HHS Public Access

Author manuscript

Expert Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2016 September 12.

Published in final edited form as:

Expert Rev Gastroenterol Hepatol. 2015 ; 9(11): 1359–1369. doi:10.1586/17474124.2015.1088384.

Management of proton pump inhibitor responsive-esophageal eosinophilia and eosinophilic esophagitis: Controversies in treatment approaches

Bharati Kochar, MD[1] and **Evan S. Dellon, MD MPH**[1]

[1]Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

Abstract

Eosinophilic esophagitis (EoE) is a chronic immune mediated clinicopathologic disease. The prevalence of EoE is approximately 1/2000 persons, EoE is now the most common cause of food impactions, and health care expenditures approach $1 billion annually. This paper will discuss challenges related to proton pump inhibitor responsive esophageal eosinophilia (PPI-REE), including distinguishing this condition from EoE and understanding mechanisms of the PPI response. For EoE, we will review multiple ongoing debates about treatment and monitoring strategies, including selecting treatment outcomes, optimizing medication formulations, approaching the steroid-refractory patient, conducting dietary elimination, prescribing long-term maintenance therapy, and performing esophageal dilation.

Keywords

Eosinophilic esophagitis; Proton pump inhibitor responsive esophageal eosinophilia; Management; Challenges; Endoscopy

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated clinicopathologic disease. Patients presenting with evidence of esophageal dysfunction with at least 15 eosinophils per high power field (eos/hpf) after a high-dose proton pump inhibitor (PPI) trial and in the absence of other known causes of eosinophilia meet diagnostic criteria for EoE [1,2]. However, the presence of high intraepithelial eosinophils in an esophageal biopsy is not specific to EoE, but can be present in gastroesophageal reflux disease (GERD), PPI-responsive esophageal eosinophilia (PPI-REE) and other disorders with systemic eosinophilia or inflammation [2,3]. The prevalence of EoE has been recently estimated to be at least 56.7/100,000 persons, with a peak prevalence of 114.6/100,000 in men between the

Corresponding Author: Evan S. Dellon MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508, edellon@med.unc.edu.

Disclosures: Dr. Kochar has nothing to disclose. Dr. Dellon has received research funding from Miraca Life Sciences, Meritage, Receptos, and Regeneron, has received an educational grant from Diagnovus, and has been a consultant for Aptalis, Novartis, Receptos, Regeneron, and Roche.

ages of 35 – 39 years [4], EoE is now the most common cause of food impactions [5], and health care expenditures approach $1 billion annually [6]. Given the rising prevalence of EoE, understanding the controversies in management of EoE is beneficial to patients, clinicians and researchers alike. This paper will therefore discuss challenges related to PPI-REE, including distinguishing this condition from EoE and understanding mechanisms of the PPI response. For EoE, we will review multiple ongoing debates about treatment and monitoring strategies, including selecting treatment outcomes, optimizing medication formulations, approaching the steroid-refractory patient, conducting dietary elimination, prescribing long-term maintenance therapy, and performing esophageal dilation.

Proton pump inhibitor-responsive esophageal eosinophilia

PPI-REE is a condition where patients have esophageal eosinophilia and clinical and endoscopic features that are consistent with EoE, but have symptom improvement and resolution of eosinophilia after PPI treatment [2]. In retrospect, this entity was first described in 2006 in a case series posing the question of whether three patients which esophageal eosinophilia who responded to PPI treatment had peptic or allergic esophagitis [7,8]. However, prior to the recognition of EoE and PPI-REE, the presence of eosinophils in the esophageal mucosa had largely been attributed to GERD [9], and the first EoE diagnostic guidelines required either a PPI trial or negative pH-testing to distinguish EoE from GERD [10]. Since then, a much more complex relation between EoE and GERD has been described [11]. Multiple prospective and retrospective studies in both children and adults have shown that at least one third of patients with esophageal eosinophilia will respond to PPI treatment [12-19]. With this increasing evidence, the more recent EoE diagnostic guidelines have required exclusion of PPI-REE with a high-dose PPI trial prior to the diagnosis of EoE [1,2]. However, as of yet there are no clinical, endoscopic, histologic, immunohistochemical, cytokine, or gene expression differences at baseline prior to the PPI trial that distinguish EoE from PPI-REE [17,19-24]. Therefore, it is possible that PPI-REE is a phenotype of EoE, instead of being a distinctly different disease [21,25,26], but further studies are needed to better elucidate this dilemma.

Mechanism of PPI response in PPI-REE

If PPI-REE is difficult to distinguish from EoE at baseline, and if GERD is not the cause of esophageal eosinophilia in PPI-REE, what acid-independent mechanisms might explain the PPI response in these patients? Available evidence suggests that in patients with a clinical EoE phenotype who respond to PPI therapy and are diagnosed with PPI-REE, allergic and immune mediators are elevated at levels similar to what would be seen in EoE [20,22,24]. Moreover, a study of genetic expression in patients with EoE and PPI-REE, prior to the PPI trial, revealed that patients in both groups had a similar molecular signature. However, in the population with PPI-REE, PPI monotherapy almost completely reversed the molecular signature. This suggests that PPIs play an anti-inflammatory role in treating PPI-REE [24]. In vitro and in vivo models have demonstrated anti-oxidant and anti-inflammatory effects of PPIs [27]. In recent work in EoE cell lines, PPIs have been shown to decrease eotaxin-3 expression by blocking the promotor region of that gene, a mechanism that can directly explain the PPI response seen clinically [28,29]. Another proposed mechanism of PPI

responsiveness is through the mucosal barrier. The esophageal mucosal barrier is impaired in both EoE and PPI-REE. However, in the patients with PPI-REE, PPIs partially restored mucosal integrity [30]. A final possible mechanism relates to polymorphisms in the CYP2C19 gene, the principle enzyme involve in hepatic activation of PPIs. Preliminary data presented in abstract form suggest that those who are rapid metabolizers may have less PPI response than slow metabolizers, as well as less durable response [31].

