

Eosinophilic Esophagitis and Proton Pump Inhibitors: Controversies and Implications for Clinical Practice

W. Asher Wolf, MD, MPH, and Evan S. Dellon, MD, MPH

Dr Wolf is a fellow in gastroenterology and hepatology and Dr Dellon is an associate professor of medicine and adjunct associate professor of epidemiology at the Center for Esophageal Diseases and Swallowing and the Center for Gastrointestinal Biology and Disease in the Division of Gastroenterology and Hepatology at the University of North Carolina School of Medicine in Chapel Hill, North Carolina.

Address correspondence to:

Dr Evan S. Dellon

University of North Carolina School of Medicine

CB#7080 Bioinformatics Building

130 Mason Farm Road

Chapel Hill, NC 27599-7080

Tel: 919-966-2513

Fax: 919-843-2508

E-mail: edellon@med.unc.edu

Abstract: Eosinophilic esophagitis (EoE) is a major cause of dysphagia and food impaction. Recognition and diagnosis of EoE have been increasing rapidly, but the role of proton pump inhibitors (PPIs) for the diagnosis of EoE and treatment of esophageal eosinophilia remains controversial. Initial diagnostic algorithms for EoE relied on a PPI trial to distinguish EoE from gastroesophageal reflux disease, a common cause of esophageal eosinophilia. This approach has become complicated by the recent recognition of PPI-responsive esophageal eosinophilia (PPI-REE), a disorder characterized by clinicopathologic features similar to EoE but that resolve with high-dose PPI therapy. The mechanism of PPI action for treatment of esophageal eosinophilia may rely not only on acid suppression but also on novel anti-inflammatory effects of the PPIs themselves. Treatment with PPI therapy is now considered a required step before a formal diagnosis of EoE can be made, and continuing PPI therapy in patients with PPI-REE is a common strategy. However, the role of continuing PPI monotherapy in patients with EoE remains a matter of debate. The decision to do so should hinge on improvement in symptoms and histology as well as the need for ongoing dilation.

Eosinophilic esophagitis (EoE) is a newly recognized and important cause of gastrointestinal illness in adults. It is a chronic, immune-mediated disorder of the esophagus defined symptomatically by esophageal dysfunction and pathologically by eosinophil infiltration into the esophageal mucosa.¹ Specifically, EoE consensus guidelines require symptoms of esophageal dysfunction, 15 or more eosinophils per high-power field (eos/hpf) on microscopic examination of esophageal biopsy after 8 weeks on a high-dose proton pump inhibitor (PPI), and the absence of alternative causes of eosinophilia.¹⁻³

The requirement that patients undergo a trial of PPI therapy was introduced because both EoE and gastroesophageal reflux disease (GERD) can cause esophageal eosinophilia.⁴⁻⁶ The use of PPI therapy

Keywords

Eosinophilic esophagitis, proton pump inhibitor, gastroesophageal reflux disease, proton pump inhibitor-responsive esophageal eosinophilia

was intended to eliminate GERD as an alternative cause of eosinophil infiltration. However, it became clear that the relationship between esophageal eosinophilia, EoE, and GERD was not this simple⁷ and that the overlapping symptoms of these disorders made definitive clinical diagnosis challenging.

The complexity of this interaction was further heightened by the suggestion of a third disorder, PPI-responsive esophageal eosinophilia (PPI-REE). This entity was first described in patients with endoscopic and symptomatic features of EoE who showed resolution of eosinophilia with PPI therapy alone.⁸ It is unclear whether PPI-REE represents an independent clinical disorder or is a subtype of either EoE or GERD.

This article will review the current understanding of EoE in the context of its interaction with GERD and PPI-REE and will also discuss the role of PPIs in the treatment of esophageal eosinophilia.

