Non-IgE Medicated Food Allergy: Eosinophilic Esophagitis Update on the Pathogenesis, Clinical Features, and Management of Eosinophilic Esophagitis in Children

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Abstract Eosinophilic esophagitis (EoE) is a chronic allergic disorder of increasing worldwide prevalence. Diagnosis and management require upper gastrointestinal endoscopy with biopsy. Therapeutic strategies in children and adults include empiric and testing-based elimination diets as well as topical esophageal corticosteroids. The last 12 months have provided a number of insights including updated diagnostic/management guidelines, the role of PPI therapy, and an understanding that EoE disease mechanisms rely on basophils and mast cells in addition to eosinophils. Novel diagnostic techniques have been described and include the esophageal string test and a molecular gene array panel. In addition, new techniques for assessing esophageal rigidity have been reported. In this review, we summarize the most impactful findings in EoE over the last 12–15 months.

Keywords Eosinophil · Gastroesophageal reflux disease · Proton pump inhibitor · Eosinophilic esophagitis · Food allergy · Remodeling · Topical corticosteroid

Introduction

Eosinophilic esophagitis (EoE) is a chronic, inflammatory, clinicopathological esophageal condition in children and

adults that is hallmarked by symptoms of esophageal dysfunction and acid-independent, multi-level (e.g., distal/proximal) esophageal eosinophilia of ≥ 15 eosinophils (eos)/high-powered field (hpf) on H&E-stained esophageal biopsies [1•, 2•]. While it is abnormal to have eosinophils within the squamous epithelium of the esophagus, the underlying etiology for esophageal eosinophilia can vary from acid to antigens and combinations thereof. As such, other causes of esophageal eosinophilia should be ruled out including gastroesophageal reflux (GERD), concurrent eosinophilic gastroenteritis disease, systemic eosinophilic disorders, celiac disease, inflammatory bowel disease, infection, vasculitis, drug-induced injury, graft versus host disease, connective tissue disorders, and major motility disorders such as achalasia [1•, 2•, 3]. It is important, however, to understand that primary EoE may co-exist with at least some of these disorders. For example, treatment of celiac disease with a gluten-free diet will result in concomitant resolution of EoE in <50 % of cases [4]. Symptoms in EoE are broad, often overlap with other diseases, and can vary based on age. Classic EoE symptoms prominently reflect either esophageal dysfunction (all ages) and/or feeding difficulties (children), with dysphagia being prominent in adults and adolescents [5•]. Endoscopic features include pallor, exudates, linear furrowing, and luminal narrowing, and microscopic histologic findings include eosinophilic micro-abscesses, rete peg elongation, dilated intracellular spaces, degranulated eosinophils, and eosinophil surface layering. However, none are pathognomonic for EoE [1•, 5•].

Current epidemiologic evidence indicates an alarming increase in the incidence and prevalence of disease in both the US and abroad [1•, 6•, 7]. Gene studies and cytokine/chemokine data strongly implicate that EoE has an allergic etiology and mechanism of disease, involving mast cells, basophils, IL-4, IL-5, IL-13, eotaxin-3, STAT-6, and TSLP

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[8•, 9]. Clinically, as many as 75 % of affected individuals are atopic (or have a family history of atopy), though up to 25 % may be non-atopic [2•]. There is a clear response to allergen removal (between 77 and 98 % in studies), and both food and inhalant allergens have been shown to be triggers of disease [10–12, 13•, 14, 15, 16•, 17–19].

Treatment options are broad and include dilation, corticosteroids, dietary elimination, and biologic immunomodulation. No treatment strategy has proven superior, and most options have shown efficacy in eliminating symptoms, histologic evidence of disease, or both [1•, 2•, 3, 5•]. Currently, EoE still lacks a clear best-practice strategy, robust outcome data, or full understanding of the natural history of the disease. In addition, in clinical practice, there is not universal consensus between allergists and gastroenterologists who manage EoE [1•, 2•, 6•]. Moreover, key patient-oriented outcomes, such as quality of life, are just beginning to be investigated [20, 21•].