With these emerging novel mechanisms of PPI-response in esophageal eosinophilia, a remaining question is whether patients maintain a response on these medications or do they evolve into EoE over time. This issue requires further study, but some early data are instructive. A pediatric study presented four patients with a transient PPI response [32]. However, newer data with 46 patients suggest that 72% of patients with PPI-REE have a sustained response to PPIs [31]. Further investigation is required to determine the optimal dose of PPIs and duration of treatment [26].

Eosinophilic Esophagitis

EoE is a chronic disease, and symptoms are varied based on age. In the pediatric population, symptoms tend to be non-specific, including failure to thrive, feeding intolerance, food aversion, abdominal pain, nausea, vomiting, regurgitation or reflux [33]. In adults, dysphagia is the prominent symptom, and EoE is the most common cause of food impactions [34-36]. These differences in symptoms may reflect progression of disease and endoscopic findings, from more of an inflammatory-predominant condition in the pediatric population as manifest by esophageal furrows, edema, and exudates, to a fibrotic condition in adults as esophageal remodeling, narrowing, and stricturing complicate chronic inflammation [5,37-39]. A Swiss retrospective cohort study of diagnostic delay in EoE concluded that for every increased decade of untreated EoE, the odds of having an esophageal stricture doubled [37]. A case series similarly highlighted that patients with long standing untreated EoE are more likely to have endoscopic complications during the removal of their food impaction [40]. Furthermore, as EoE is now the leading cause of food impactions in the United States [5], treating EoE will presumably result in decreased incidence of food impactions and associated costs. In this context, there are several rationales for treating EoE: first is to improve symptoms and help patients feel better; second is to prevent complications, such as food impactions and esophageal strictures; and third is to prevent possible progression of disease manifest by esophageal remodeling.

Selection of treatment outcomes in EoE

Therapeutic endpoints in EoE are not well established, and understanding when EoE treatment is “successful” is a major challenge both in clinical practice and in research studies. Symptoms and histology are the most widely used endpoints in the study of EoE, but these are not the only potential endpoints. Others could include quality of life, complications, endoscopic findings, esophageal compliance, and biomarkers [41-43] and after treatment ideally all of these components would improve or normalize.

In practice, however, these outcomes can be difficult to assess. Symptoms do not always correlate with histologic response [44-48]. Symptoms can improve despite persistent

inflammation if patients modify their diet by being careful with what they eat and by chewing slowly and thoroughly, or if they undergo esophageal dilation. Conversely, symptoms can persist despite resolution of inflammation if a stricture is present but has not been dilated, if there is an infection complicating treatment, or if there is a superimposed functional gastrointestinal disorder. Because there are few data examining the decrease in eosinophil density needed to prevent the progression of esophageal injury or improve symptoms [49], studies have used varying and empirically determined histologic endpoints based on number of eosinophils per high power field or percent decline in the eosinophil count to define response to therapy [42]. Some studies also use the concept of a partial historic response, again with variable definitions.

Recognizing the need for validated outcomes for EoE, there has been a major effort by researchers over the past several years to develop measures specifically for EoE [41]. Symptom based patient reported outcomes, quality of life measures, and endoscopic scoring systems have been developed and validated for EoE [50-56] and are currently being assessed in ongoing trials. A validated histologic score is also under development [57] and the utility of the functional luminal impedance probe on measuring esophageal compliance is under investigation [58]. Having well defined treatment outcomes will aid practitioners to assess the efficacy of therapy and will allow use of comparable outcomes in clinical trials.

Optimizing topical steroid treatment for EoE

Swallowed topical steroids are an effective therapy for EoE, but it is important to note that there is no Food and Drug Administration (FDA) approved steroid formulation for the treatment of EoE and therefore steroid use is off-label at this time. Fluticasone and budesonide are commonly used steroid formulations in EoE [2] and have been shown in meta-analyses to markedly decrease esophageal eosinophilia [59]. In the pediatric EoE population, swallowed fluticasone has been proven to improve histology in more than 50% of patients [60-62]. However, for very young children with EoE, delivery of fluticasone via a multi-dose inhaler may not be feasible. Placebo controlled trials of swallowed fluticasone in adults with EoE also demonstrated histologic remission thought symptom response was not consistent [44,62]. Oral budesonide has been shown to improve EoE from histologic, clinical and endoscopic standpoints in both children and adults [63,64]. As of yet, there are no completed trials directly comparing fluticasone to budesonide. In a trial comparing budesonide formulations, oral viscous budesonide was found to decrease esophageal eosinophil counts significantly more than nebulized budesonide [65]. This was because oral viscous budesonide was found to have more contact time with the esophageal mucosa [65], highlighting the point that more effective methods are needed to deliver medication topically to the esophagus.

Several recent studies have explored ways to optimize topical steroid delivery to the esophagus. One study in children showed that mixing aqueous budesonide with elemental formula powder to form a thick slurry was effective for decreasing eosinophil counts [66]. In a randomized trial where a viscous budesonide suspension was compared to an effervescent budesonide tablet that dissolved on the tongue and was then swallowed, both were found to be superior to placebo and comparable to each other in inducing histologic remission as well

as improving endoscopic severity [47]. Interestingly, however, symptoms improved equally in the placebo and active treatment arms after the two week induction course. A different randomized trial compared oral budesonide suspension, a formulation previously studied in children [67] to placebo using validated symptom and endoscopic metrics [51,52,68]. Here, there was concordant improvement in symptoms of dysphagia, eosinophil counts, and endoscopic appearance compared with placebo. These investigations into novel medication formulations show that more effective targeted medications can lead to improved clinical outcomes.

Approaching patients refractory to topical steroids

There are few studies that have specifically addressed non-response to topical steroids in EoE [69]. In reviewing published clinical trials, rates of non-response range from 0 – 50% [44,47,60,62,63]. It is important to note, however, that the definition of steroid non-response is variable across studies. There are a number of possible reasons why steroids may not be effective in inducing remission in EoE. The dosage may be too low, the formulation may be sub-optimal, the patient may not be using the formulation appropriately and, of course, there may be unreported medication non-adherence. Non-medication related reasons for persistent symptoms after topical steroid use include a superimposed infection, persistent allergen exposure, a concomitant functional GI disorder or that the diagnosis is not EoE.

