosinophils per high power field (HPF) is required for the diagnosis. Other typical histologic findings include eosinophil microabscessess, basal zone and/or papillary hyperplasia, and dilated intercellular spaces. There also can be striking fibrosis in the lamina propria. Thus, a patient with symptoms of esophageal dysfunction and at least 15 eosinophils/HPF on esophageal biopsy would be suspected of having EoE, but EoE is only diagnosed after other non-EoE disorders (i.e. vasculitis, eosinophilic gastroenteritis, Crohn's disease, connective tissue disease) that can cause esophageal eosinophilia and esophageal symptoms have been excluded (Table 1).[7]

Table 1. 2019 Eosinophilic Esophagitis (EoE) Diagnostic Criteria

Diagnostic Criteria for EoE
Symptoms of esophageal dysfunction
At least 15 eosinophils per high power field on esophageal biopsy
Exclusion of other non-EoE disorders that cause esophageal eosinophilia

*Modified from Dellon et al.[7]

Pathogenesis of EoE

There is significant evidence that EoE is an allergic disorder. Atopy is more common in EoE patients than in the general population.[6] Most patients will exhibit sensitization to food or aeroallergens with formal allergy testing. In fact, 15% of EoE patients have food anaphylaxis, a very good reason to refer to an allergist early in the care of these patients.[1] Perhaps the most compelling evidence that EoE is a food allergy comes from the dramatic response to elemental diets, which eliminate dietary allergens.[9] Well, if EoE is caused by a food allergy, then why do eosinophils home exclusively to the esophagus?

Eotaxin-3, a potent chemoattractant for eosinophils, has been shown to be increased (>50 fold) in esophageal biopsy specimens from patients with EoE compared to controls, and eotaxin-3 could draw eosinophils into the esophagus.[10] To understand the driving force behind eotaxin-3 upregulation, a brief discussion of immune system activation is warranted. 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 naïve CD4+ T cells into Th1 or Th2 cells. Th2 cells secrete cytokines like interleukin (IL)-5, IL-4, and IL-13, and overproduction of Th2 cells is characteristic of

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a number of allergic disorders, including EoE. In human esophageal epithelial cells cultured *in vitro,* the Th2 cytokines IL-4 and IL-13 have been shown to stimulate eotaxin-3 production and secretion.[11] Thus, these 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 antigen presenting cells which, in this genetically susceptible person, induces a Th2 response with the production of Th2 cytokines like IL-5, IL-4, and IL-13. IL-5 activates eosinophils that reside in the bone marrow while IL-13 and IL-4 stimulate the production of eotaxin-3 by the esophageal epithelial cells. Eotaxin-3 is a potent chemoattractant that causes the activated eosinophils to home to the esophagus, and the eosinophils cause epithelial injury from their degranulation products. (Figure 1) So this is a reasonable model for the pathogenesis of EoE, but why is this happening now?

Proposed Hypothesis to Explain the Increase in Frequency of EoE

EoE was not even recognized until the early 1990s, and its incidence has increased dramatically ever since. So why didn't we see EoE before 1990, and why are we seeing so much more of it now? The answer is we really don't know, but a number of hypotheses have been proposed (Reviewed in [12]). The hygiene hypothesis holds that modern hygienic conditions result in far fewer encounters with bacterial, viral, and parasitic infections during childhood, and this paucity of pathogen exposure somehow leads to allergic diseases in adults. A related hypothesis is that of microbial dysbiosis in which a change in the composition and diversity of the microbiome associated with