Eosinophilic Esophagitis, Esophageal Eosinophilia, and the Role of Reflux

EoE is driven by inappropriate immune activation of the esophagus.³ The resulting chronic inflammation causes esophageal fibrosis, decreases esophageal compliance, and leads to an increased risk of food impaction, particularly in adolescents and adults.⁹⁻¹² Other classic symptoms include dysphagia, chest discomfort, and heartburn and, in children, abdominal pain, vomiting, and failure to thrive.¹³ The esophagus has a typical appearance on upper endoscopy with rings, furrows, edema, white exudates, and mucosal fragility (crêpe paper).^{14,15} The diagnosis of EoE is based on the combination of symptoms of esophageal dysfunction and biopsy findings of 15 or more eos/hpf while on high-dose PPI therapy in the absence of an alternative diagnosis.^{1,3}

The mainstay of EoE treatment in adults has been topical corticosteroids, but there is an evolving role for dietary elimination therapy. Corticosteroids such as budesonide and fluticasone have been used successfully to control symptoms, decrease esophageal eosinophilia, and slow or reverse tissue remodeling.¹⁶⁻¹⁸

In children, dietary therapy is a highly successful treatment modality.^{13,18-21} Data in adults are more mixed, but food elimination diets have been shown to achieve similar results to those achieved with topical corticosteroids.²²⁻²⁴

A key point in making the diagnosis of EoE is recognizing that the finding of esophageal eosinophilia on biopsy does not equate to a diagnosis of EoE. A differential diagnosis for esophageal eosinophilia must be considered.¹⁻³ Although a number of potential causes of esophageal eosinophilia—such as hypereosinophilic syndrome, Crohn's disease of the esophagus, infections,

drug reactions, and connective tissue diseases—can often be excluded by a thorough patient history and physical examination, basic laboratory tests, and endoscopic findings, it can be difficult to separate the esophageal eosinophilia caused by EoE from that caused by GERD. It was observed several decades ago that low levels of esophageal eosinophilia might be a consequence of acid injury in the lower esophagus,⁴ but even higher levels of esophageal eosinophilia are not specific for EoE and could be a consequence of reflux.^{5,6} Because of this, the first EoE consensus guidelines required that patients undergo a PPI trial with the expectation that acid suppression would control GERD, thus differentiating the 2 diseases.² Similarly, the cutoff of 15 or more eos/hpf served, in part, to exclude low-grade esophageal eosinophilia typical of GERD.²⁵

It quickly became clear, however, that the relationship between EoE and GERD was not so simple. Spechler and colleagues highlighted that the 2 diseases may interact in a complex manner.⁷ Specifically, there are 4 possible scenarios: 1) GERD causes reflux-mediated esophageal injury that results in a mild eosinophilic infiltration; 2) GERD and EoE coexist but are unrelated, as might be expected given how common GERD is among the general population; 3) EoE contributes to or causes GERD, for example, with the eosinophilic infiltrate causing esophageal dysmotility that would predispose patients to reflux; or 4) GERD contributes to or causes EoE, potentially by causing barrier breaks in the esophageal epithelium, which would allow new antigens or allergens to be exposed to the immune system.⁷ This framework also provides hypotheses as to how PPIs might benefit some patients with EoE. PPIs would treat reflux-mediated esophageal eosinophilia, decrease the symptoms related to reflux when EoE and GERD overlap, and heal esophageal barrier function, leading to less antigen exposure.

Because the PPI trial would not then simply distinguish EoE from GERD, additional clinical testing may be required in patients with esophageal eosinophilia who are suspected of having reflux. One reasonable approach to assess the contribution of gastric acid is to use pH monitoring. However, even ambulatory 24-hour pH testing does not reliably predict response to PPI or swallowed corticosteroid therapy.²⁶

Proton Pump Inhibitor-Responsive Esophageal Eosinophilia

Over the past several years, the approach to esophageal eosinophilia has become more complicated with the recognition of PPI-REE. This condition was first described in a series of 3 pediatric patients with clinical, endoscopic, and histologic features of EoE but who completely responded to a course of PPI treatment.⁸ Since that time, retrospec-

tive and prospective studies in both children and adults consistently show that at least one-third of patients with esophageal eosinophilia respond to a course of high-dose PPIs.²⁶⁻³¹ Although the mechanisms of this PPI response are currently being elucidated (see below), the critical point is that patients with esophageal eosinophilia that responds to PPI therapy are currently not considered to have EoE.^{1,3} Specifically, guidelines require that patients undergo a PPI trial before they can receive a formal diagnosis of EoE.¹⁻³ It is unclear, however, whether a patient has PPI-REE or GERD based on PPI response alone. It is also unclear if PPI-REE is a form of GERD, a subtype of EoE, a result of their interaction, or an independent condition. Adding to the confusion, PPI-REE can be a transient condition. Dohil and colleagues have presented a series of patients who had an initial response to PPI therapy, but on long-term follow-up, and in the absence of medication adherence issues, seasonality, changes in diet, or new allergen triggers, subsequently developed recurrent esophageal eosinophilia consistent with EoE in spite of ongoing PPI therapy for PPI-REE.³²