Clinically, it would be helpful to predict which patient might respond to topical steroid treatment, but there are few data informing this issue. In one large retrospective analysis, 48% of EoE patients receiving topical corticosteroids were defined as non-responders as defined by post-treatment histology revealing >15 eos/hpf [69]. Analysis revealed that esophageal dilation at baseline and abdominal pain were clinical predictors of non-response, but that there were no other clinical, endoscopic, or histologic predictors. These results are similar to those presented in abstract form at a different center [70]. This study of predictors also conducted an immunohistochemical analysis demonstrating that patients who responded to topical corticosteroids had higher baseline levels of tryptase and eotaxin-3, but not major basic protein [69]. Of the patients who were steroid-refractory, 47% underwent second line therapy, and the overall response rate to second line therapies for steroid-refractory patients was 48% [69]. In a prospective randomized trial of high dose swallowed fluticasone, molecular gene expression profiles of responders to therapy and non-responders were evaluated [62]. In those patients who responded to steroids, the molecular signature normalized, although it was still significantly different from healthy controls. This group identified a small subset of genes that may predict steroid efficacy, but additional studies are required to validate this approach.

Optimizing dietary therapy in EoE

Because EoE is thought to be caused by food antigens in a majority of patients [71], dietary elimination has been extensively tested for EoE. The current guidelines suggest that dietary therapy is a first line treatment option, and should also be used for those patients who failed topical corticosteroids [2]. There are three strategies for dietary therapy in EoE: elemental formulas which completely eliminate all food allergens; a targeted elimination diet guided

by allergy testing; and an empiric elimination diet of the six foods most commonly known to be triggers of EoE (wheat, milk, eggs, soy, nuts and seafood) [42,72].

In pediatric case series, elemental diets have been shown to be an effective method of improving histology in EoE [73,74], and this has recently been confirmed in adults [75]. Despite its efficacy, elemental formulas are expensive and difficult to tolerate. Therefore, allergy testing directed elimination was studied and found to be effective in inducing histologic remission in EoE and triggers could be identified upon reintroduction of the food [76-79]. Such studies revealed commonly implicated foods. Because there was no good agreement or reproducibility for skin-based allergy testing, the six food elimination diet (SFED) was developed and was found to be equally or more effective, as well as more palatable than the very restrictive elemental diets [80-83].

Though effective, the SFED and other restrictive diets can still be rather limiting, and food reintroduction process is cumbersome, time-intensive, and expensive, with a follow-up endoscopy often required after every food or food group has been reintroduced. Therefore, less restrictive empiric elimination diets are currently being studied. A diet eliminating four of the more commonly implicated food groups, dairy, wheat, egg and legumes, was prospectively tested in Spain and demonstrated a 54% clinicopathologic remission rate in adult patients [84]. Non-responders were then offered a SFED, which was effective in one third of non-responders to the four food elimination diet [84]. A subsequent study of the four food elimination diet in adults in the U.S. where dairy, wheat, egg, and soy were eliminated had comparable results, with a 46% response rate [85]. In children, responses might be better for the four food elimination, with one study reporting response rates of 71% [86]. To simplify dietary elimination more, there have been studies of dairy elimination alone, given that dairy appears to be the most common trigger of EoE. Two studies of cow's milk elimination in children have both shown a 65% rate of clinical and histologic remission [87,88].

Once identified, long term exclusion of trigger foods from the diet is recommend [2]. Food re-introduction after histologic remission has been studied most commonly with single-food reintroduction, followed by endoscopy with biopsies after each reintroduction, but this process is not standardized and remains somewhat controversial [42]. While this method allows one to determine the specific food trigger in the development of EoE [81,89], it can be challenging both for patients and physicians as noted above. This remains an area where additional research is required to guide practice, and emerging non-invasive or minimally invasive techniques may change paradigms in the future [90-92].

The role of esophageal dilation in EoE

Fibrostenotic complications of EoE such as strictures and narrow caliber esophagus may not be adequately treated with diet elimination or pharmacotherapy, [2,93] treatments which primarily are anti-inflammatory rather than anti-fibrotic. Because esophageal dilation is effective in increasing the esophageal luminal diameter as well as improving dysphagia for as long as one year [94-98], it has become an important treatment option for EoE. It must be noted, however, that while symptoms improve post-dilation, eosinophilic inflammation persists so should still be separately addressed [94]. Both though-the-scope balloon dilators

and wire- and non-wire-guided dilators have been used and shown to be safe, though there are no head-to-head comparisons of these techniques [94-99]. Dilation in EoE is relatively safe; a 2-9% rate of deep mucosal tears is reported, the risk of major bleeding is <1%, but the perforation rate is 1% or lower, with many reviews reporting no perforations in their cohorts, and this safety has been confirmed in meta-analyses [96-103]. Novel techniques for dilation, such as the pull through technique, have been proposed to better appreciate subtle luminal narrowing that may be present in EoE [99]. As the fibrostenotic complications of EoE tend to occur with longer duration of disease [37], esophageal dilation is primarily studied in the adults, however a recent abstract presented the first evidence that dilation can be safely performed in children [104]. A retrospective analysis of the risk factors associated with endoscopic complications revealed that luminal narrowing in the upper or middle third of the esophagus or esophageal stricture that cannot be traversed with a standard upper endoscope increases the risk of complications [100]. Overall, the complication rate of dilation in eosinophilic esophagitis can be low and endoscopic therapy should be considered as an adjunct for the management of dysphagia in patients with EoE.

What is the best first line therapy for EoE?

The current guidelines state that either topical corticosteroids or dietary elimination can be considered first line treatment option for EoE [2] based on the studies reviewed above. However, to date there are no prospective studies directly comparing these two modalities for inducing remission in EoE. Therefore, the choice of therapy should be guided by patient preference, tailored to the clinical scenario, and take into account local provider expertise and resources [105]. A recent cost-utility analysis has attempted to inform this decision making, and shows that even after accounting for the multiple endoscopies required for food trigger identification, dietary elimination is cost-effective compared to topical steroids, primarily related to the ongoing requirement for and high cost of these medications [106].