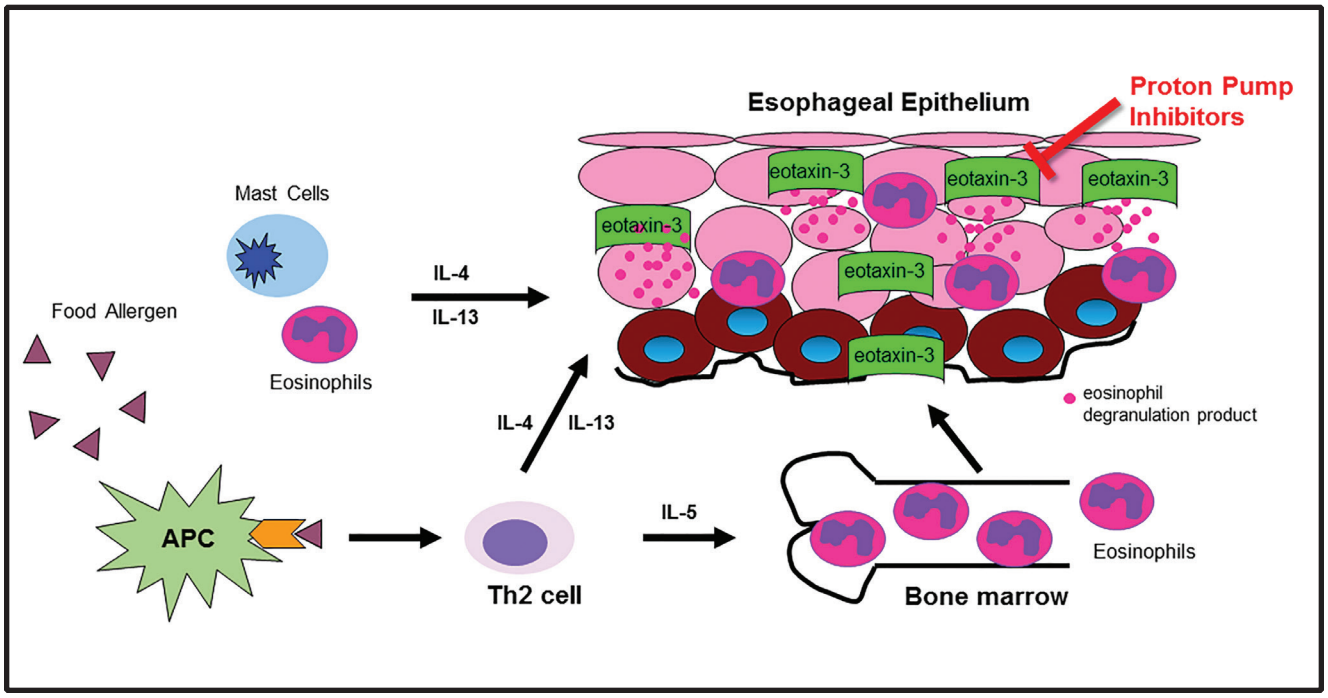

Figure 1. Eosinophilic Esophagitis Pathogenesis Model and Proposed Site of Action for Proton Pump Inhibitors. In a genetically-susceptible individual, some food allergen activates the immune system by binding to antigen presenting cells (APC) which, in this genetically susceptible person, induces a Th2 response with the production of Th2 cytokines like IL-5. IL-5 activates eosinophils which reside in the bone marrow. In addition, the surrounding Th2 cells, mast cells and even eosinophils 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 the activated eosinophils to home to the esophagus and the eosinophils cause epithelial injury from their degranulation products. Therapy with proton pump inhibitors block the secretion of eotaxin-3, in response to Th2 cytokines, by the esophageal epithelial cells therefore decreasing esophageal eosinophilia.

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a Western lifestyle somehow contributes to EoE development. It's also been proposed that environmental factors such as genetic modification or chemical treatment of crops, hormone and antibiotic treatment of livestock, changes in food additives and in the processing and packaging of foods, and air and water pollutants might contribute to the development of EoE. A declining frequency of *Helicobacter pylori* infection might contribute to the rising frequency in EoE because data suggest that *H. pylori* induces T regulatory cells that protect against allergy development. Alternatively, *H. pylori* infection might just be a marker of poor hygiene which may be protective against allergic diseases, as suggested by the hygiene hypothesis. An increase in the frequency of gastroesophageal reflux disease (GERD) might increase esophageal permeability allowing food allergens to enter the esophageal epithelium leading to EoE. The most fascinating hypothesis, however, has to do with the use of acid suppressant medications.