The Role of Proton Pump Inhibitor Therapy for Esophageal Eosinophilia

In spite of the diagnostic uncertainty associated with EoE, GERD, and PPI-REE, there are benefits to PPI therapy in a subset of patients with esophageal eosinophilia. A review by Molina-Infante and colleagues indicated that the rate of symptom improvement in adults with esophageal eosinophilia who were treated with PPI therapy ranged from 25% to 80% and histologic remission from 33% to 61%, depending on the study design and patient population.³³

One of the most fascinating areas of emerging data concerns the mechanism of PPI response in patients with esophageal eosinophilia. For example, several studies have suggested that PPIs may have novel anti-inflammatory effects that are independent of their acid suppression. PPIs can act as antioxidants, directly inhibit neutrophils and monocytes, decrease expression of proinflammatory cytokines, and inhibit or kill multiple bacteria and fungi.³⁴⁻³⁶ PPIs also have been shown to inhibit eosinophil recruitment from blood to tissue, not just into the gastrointestinal tract but also into lung tissue and secretions.³⁷ Specifically applicable to esophageal eosinophilia are studies that show that PPIs block interleukin (IL)-4- and IL-13-stimulated secretion of eotaxin-3 in esophageal cell lines from patients with EoE, likely by impacting STAT6 binding to the eotaxin-3 promoter.^{35,36} This not only provides a direct mechanism of action for the clinical improvement noted in patients who have PPI-REE^{8,29,30,38} but also potentially explains why it is difficult to predict which patients with suspected EoE will have a PPI response.³⁸ Interestingly,

the same eotaxin-blocking effect is not seen when PPIs are applied to a fibroblast culture system.³⁹ The similarities between patients with EoE and some with PPI-REE are further highlighted by the fact that the same genes, including eotaxin-3 and Th2 cytokines, are downregulated after treatment.⁴⁰ Finally, use of PPIs can restore esophageal mucosal barrier function in patients with esophageal eosinophilia, potentially decreasing the route of exposure for allergen triggers to inflammation.⁴¹

The PPI response goes beyond the effect on histology and improvement in esophageal eosinophilia and leads to other clinical improvements as well. PPI therapy may play a role in combination therapy with patients who require dilation.⁴² In a systematic review examining dilation in patients with EoE, Bohm and Richter found that inflammation was reduced in patients who underwent dilation and PPI therapy but not in patients who underwent dilation alone.⁴³

There can also be significant improvement in dysphagia with PPI therapy in those with esophageal eosinophilia. Two studies have randomized patients with esophageal eosinophilia and possible (although not confirmed with a PPI trial) EoE to fluticasone or high-dose esomeprazole. In both studies, patients had greater improvement in dysphagia on PPI therapy than on fluticasone therapy.^{44,45} In a study by Moawad and colleagues, although abnormal pH testing or erosive esophagitis predicted a greater histologic response to PPIs, patients without clinical features of GERD also had a robust histologic response to PPIs.⁴⁴ It is likely that the patient groups enrolled in these studies included a combination of GERD, PPI-REE, and EoE, and those differences may explain the underlying response rates.