Endoscopic therapy with dilation is considered adjunctive in the treatment of EoE to address the fibrostenotic aspect of the disease, which is predominantly in adult patients [2]. Some research suggested that esophageal dilation alone may effectively treat symptoms related to EoE, specifically dysphagia [94,97], and it is reasonable to perform dilation even at the diagnostic endoscopic if there is a critical stricture. A cost analysis of fluticasone as first line therapy with subsequent dilation if needed and dilation as first line therapy with subsequent fluticasone if needed revealed that the cost of both modalities is nearly the same [107]. Further data are needed to support the decision making process for the optimal first line therapy in EoE.

Long-term therapy to maintain remission

Because EoE is a chronic disease, symptoms, endoscopic signs, and eosinophilic inflammation tend to recur when treatment is discontinued [33,61,108-113]. Moreover, recent studies demonstrate that a longer symptom duration prior to diagnosis of EoE, a proxy for untreated eosinophilic inflammation, is associated with the increasing of strictures over time [37,38]. These findings support the need for maintaining remission with ongoing treatment, but data on long-term outcomes remain somewhat limited.

There is only one prospective randomized trial on this topic, but it has confirmed that oral budesonide use is effective in maintaining remission with one year of use [112]. Furthermore, long term topical steroid use in patients with EoE has been shown to decrease the occurrence of complications such as food impactions in adults [114] and suppress symptoms and endoscopic findings in children [115]. While long term safety data are lacking, topical corticosteroid therapy for the treatment of EoE has also been shown to be relative safe in the short and mid-term. Studies reported 0 - 30% rates of esophageal candidiasis, the majority of which were mild, asymptomatic and detected on routine endoscopy [44,47,59,62,64,67,111-113]. Furthermore, endoscopy did not reveal signs of esophageal atrophy [111,112]. A recently published small pilot study of pediatric patients with EoE receiving oral viscous budesonide for more than three months revealed that there may be a risk of adrenal insufficiency [116]. However, larger studies of adults and children did not observe an effect on the adrenal axis [44,62,63,67,68,117]. Clinical and histologic remission can also be maintained in both children and adults with long term avoidance of the identified food trigger [33,74,81,82]. When either diet or steroid therapy decreases esophageal inflammation, esophageal fibrosis and remodeling improve as well, shown either by a decrease in lamina propria fibrosis, a decrease in esophageal wall thickness as measured by endoscopic ultrasound, or by an increase in esophageal compliance [58,112,118-122]. Therefore, current guidelines support the use of maintenance therapy for EoE, and particularly recommend this approach for patients who have had food impactions, development of esophageal strictures or other signs of remodeling, and symptoms that rapidly recur after initially stopping treatment [2]. As with inducing remission, there are no studies comparing the efficacy and long term safety of pharmacotherapy and diet elimination strategies for maintenance therapy.

Emerging pharmacologic agents

At this time, there are no FDA approved medical therapies for the treatment of eosinophilic esophagitis. Therefore, there is a pressing need for drug development in this field. Novel steroid delivery vehicles are under development and have been previously discussed. Another topical steroid that holds some promise is ciclesonide. It has been shown to bind to esophageal glucocorticoid receptors with more affinity than budesonide, and requires activation by an epithelial esterase [123]. Furthermore, it is rapidly metabolized, minimizing systemic side effects [124]. However, there are only two small cases series of patients who were treated with ciclesonide. In one series, all four patients had clinical and histologic responses [125]. In another series of four patients who did not respond to topical budesonide or fluticasone, only 50% of the patients demonstrated a histologic response to ciclesonide [126].

Novel biologic agents, immunomodulators, and leukotriene antagonists are also being studied for the treatment of EoE [127]. Since EoE is thought to be a Th2 lymphocyte mediated process, a suppressor of T cell proliferation such as 6-mercaptopurine (6-MP), or its prodrug azathioprine, have been proposed for the treatment of EoE. A case series of two patients on azathioprine and one patient on 6-MP for treatment of corticosteroid dependent EoE reported that these agents were able to induce and maintain remission in EoE [128], but there are no other studies examining these agents in EoE.

Biologics offer a promising approach to target key cytokines in the Th2 pathway. Reslizumab and mepolizumab are monoclonal antibodies against IL-5 that have been studied for treating EoE. There are three published RCTs studying these agents, two large studies in children and a smaller one in adults [43,46,129]. While these agents were able to significantly improve eosinophil counts, there was not a clear symptom benefit, these agents are not currently available, and there are no active protocols with them currently. A small phase II proof of principle study of the efficacy of an anti-IL-13 antibody in EoE did not achieve the primary end point, but did significantly decrease esophageal eosinophilia and demonstrate a trend toward an improvement in dysphagia [130]. This class of medication is currently under further investigation [131]. There is also a study underway examining whether an anti-IL-4 antibody is effective for EoE [132].

Leukotriene D4 is a known eosinophil chemoattractant. Montelukast is a leukotriene D4 receptor antagonist that is widely used in treatment of pulmonary disease, and has been studied for use in EoE. While an initial prospective observational study reported that patients had symptomatic improvement with montelukast treatment [133], subsequent pediatric and adult data failed to show that montelukast was effective in inducing or maintaining remission [134,135]. There are two ongoing trials to study montelukast in EoE [136,137].

Th-2 cells express prostaglandin-D2 receptors which mediate eosinophil chemotaxis and activation. OC000459 is a prostaglandin-D2 receptor antagonist which has been studied in the treatment of steroid-dependent and steroid-refractory EoE. When compared to placebo, OC000459 significantly decreased esophageal eosinophilia and resulted in an improvement in the physician's global assessment of disease activity [138]

Expert commentary

Eosinophilic esophagitis is a newly described chronic disease with an increasing incidence and prevalence. While great strides have been made to characterize EoE and understand its pathogenesis, there are a number of challenges to accurate diagnosis and optimal management of EoE. First, the distinction between PPI-REE and EoE is critical and needs to be better understood. If new data continue to support what has already been reported, we would predict that in the future PPI-REE may be defined as a phenotype of EoE, and PPI use may shift from a diagnostic maneuver to a therapeutic option. Second, the optimal treatment endpoints for EoE need to be defined. Current studies use varying symptoms and histologic cutoffs to define successful therapy, but symptom and histologic responses can be discordant. Advances in the development of validated symptom, quality of life, endoscopic, and histologic outcome measures present the opportunity to bring much needed consistency to the field.