The steep rise in the frequency of EoE begins in the early 1990s, just when the therapeutic use of PPIs becomes widespread. As we discussed earlier, every day, we ingest a huge numbers of protein allergens that have the potential to evoke an immune response. When a protein allergen enters the stomach, it is digested by pepsin into small peptide fragments that may no longer by allergenic. However, PPIs raise the gastric pH to levels above 4.5 which, at these pH levels, the enzymatic activity of pepsin is no longer active. In addition, PPIs have been found to increase gastric mucosal permeability.[13] As a result, allergenic peptides are not degraded in the stomach, and instead get absorbed intact through the gastric mucosa or through the small intestine where they might evoke an allergic response. Intriguingly, there is some experimental support for this hypothesis. Food-specific IgE antibodies can develop in patients taking PPIs or H2-receptor blockers for three months,[14] despite having negative histories for atopy or allergies. After three months of treatment with an acid reducing medication, however, 10% of patients boosted their pre-existing IgE levels, and 15% of patients with no detectable IgE at baseline developed new, food-specific IgE antibodies suggesting that acid suppressing medications might predispose to the development of food allergies.[14] Moreover, a recent case-control study explored the association between prenatal, intrapartum, and postnatal factors and the risk of developing EoE later on in childhood.[15] Several prenatal factors were significantly associated with EoE including maternal fever, pregnancy complications, and preterm labor. Cesarean delivery also was associated with later development of EoE. Postnatal, during infancy, the use of antibiotics was associated with EoE whereas having a dog or cat at home was protective. However, the single strongest risk factor (odd ratio >7) for the development of EoE later on in childhood was the use of acid suppressant medications during the first year of life.[15]

Why Do We Use Proton Pump Inhibitors to Treat EoE

It may seem paradoxical that PPIs are used to treat EoE after our previous discussion on how PPIs might cause the disease. So, let's consider why PPIs are used for treatment. Esophageal symptoms, endoscopic findings, and esophageal eosinophilia are not specific for EoE as these features can also be seen in other esophageal conditions including GERD. Initially, a PPI trial was used as a diagnostic test for EoE because it was thought that a symptomatic response to PPIs meant that the patient has GERD since there was no way that an antigen-driven condition like EoE could respond to a PPI. In 2007, a subcommittee of the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) composed of physicians and researchers with expertise in EoE put forth the first consensus recommendations based on a systematic review of the literature and expert opinion specially stating that, to make a diagnosis of EoE, a lack of response to high-dose PPI treatment was required.[16] This approach sounded reasonable until investigators began to recognize patients with esophageal symptoms and histology typical of EoE, but who had no evidence of GERD either by endoscopy or pH monitoring, and who responded to PPIs nevertheless.[17] At that time, however, our prevailing definition of EoE excluded patients who responded to PPIs, so investigators had to use another term to described such patients and coined the phrase "PPI-responsive esophageal eosinophilia" (PPI-REE). Since then,

several studies have found histologic response rate of 30% to 50% among patients with esophageal eosinophilia treated with PPIs (Reviewed in [18]).