Controversy

Because of the clinical confusion that can arise from determining if esophageal eosinophilia is due to GERD, PPI-REE, or EoE, and because of the multiple roles that PPIs occupy in this clinical scenario (diagnostic requirement, therapeutic test, antisecretory actions, and anti-inflammatory actions), it is not surprising that there are a number of controversies related to PPI use.^{1-4,6-8,33,36,46}

First, while there has been consistent findings in the literature that PPI therapy resolves esophageal eosinophilia in at least one-third of patients,^{8,26-31} many of the details of the PPI trial remain controversial. Specifically, the length of PPI treatment, the type of PPI, the dose, the frequency of dosing, and whether the approach should be different in children or adults have not been determined. Although many of the PPI-REE studies use either twice-daily or high-dose PPIs, this dose level is not approved by the US Food and Drug Administration, and the utility of high-dose PPIs remains controversial even in GERD.⁴⁷ This

lack of data supporting the exact strategy for the PPI trial is recognized in the most recent EoE clinical guidelines, with a grade of “low evidence.”²³ Additional research that helps delineate the optimal approach to PPI treatment in patients with esophageal eosinophilia would be welcome.

Second, although PPIs can be effective for a subgroup of patients, it is possible that the opposite could be the case: Merwat and Spechler have suggested, using several lines of evidence, that the use of PPIs may actually cause EoE.⁴⁸ The authors note that there is a synchronous rise in both the use of PPIs and the diagnosis of EoE, which is an ecologic association. Furthermore, they lay out evidence demonstrating that acid suppressive medications may interfere with peptic food digestion, thereby contributing to an increase in food-specific antigens, and may also increase mucosal permeability. These effects together may cause increased allergic reactivity to foods over time, perhaps sensitizing persons and eventually triggering EoE. In fact, in animal models, PPI use can cause the formation of food-specific immunoglobulin (Ig) E antibodies and trigger food allergy.^{49,50} However, there are some counterarguments to PPIs as the cause of EoE. So far, the mechanism described is IgE-mediated, and EoE is most likely not an IgE-mediated disease.⁵¹ Also, case reports of esophageal changes consistent with EoE predate the introduction of PPIs.⁵² Finally, it has yet to be shown prospectively, either in animals or humans, that PPIs cause EoE, and typically in humans, a preexisting symptom would trigger the use of a PPI. However, there is increasing use of PPIs in early childhood to treat presumed reflux or colic,⁵³ and this could provide the early exposure needed to trigger EoE.

Third, the inclusion of a PPI trial in the diagnostic algorithm for EoE, although currently necessary, is somewhat unsatisfying. There are few conditions in which response or lack of response to a medication is a diagnostic requirement, and the PPI trial adds risk, expense, and time to the diagnostic process. (If a patient is not on a PPI for their first esophagogastroduodenoscopy, then a second procedure is required to confirm the EoE diagnosis.) Moreover, the PPI, by itself, is not helpful for distinguishing GERD from PPI-REE as the cause of esophageal eosinophilia, and it similarly cannot distinguish between patients who might have EoE and respond to a PPI as an anti-inflammatory agent and those who have non-EoE PPI-REE and respond for other reasons. One reason that the guidelines require a PPI trial is to help establish a consistent definition of EoE in a field where multiple definitions were used,⁵⁴ but the guidelines have evolved over time as more data have emerged to inform the diagnostic process.¹⁻³ Ideally, clinicians would be able to characterize a patient with esophageal eosinophilia at the time of biopsy with either specialized testing or new biomarkers and would be able to avoid a PPI trial altogether.

Although there has been novel and exciting diagnostic work with gene expression profiling and minimally invasive biomarker measurement,^{55,56} there is still no way to distinguish EoE from PPI-REE with the current clinically available testing. Although potentially desirable, there are not yet enough data to conclude that EoE and PPI-REE are the same. Because of this controversy, the role of PPIs in the diagnostic approach to EoE should be a point of emphasis for future research, and new or emerging data may eventually challenge the current guidelines.

Conclusions

EoE is an increasingly important cause of dysphagia and food impaction in adults and adolescents and of abdominal pain, vomiting, and failure to thrive in children. Clinical awareness has risen rapidly, with an associated rise in the incidence and prevalence of this condition. Accurate diagnosis of EoE hinges on a thorough evaluation of the cause of esophageal eosinophilia. Diagnostic algorithms were first created with the intention of distinguishing EoE from GERD with a PPI trial. However, the role of PPIs in the treatment of esophageal eosinophilia remains complex. One reason is the recognition of PPI-REE as a new clinical entity. It remains unclear whether PPI-REE is a subset of GERD or of EoE, a separate disease state, or a result of the interaction of GERD and EoE.