Finally, a careful and deliberate approach is needed when treating EoE, but additional data are needed to inform the choice of a first line approach, be it diet or steroids, to understand why some patients are refractory to topical steroid treatment, dietary elimination, or both approaches, and to determine predictors of response. Novel and emerging therapeutic options hold promise not only that there will be approved medications for treatment of EoE,

but by targeting pathogenic mechanisms the natural history of the disease can be altered. We would predict that certain clinical, endoscopic, histologic, molecular, or genetic markers will be identified to aid in characterizing clinical phenotypes, selecting appropriate therapies, and predicting treatment response.

Eosinophilic esophagitis, as a field, has made tremendous advances in a short time, from being first described two decades ago to having phenotypes characterized and novel therapeutics developed in this decade. The field continues to be rapidly evolving and therefore, guidelines, diagnostic modalities and management strategies may change in the future.

Acknowledgments

Financial support: This paper was supported, in part, by NIH awards T32DK007634 (BK), K23DK090073 (ESD), R01DK101856 (ESD), and U54AI117804 (CEGIR), which is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Disease Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS.

Works Cited

1**. 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. [PubMed: 21477849] [These consensus recommendations provide information and recommendations for diagnostics, genetics, allergy testing, therapeutics and disease complications in eosinophilic esophagitis.]

2. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterology. 2013; 108(5):679–692.

3. 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. [PubMed: 18289205]

4. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014; 12(4):589–596. [PubMed: 24035773]

5. Dellon ES. Epidemiology of eosinophilic esophagitis. Gastroenterol Clin North Am. 2014; 43(2): 201–218. [PubMed: 24813510]

6. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. Am J Gastroenterol. 2015; 110(5): 626–632. [PubMed: 25267327]

7. 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. [PubMed: 16863575]

8*. Molina-Infante J, Katzka DA, Dellon ES. Proton pump inhibitor-responsive esophageal eosinophilia: a historical perspective on a novel and evolving entity. Rev Esp Enferm Dig. 2015; 107(1):29–36. [PubMed: 25603329] [This article reviews the history of proton pump inhibitor responsive esophageal eosinophilia, details the pathophysiology of PPI-REE and discusses the relationship between PPI-REE and eosinophilic esophagitis.]

9. 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. [PubMed: 7106512]

10. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterol. 2007; 133(4):1342–1363.

11. 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. [PubMed: 17531015]
12. 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. [PubMed: 18783791]
13. Sayej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2009; 49(4):393–399. [PubMed: 19633574]
14. 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. [PubMed: 19533356]
15. 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. [PubMed: 20920599]
16. 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 oesophagitis. Aliment Pharmacol Ther. 2012; 35(2):300–307. [PubMed: 22111863]
17. 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. [PubMed: 24145677]
18. 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. [PubMed: 23325438]
19. Vazquez-Elizondo G, Ngamruengphong S, Khrisna M, Devault KR, Talley NJ, Achem SR. The outcome of patients with oesophageal eosinophilic infiltration after an eight-week trial of a proton pump inhibitor. Aliment Pharmacol Ther. 2013; 38(10):1312–1319. [PubMed: 24117619]
20. Dellon ES, Speck O, Woodward K, et al. Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia: a prospective study. Clin Gastroenterol Hepatol. 2014; 12(12):2015–2022. [PubMed: 24993367]
21. Eluri S, Dellon ES. Proton pump inhibitor-responsive oesophageal eosinophilia and eosinophilic oesophagitis: more similarities than differences. Curr Opin Gastroenterol. 2015; 31(4):309–315. [PubMed: 26039722]
22. Molina-Infante J, Rivas MD, Hernandez-Alonso M, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. Aliment Pharmacol Ther. 2014; 40(8):955–965. [PubMed: 25112708]
23. Moawad FJ, Schoepfer AM, Safroneeva E, et al. Eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. Aliment Pharmacol Ther. 2014; 39(6):603–608. [PubMed: 24461332]
24**. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol. 2015; 135(1):187–197. [PubMed: 25441638] [This study demonstrated that PPI-REE and EoE have significant molecular overlap by evaluating the EoE diagnostic panel signature from biopsy samples of adult and pediatric patients. They showed that PPI reverse gene expression associated with PPI-REE, providing new information about disease etiology and management.]
25. Molina-Infante J, Katzka DA. Proton-pump inhibitor-responsive esophageal eosinophilia. Curr Opin Gastroenterol. 2014; 30(4):428–433. [PubMed: 24837227]
26. Asher Wolf W, Dellon ES. Eosinophilic esophagitis and proton pump inhibitors: controversies and implications for clinical practice. Gastroenterol Hepatol. 2014; 10(7):427–432.
27. 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. [PubMed: 19714466]

28. Park JY, Zhang X, Nguyen N, Souza RF, Spechler SJ, Cheng E. Proton pump inhibitors decrease eotaxin-3 expression in the proximal esophagus of children with esophageal eosinophilia. PLoS One. 2014; 9(7):e101391. [PubMed: 24988451]

29*. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013; 62(6):824–832. [PubMed: 22580413] [This group demonstrated that omeprazole blocks cytokine stimulated increase in eotaxin-3, an eosinophil chemoattractant, in patients with both gastroesophageal reflux disease and EoE. This suggests that response to PPI is not sufficient to distinguish EoE from other entities of esophageal eosinophilia.]

30. van Rhijn BD, Weijenborg PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2014; 12(11):1815–1823. [PubMed: 24657840]

31. Molina-Infante JMJ, Martinez-Alcala C, Krajciova J, Moawad FJ, Dellon ES. Long-term efficacy of PPI therapy in patients with PPI-responsive esophageal eosinophilia: An international multicenter study. Gastroenterology. 2014; 146(Suppl 1) (S-17):Ab 58.