In 2011, an interdisciplinary expert panel of EoE investigators was convened to update the 2007 consensus recommendations.[1] These updated recommendations removed the requirement for "lack of PPI responsiveness" from the diagnostic criterion and considered PPI-REE as a separate and distinct entity from EoE.[1] Around this same time, data were emerging about potential anti-inflammatory effects of PPIs that were entirely independent of their effects on gastric acid secretion.[19] Indeed, Cheng et al. reported that PPIs block the secretion of eotaxin-3 by Th2 cytokine-simulated esophageal epithelial cells in culture (Figure 1).[11] Since these studies were performed in esophageal squamous cells in culture, this anti-inflammatory effect of the PPI clearly was entirely independent of effects on gastric acid secretion. Subsequently, Zhang et al. showed that PPIs causes chromatin remodeling in the eotaxin-3 promoter, resulting in decreased eotaxin-3 transcriptional activity in Th2 cytokine-stimulated esophageal squamous cells in culture.[20] Thus, these studies provided a molecular mechanism underlying PPI-REE. In addition, multiple clinical studies found that EoE that does not respond to PPIs cannot be distinguished from PPI-REE based on any clinical, endoscopic, or histological findings suggesting that they are the same disorder (Reviewed in [6]). Indeed, studies using RNA microarrays found a similar esophageal transcriptome in patients with EoE and PPI-REE.[21, 22] Finally, two reports described EoE patients treated with diet or topical steroids, who for various reasons did not want to continue those treatments, who also achieved remission on PPI therapy (Reviewed in [6]). In 2017, guidelines published by a European task force composed of physicians and researchers with expertise in EoE formally put forth the notion that PPI-REE is part of an EoE continuum and not a separate entity.[6] Moreover, they proposed that treatment with PPIs should be used as a first-line therapy and not as a diagnostic test. Most recently, the proceeding from the International AGREE Conference which included United States physicians and researchers with expertise in EoE also concluded that PPIs should be classified as a first-line treatment for EoE and not as a diagnostic criterion.[7]

Practical Management Considerations of Using Proton Pump Inhibitors in EoE

It should be noted that the United States Food and Drug Administration to date has not approved any medication to treat EoE, and all medications including PPIs are used off label. At our Center for Esophageal Diseases, for a patient with esophageal symptoms and an esophageal biopsy showing more than 15 eosinophils/HPF, we first exclude non-EoE disorders that can cause esophageal eosinophilia (i.e. vasculitis, eosinophilic gastroenteritis, Crohn's disease, and connective tissue disease), to establish the diagnosis of EoE. Although most gastroenterologists are aware of the condition PPI-REE, they have been told for over 10 years that this condition is not EoE, and it will take some time before the practicing community accepts the notion that PPI-REE is really just EoE that responds to PPIs. Therefore, if your patient is scheduled for a diagnostic endoscopy in which EoE is a consideration, we recommend that you stop PPIs for 3-4 weeks before performing diagnostic endoscopy.[23] Once EoE is diagnosed, we usually begin treatment with PPIs because of the safety profile, ease of use, and high response rate. PPIs are given twice a day for 4-8 weeks and we perform a follow up endoscopy with biopsies while the patient is on PPIs to document histological remission of the esophageal eosinophilia. If patients respond to PPIs, then PPIs are continued. In a retrospective study, 75 patients with PPI-REE from a European and US cohort in remission with PPIs taken more than once daily, had their PPI dose tapered down to once daily with a follow up endoscopy performed 1 year later.[24] Fifty-five patients (73%) had fewer than 15 eosinophils/HPF and were in remission at 1 year. Another 9 patients (45%) regained histologic remission when their PPI dose was increased to omeprazole 40 mg twice daily. So it appears that

PPI therapy works long term to maintain remission in most adults with PPI-REE.[24] For patients that are unresponsive to PPIs, a choice between topical steroids or diet therapy is then offered.

SUMMARY

EoE is a chronic, antigen-mediated esophageal disorder whose incidence has increased dramatically since the early 1990s for reasons that remain unclear. EoE should be suspected in patients with symptoms of esophageal dysfunction, ≥15 eosinophils/HPF on esophageal biopsies, and the absence of a non-EoE disorder that can cause esophageal eosinophilia. Esophageal eosinophilia that responds to PPIs is called PPI-REE, a term that initially arose from the need to distinguish EoE from GERD. Since 2007, multiple lines of evidence have supported the notion that PPI-REE is on the spectrum of an EoE continuum and not a separate, distinct entity. Although the term PPI-REE is still used, it is now a description of EoE and not a separate diagnosis. In vitro studies have provided plausible molecular mechanisms regarding how EoE may respond to treatment with PPIs. Finally, and most importantly, PPIs are now used as first-line treatment for EoE, and not used as a means to exclude this diagnosis. ■

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