In this complex setting, the role of PPI therapy continues to evolve. PPIs currently are a necessary part of the diagnostic algorithm of EoE, and the diagnosis of EoE cannot be confirmed without a PPI trial.³ Furthermore, PPIs appear to have benefit both in improving symptoms of dysphagia in patients with esophageal eosinophilia^{44,45} and reducing inflammation in patients who undergo dilation for EoE-related esophageal narrowing.⁴³ The mechanisms of the PPI response in patients with esophageal eosinophilia are beginning to be elucidated. In particular, PPIs have an anti-inflammatory/antieosinophilic effect by decreasing Th2 cytokine-mediated eosinophil chemoattraction and may decrease allergen exposure by restoring esophageal mucosal integrity.^{34,35,40,41} In spite of these benefits, researchers have intriguingly hypothesized that PPIs may cause EoE,⁴⁸ although evidence to support this position is largely theoretical.

Long-term use of PPIs in patients with esophageal eosinophilia should be driven by clinical and histologic response to therapy. In patients with persistent esophageal eosinophilia who are taking PPIs, therapy should continue with the medication at the lowest effective dose only if the PPI reduces dysphagia, heartburn, or other clinical symptoms. In patients who have histologic resolution of eosinophilia after a PPI trial, a diagnosis of PPI-REE should be made, and PPIs should be continued. If neither

symptoms nor histology improves, the diagnosis of EoE is confirmed, and PPIs should be discontinued to minimize associated risks such as calcium malabsorption and *Clostridium difficile* infection.^{57,58} One important exception may be in patients who require serial dilation, as those patients may have decreased inflammation when a PPI is part of their regimen. In patients who respond to PPIs, reevaluation of both the indication for the medication and monitoring for recurrent symptoms should be ongoing, as eosinophilia may recur and PPI-REE may progress to EoE. Because the complex relationship between EoE, PPI-REE, and GERD is only now being fully appreciated, it is expected that diagnostic algorithms and treatment approaches with PPIs will change in the future.

The authors have no relevant conflicts of interest to disclose.

References

- Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6, quiz 21-22.
- Furuta GT, Liacouras CA, Collins MH, et al; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133(4):1342-1363.
- Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol*. 2013;108(5):679-692; quiz 693.
- Winter HS, Madara JL, Stafford RJ, Grand RJ, Quinlan JE, Goldman H. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology*. 1982;83(4):818-823.
- Ruchelli E, Wenner W, Voytek T, Brown K, Liacouras C. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol*. 1999;2(1):15-18.
- Rodrigo S, Abboud G, Oh D, et al. High intraepithelial eosinophil counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2008;103(2):435-442.
- Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102(6):1301-1306.
- Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol*. 2006;101(7):1666-1670.
- Nicodème F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2013;11(9):1101-1107.e1.
- Desai TK, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc*. 2005;61(7):795-801.
- Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2007;119(1):206-212.
- Sperry SL, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. *Gastrointest Endosc*. 2011;74(5):985-991.
- Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr*. 2009;48(1):30-36.
- Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology*. 2013;145(6):1230-1236.e1.
- Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(9):988-996.e5.
- Caldwell JM, Blanchard C, Collins MH, et al. Glucocorticoid-regulated genes in eosinophilic esophagitis: a role for FKBP51. *J Allergy Clin Immunol*. 2010;125(4):879-888.e8.
- Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy*. 2010;65(1):109-116.
- Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006;131(5):1381-1391.
- Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. *Curr Opin Allergy Clin Immunol*. 2007;7(3):274-278.
- Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr*. 2011;53(2):145-149.
- Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4(9):1097-1102.
- Gonzalez-Cervera J, Angueira T, Rodriguez-Dominguez B, Arias A, Yague-Compadre JL, Lucendo AJ. Successful food elimination therapy in adult eosinophilic esophagitis: not all patients are the same. *J Clin Gastroenterol*. 2012;46(10):855-858.
- Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol*. 2013;131(3):797-804.
- Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol*. 2013;108(5):759-766.
- Hirano I. Editorial: should patients with suspected eosinophilic esophagitis undergo a therapeutic trial of proton pump inhibition? *Am J Gastroenterol*. 2013;108(3):373-375.
- Francis DL, Foxx-Orenstein A, Arora AS, et al. Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic esophagitis. *Aliment Pharmacol Ther*. 2012;35(2):300-307.
- Schroeder S, Capocelli KE, Masterson JC, et al. Effect of proton pump inhibitor on esophageal eosinophilia. *J Pediatr Gastroenterol Nutr*. 2013;56(2):166-172.
- Abe Y, Iijima K, Ohara S, et al. A Japanese case series of 12 patients with esophageal eosinophilia. *J Gastroenterol*. 2011;46(1):25-30.
- Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol*. 2011;9(2):110-117.
- Sayej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from non-eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2009;49(4):393-399.
- Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr*. 2009;154(1):96-100.
- Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci*. 2012;57(5):1413-1419.
- Molina-Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic esophagitis. *Aliment Pharmacol Ther*. 2013;37(12):1157-1164.
- Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci*. 2009;54(11):2312-2317.
- Zhang X, Cheng E, Huo X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One*. 2012;7(11):e50037.
- Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic esophagitis and GORD. *Gut*. 2013;62(6):824-832.
- Cortes JR, Rivas MD, Molina-Infante J, et al. Omeprazole inhibits IL-4 and IL-13 signaling signal transducer and activator of transcription 6 activation and reduces lung inflammation in murine asthma. *J Allergy Clin Immunol*. 2009;124(3):607-610.e1.
- Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am J Gastroenterol*. 2013;108(12):1854-1860.
- Cheng E, Zhang X, Zhang Q, et al. TH2 cytokines stimulate eotaxin-3 secretion by esophageal fibroblasts: an effect that is not blocked by omeprazole. *Gastroenterology*. 2013;144(5):S79-S80.