32. 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. [PubMed: 22134787]

33. 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. [PubMed: 19172120]

34. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2009; 7(12):1305–1313. [PubMed: 19733260]

35. 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. [PubMed: 15933677]

36. Kerlin P, Jones D, Remedios M, Campbell C. Prevalence of eosinophilic esophagitis in adults with food bolus obstruction of the esophagus. J Clin Gastroenterol. 2007; 41(4):356–361. [PubMed: 17413601]

37**. 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. [PubMed: 23954315] [This retrospective review of 200 patients in a Swiss database with symptomatic EoE revealed that delaying the diagnosis of EoE, a proxy for untreated inflammation, placed patients at higher risk for development of fibrotic complications of EoE, such as strictures.]

38. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc. 2014; 79(4):577–585. [PubMed: 24275329]

39. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. J Clin Gastroenterol. 2015 [Epub ahead of print].

40. Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clin Gastroenterol Hepatol. 2008; 6(5):598–600. [PubMed: 18407800]

41. Hirano I. Therapeutic end points in eosinophilic esophagitis: is elimination of esophageal eosinophils enough? Clin Gastroenterol Hepatol. 2012; 10(7):750–752. [PubMed: 22366179]

42. Dellon ES, Liacouras CA. Advances in clinical management of eosinophilic esophagitis. Gastroenterology. 2014; 147(6):1238–1254. [PubMed: 25109885]

43. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011; 141(5):1593–1604. [PubMed: 21835135]

44. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2012; 10(7):742–749. [PubMed: 22475741]

45. Pentiuk S, Putnam PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2009; 48(2):152–160. [PubMed: 19179876]

46. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2012; 129(2):456–463. [PubMed: 22206777]

47*. Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut. 2015 [Epub ahead of print]. [This randomized controlled trial evaluated the efficacy of two novel formulations and doses of budesonide for the treatment of EoE. They found that both an effervescent tablet and viscous solution were effective at the lower dose of 1mg twice daily, but patients preferred the effervescent tablet.]

48. Green DJWW, Hughes JT, Cotton CC, Woosley JT, Shaheen NJ, Dellon ES. Most patients demonstrate correlation between symptoms, endoscopic findings, and histology in response to topical steroid treatment in eosinophilic esophagitis. Gastroenterology. 2014; 146(Suppl 1) Ab Mo1840.

49. Wolf WAGD, Hughes JT, Cotton CC, Woosley JT, Shaheen NJ, Dellon ES. What cut-point should be used to define a histologic response to topical steroid use in eosinophilic esophagitis? A data-driven approach using symptoms and endoscopic findings. Gastroenterology. 2014; 146(Suppl 1) Mo1832.

50**. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology. 2014; 147(6): 1255–1266. [PubMed: 25160980] [This study reports on the development and validation of a patient reported outcome based scoring system to assess the activity of EoE.]

51. Dellon ES, Irani AM, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther. 2013; 38(6):634–642. [PubMed: 23837796]

52. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013; 62(4):489–495. [PubMed: 22619364]

53. Taft TH, Kern E, Kwiatek MA, Hirano I, Gonsalves N, Keefer L. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. Aliment Pharmacol Ther. 2011; 34(7):790–798. [PubMed: 21806649]

54. Franciosi JP, Hommel KA, DeBrosse CW, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. BMC Gastroenterol. 2011; 11:126–137. [PubMed: 22099448]

55. Franciosi JP, Hommel KA, Greenberg AB, et al. Development of the Pediatric Quality of Life Inventory Eosinophilic Esophagitis module items: qualitative methods. BMC Gastroenterol. 2012; 12:135–142. [PubMed: 23009120]

56. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol. 2015; 135(6):1519–1528. [PubMed: 26051952]

57. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am. 2014; 43(2):257–268. [PubMed: 24813514]

58. Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology. 2011; 140(1):82–90. [PubMed: 20858491]

59. Chuang MY, Chinnaratha MA, Hancock DG, et al. Topical Steroid Therapy for the Treatment of Eosinophilic Esophagitis (EoE): A Systematic Review and Meta-Analysis. Clin Transl Gastroenterol. 2015; 6:e82. [PubMed: 25809314]

60. 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. [PubMed: 17101314]

61. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008; 6(2):165–173. [PubMed: 18237866]

62. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. Gastroenterology. 2014; 147(2):324–333. [PubMed: 24768678]

63. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010; 139(5):1526–1537. [PubMed: 20682320]

64. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010; 139(2):418–429. [PubMed: 20457157]

65. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology. 2012; 143(2):321–324. [PubMed: 22561055]

66. Rubinstein E, Lee JJ, Fried A, et al. Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2014; 59(3):317–320. [PubMed: 24821535]

67. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2015; 13(1):66–76. [PubMed: 24907502]

68. Dellon ESKD, Collins MH, Hirano I for the MPI-101-06 Investigators. Oral budesonide suspension significantly improves dysphagia and esophageal eosinophilia: Results from a multicenter randomized double-blind placebo-controlled trial in adolescents and adults with eosinophilic esophagitis. Gastroenterology. 2015; 148(Suppl 1) Ab 813.

69. Wolf WA, Cotton CC, Green DJ, et al. Predictors of response to steroid therapy for eosinophilic esophagitis and treatment of steroid-refractory patients. Clin Gastroenterol Hepatol. 2015; 13(3): 452–458. [PubMed: 25086190]

70. Moawad FAD, Heifert T, Min S, Maydonovitch C, Wong R. Predictors of non-response to topical steroids treatment in eosinophilic esophagitis. Am J Gastroenterol. 2013; 108(Suppl 1):S14.

71. Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. Gastroenterology. 2015; 148(6):1143–1157. [PubMed: 25666870]

72**. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology. 2014; 146(7):1639–1648. [PubMed: 24534634] [This systematic review of dietary interventions in the treatment of EoE included 33 studies with 1317 patients. The meta-analysis concluded that elemental diets and six food elimination diets are the most effective in inducing histologic remission in EoE.]

73. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol. 2003; 98(4):777–782. [PubMed: 12738455]

74. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005; 3(12):1198–1206. [PubMed: 16361045]

75. 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. [PubMed: 23381017]

76. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol. 2005; 95(4):336–343. [PubMed: 16279563]

77. Syrigou E, Angelakopoulou A, Zande M, Panagiotou I, Roma E, Pitsios C. Allergy-test-driven elimination diet is useful in children with eosinophilic esophagitis, regardless of the severity of symptoms. Pediatr Allergy Immunol. 2015; 26(4):323–329. [PubMed: 25845555]

78. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012; 130(2):461–467. [PubMed: 22743304]

79. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2012; 129(6):1570–1578. [PubMed: 22541246]

80. 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. [PubMed: 16860614]

81. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012; 142(7):1451–1459. [PubMed: 22391333]

82. 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. [PubMed: 23375693]

83. Wolf WA, Jerath MR, Sperry SL, Shaheen NJ, Dellon ES. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2014; 12(8): 1272–1279. [PubMed: 24440337]

84. Molina-Infante J, Arias A, Barrio J, Rodriguez-Sanchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol. 2014; 134(5):1093–1099. [PubMed: 25174868]

85. Gonsalves NDB, Schwartz S, Guang-Yu Y, Zalewski A, Amsden K, Mughal S, Manuel-Rubio M, Melin-Aldana H, Wershil BK, Hirano I, Kagalwalla A. Prospective trial of four food elimination diet demonstrates comparable effectiveness in the treatment of adult and pediatric eosinophilic esophagitis. Gastroenterology. 2013; 144(Suppl 1) AB 877.

86. Kagalwalla AAK, Makhija M, Wechsler JB, Olive A, Schwartz S, Davis CM, Johnson K, Groetch M, Riffle ME, Manuel-Rubio M, Melin-Aldana H, Wershil BK, Collins MH, Chehade M. A Multicenter Study Assessing the Clinical, Endoscopic and Histologic Response to Four Food Elimination Diet for the Treatment of Eosinophilic Esophagitis. Gastroenterology. 2015; 148(Suppl 4) Ab 114.

87. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2012; 55(6):711–716. [PubMed: 22820121]

88. Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus. 2015 [Epub ahead of print].

89. 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. [PubMed: 21788754]

90. 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. [PubMed: 22895393]

91. Friedlander JA, DeBoer EM, Soden JS, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. Gastrointest Endosc. 2015 [Epub ahead of print].

92. Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2015; 13(1):77–83. [PubMed: 24997328]

93. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology. 2003; 125(6):1660–1669. [PubMed: 14724818]

94. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol. 2010; 105(5):1062–1070. [PubMed: 19935783]

95. Schoepfer AM, Gschossmann J, Scheurer U, Seibold F, Straumann A. Esophageal strictures in adult eosinophilic esophagitis: dilation is an effective and safe alternative after failure of topical corticosteroids. Endoscopy. 2008; 40(2):161–164. [PubMed: 18253909]

96. 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. [PubMed: 20353444]

97. Lipka S, Keshishian J, Boyce HW, Estores D, Richter JE. The natural history of steroid-naive eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. Gastrointest Endosc. 2014; 80(4):592–598. [PubMed: 24703087]

98. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointest Endosc. 2010; 71(4):706–712. [PubMed: 20170913]

99. Madanick RD, Shaheen NJ, Dellon ES. A novel balloon pull-through technique for esophageal dilation in eosinophilic esophagitis (with video). Gastrointest Endosc. 2011; 73(1):138–142. [PubMed: 21184880]

100. Jung KW, Gundersen N, Kopacova J, et al. Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis. Gastrointest Endosc. 2011; 73(1):15–21. [PubMed: 21067739]

101. Saligram S, McGrath K. The safety of a strict wire-guided dilation protocol for eosinophilic esophagitis. Eur J Gastroenterol Hepatol. 2014; 26(7):699–703. [PubMed: 24901815]

102. Jacobs JW Jr. Spechler SJ. A systematic review of the risk of perforation during esophageal dilation for patients with eosinophilic esophagitis. Dig Dis Sci. 2010; 55(6):1512–1515. [PubMed: 20238250]

103. Robles-Medranda C, Villard F, le Gall C, et al. Severe dysphagia in children with eosinophilic esophagitis and esophageal stricture: an indication for balloon dilation? J Pediatr Gastroenterol Nutr. 2010; 50(5):516–520. [PubMed: 19934772]

104. Menard-Katcher CFG, Kramer R. Dilation outcomes in pediatric eosinophilic esophagitis. Gastrointestinal Endoscopy. 2015; 81(Suppl 1) AB 299.

105. Peterson KA, Boynton KK. Which patients with eosinophilic esophagitis (EoE) should receive elemental diets versus other therapies? Curr Gastroenterol Rep. 2014; 16(1):364. [PubMed: 24338572]

106. Cotton CCHS, Green DJ, Wolf WA, Wheeler SB, Shaheen NJ, Dellon ES. Six-Food Elimination Diet or Topical Steroids for First-Line Treatment of Eosinophilic Esophagitis: A Cost-Utility Analysis. Gastroenterology. 2015; 148(Suppl 1) Ab 4.

107. Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. Dis Esophagus. 2014; 27(5):418–423. [PubMed: 22947137]

108. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. J Allergy Clin Immunol. 2007; 119(3):731–738. [PubMed: 17258309]

109. DeBrosse CW, Franciosi JP, King EC, et al. Long-term outcomes in pediatric-onset esophageal eosinophilia. J Allergy Clin Immunol. 2011; 128(1):132–138. [PubMed: 21636117]

110. Elliott EJ, Thomas D, Markowitz JE. Non-surgical interventions for eosinophilic esophagitis. Cochrane Database Syst Rev. 2010; (3):CD004065. [PubMed: 20238328]

111. Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastrointest Endosc. 2006; 63(1):3–12. [PubMed: 16377308]

112*. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2011; 9(5):400–409. [PubMed: 21277394] [This randomized controlled trial studied the efficacy of budesonide over 50 weeks to maintain remisison in EoE. They found that low dose budeosnide is more effective than placebo for maintaining clinical and histologic remission in EoE.]

113. Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. Am J Gastroenterol. 2008; 103(9):2194–2199. [PubMed: 18637093]
114. Kuchen T, Straumann A, Safroneeva E, et al. Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis. Allergy. 2014; 69(9):1248–1254. [PubMed: 24894658]
115. Andreae DAHM, Magid M, Bagiella E, Malerba S, Chehade M. Swallowed Fluticasone Is an Effective and Safe Long-Term Maintenance Therapy in Children With Eosinophilic Esophagitis. Gastroenterology. 2015; 148(Suppl 1) Ab 116.
116. Harel S, Hursh BE, Chan ES, Avinashi V, Panagiotopoulos C. Adrenal Suppression in Children Treated With Oral Viscous Budesonide for Eosinophilic Esophagitis: A Pilot Study. J Pediatr Gastroenterol Nutr. 2015 [Epub ahead of print].
117. Dellon ES, Speck O, Woodward K, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. Mod Pathol. 2015; 28(3):383–390. [PubMed: 25216228]
118. Kagalwalla AF, Akhtar N, Woodruff SA, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. J Allergy Clin Immunol. 2012; 129(5):1387–1396. [PubMed: 22465212]
119. Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007; 45(3):319–328. [PubMed: 17873744]
120. 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. [PubMed: 19796194]
121. Lucendo AJ, Arias A, De Rezende LC, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. J Allergy Clin Immunol. 2011; 128(5):1037–1046. [PubMed: 21880354]
122. Fox VL, Nurko S, Teitelbaum JE, Badizadegan K, Furuta GT. High-resolution EUS in children with eosinophilic “allergic” esophagitis. Gastrointest Endosc. 2003; 57(1):30–36. [PubMed: 12518127]
123. Stoeck M, Riedel R, Hochhaus G, et al. In vitro and in vivo anti-inflammatory activity of the new glucocorticoid ciclesonide. J Pharmacol Exp Ther. 2004; 309(1):249–258. [PubMed: 14718604]
124. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. J Clin Pharmacol. 2007; 47(6):782–789. [PubMed: 17412829]
125. Schroeder S, Fleischer DM, Masterson JC, Gelfand E, Furuta GT, Atkins D. Successful treatment of eosinophilic esophagitis with ciclesonide. J Allergy Clin Immunol. 2012; 129(5):1419–1421. [PubMed: 22480537]
126. Lee JJ, Fried AJ, Hait E, Yen EH, Perkins JM, Rubinstein E. Topical inhaled ciclesonide for treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2012; 130(4):1011–1012. [PubMed: 23021144]
127. Kern E, Hirano I. Emerging drugs for eosinophilic esophagitis. Expert Opin Emerg Drugs. 2013; 18(3):353–364. [PubMed: 23937314]
128. Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroenterol Hepatol. 2007; 19(10):865–869. [PubMed: 17873610]
129. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut. 2010; 59(1):21–30. [PubMed: 19828470]
130. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2015; 135(2):500–507. [PubMed: 25226850]

131. Dose Ranging Study of RPC4046 in Eosinophilic Esophagitis. National Library of Medicine; Bethesda, MD: 2014. Available from: https://clinicaltrials.gov/ct2/show/NCT02098473 [07/27/15]

132. Study of Dupilumab in Adult Patients With Active Eosinophilic Esophagitis (EoE). National Library of Medicine; Bethesda, MD: 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT02379052. [07/27/15]

133. Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using Montelukast. Gut. 2003; 52(2):181–185. [PubMed: 12524397]

134. Stumphy J, Al-Zubeidi D, Guerin L, Mitros F, Rahhal R. Observations on use of montelukast in pediatric eosinophilic esophagitis: insights for the future. Dis Esophagus. 2011; 24(4):229–234. [PubMed: 21073625]

135. Lucendo AJ, De Rezende LC, Jimenez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. Dig Dis Sci. 2011; 56(12):3551–3558. [PubMed: 21674173]

136. Trial of Montelukast in Eosinophilic Esophagitis. National Library of Medicine; Bethesda, MD: 2007. Available from: https://clinicaltrials.gov/ct2/show/NCT00511316. [07/27/15]

137. Eosinophilic Esophagitis Treatment: Montelukast vs Fluticasone. National Library of Medicine; Bethesda, MD: 2012. Available from: https://clinicaltrials.gov/ct2/show/NCT01702701. [07/27/15]

138. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. Allergy. 2013; 68(3):375–385. [PubMed: 23379537]

Five Year View

Eosinophilic esophagitis has rapidly emerged as an important cause of upper gastrointestinal morbidity in both children and adults. As with any new field of study, there are many questions raised by the existing knowledge base, and multiple challenges associated with management. Over the next five years, it seems likely that PPI-REE may be reclassified as a subset of EoE rather than a different disease process. Currently, endoscopy is the mainstay of monitoring disease activity, but this is both expensive and invasive. In the near future, minimally invasive and non-invasive methods of monitoring disease activity will be established. As therapeutic endpoints are better defined, drug development can progress and novel treatment options can be can brought to market. These endpoints will not only help determine which agents are most effective in the management of EoE, but will also help establish the comparative efficacy of topical corticosteroids, dietary therapies and new therapeutics. Finally, it is possible that in five years, a patient's diagnosis, prognosis, and treatment options will be determined by molecular and genetic profiling techniques.

Key Issues

- PPI-REE and EoE may be a spectrum of the same disease
- Topical corticosteroids are first line therapy for the management of EoE
- Dietary therapies can also be first line agents for the management of EoE or can be used as second line treatment or adjunctively with steroid therapy
- Esophageal dilation is a safe and effective adjunctive tool in the management of EoE
- Maintenance therapy is typically required for EoE
- Many novel therapeutics are being studied for the treatment of EoE
- Treatment endpoints need to be better defined