40. Molina-Infante J, Rivas MD, Rodriguez GV, et al. Remission in proton pump inhibitors-responsive esophageal eosinophilia correlates with downregulation of eotaxin-3 and TH2 cytokines, similarly to eosinophilic esophagitis after steroids. *Gastroenterology*. 2013;144(5):S484.
41. van Rhijn BD, Weijenberg PW, Verheij J, et al. Acid suppression restores impaired esophageal mucosal integrity in patients with esophageal eosinophilia. *Gastroenterology*. 2013;144(5):S155.
42. Bohm M, Richter JE, Kelsen S, Thomas R. Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing. *Dis Esophagus*. 2010;23(5):377-385.
43. Bohm ME, Richter JE. Review article: oesophageal dilation in adults with eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2011;33(7):748-757.
44. Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol*. 2013;108(3):366-372.
45. Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci*. 2010;55(5):1313-1319.
46. Elitsur Y. Current and emerging treatment options for pediatric eosinophilic esophagitis. *Ped Health Med Ther*. 2013;4:101-107.
47. Kahrilas PJ, Shaheen NJ, Vaezi MF. American gastroenterological association medical position statement on the management of gastroesophageal reflux disease. *Gastroenterology*. 2008;135(4):1383-1391.e5.
48. Merwat SN, Spechler SJ. Might the use of acid-suppressive medications predispose to the development of eosinophilic esophagitis? *Am J Gastroenterol*. 2009;104(8):1897-1902.
49. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. *J Allergy Clin Immunol*. 2008;121(6):1301-1308, quiz 1309-1310.
50. Untersmayr E, Schöll I, Swoboda I, et al. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. *J Allergy Clin Immunol*. 2003;112(3):616-623.
51. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? *Clin Gastroenterol Hepatol*. 2004;2(7):523-530.
52. Kelley ML Jr, Frazer JP. Symptomatic mid-esophageal webs. *JAMA*. 1966;197(2):143-146.
53. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al; North American Society for Pediatric Gastroenterology Hepatology and Nutrition; European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49(4):498-547.
54. Dellon ES, Aderoju A, Woosley JT, Sandler RS, Shaheen NJ. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. *Am J Gastroenterol*. 2007;102(10):2300-2313.
55. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology*. 2013;145(6):1289-1299.
56. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut*. 2013;62(10):1395-1405.
57. Loo VG, Bourgault AM, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med*. 2011;365(18):1693-1703.
58. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med*. 2005;118(7):778-781.