This review will cover the recent developments in EoE in the past year, focusing on updates to the diagnostic guidelines; the emerging evidence for/against proton-pump-responsive esophageal eosinophilia (PPI-REE) as a staging classification; updates on dietary avoidance strategies; pathophysiologic updates that may have treatment implications; and potential new methods for esophageal assessment and EoE diagnosis.

Updates on Clinical Guidelines for Diagnosing and Managing EoE

The American College of Gastroenterology (ACG) recently published clinical guidelines for diagnosing and managing EoE [1•]. Though exclusively authored by gastroenterologists, these guidelines are essentially in line with the 2011 consensus guidelines written by pathologists, allergists, and gastroenterologists [2•], but include the use of the GRADE system for evidence evaluation, which is a strength of the approach [22]. Most recommendations were given a conditional label (trade-offs less certain) and low to moderate evidence ratings (further studies likely or very likely to change the confidence of the recommendation) given limited randomized or controlled supporting data for many scenarios. The main diagnostic recommendation was the need for a trial of 2 months of high-dose proton pump inhibitor therapy in order to rule out gastroesophageal reflux disease (GERD) or proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) [1•]. In terms of therapeutic options, dietary elimination and topical esophageal corticosteroid remain the mainstays, but the ACG guidelines provide a focus on the evidence surrounding esophageal dilation and advocate a conservative use of dilation to assist with symptomatic treatment from fibrostenotic

complications. Although dilation provides symptomatic relief, it does not provide any inflammatory control and is complicated by 75 % of patients experiencing post-dilation pain. Importantly, there is an expansion of the evidence regarding the concept of PPI-REE as a potentially distinct entity from GERD and EoE that also requires clinical follow-up.

The Emergence of PPI-REE as a Key Condition to Rule Out Prior to Diagnosis of EoE

While esophageal eosinophilia has been noted for decades, this is distinct from the clinicopathologic diagnosis of EoE [1•, 2•]. All recent guidelines have cautioned against a strict overreliance on an “exact” number of eosinophils that are diagnostic. Indeed, the number of 15 is based not on evidence but on expert opinion. The guidelines all further emphasize that isolated counts ≥ 15 eos/hpf in asymptomatic patients or patients without a clinical context should not be considered pathognomonic of EoE and that subjects with <15 eos/hpf but typical symptoms despite PPI therapy may warrant therapy.

The original consensus guidelines recommended an 8-week trial of high-dose PPI (e.g., twice daily), based on case report evidence that esophageal eosinophilia in some patients may respond to this treatment, and to rule out GERD as a contributing factor [23–27]. It is currently appreciated that there may be at least two distinct populations of patients with esophageal eosinophilia, which has prompted a shifting of the nomenclature—those with abnormal pH studies and GERD with high numbers of eosinophils and those with normal pH and eosinophilia responsive to PPI [2•]. For this reason, the new term PPI-REE more accurately describes the symptomatic patient with high-grade and often diffuse esophageal eosinophilia who responds clinically and histologically to the 8-week high-dose PPI. Future studies will need to decipher whether individuals with PPI-REE have antigen-induced eosinophilia and what mediates the therapeutic effect of PPI. To this end, recent work has demonstrated the PPI effects may not merely be due to acid suppression but also to decreasing pro-eosinophil chemokines. Using esophageal EoE epithelial cells, Zheng et al. demonstrated that omeprazole decreases eotaxin-3 induction by IL-13, supporting the hypothesis that PPIs may be able to inhibit eosinophils via a gastric-acid independent, immunologically mediated pathway. Omeprazole at 5 μ M or higher concentrations decreased IL-4-stimulated eotaxin-3 protein secretion and mRNA expression, likely through chromatin remodeling at the promoter, but had no effect on eotaxin-3 mRNA stability, STAT-6 phosphorylation or nuclear translocation.

Clinically, the evidence supporting PPI-REE remains largely based on uncontrolled, descriptive studies, although some randomized trial data have emerged [1•, 2•, 3, 28•]. Schroeder et al. [29] performed a retrospective analysis of 204 children diagnosed with EoE to identify responders to an 8-week PPI treatment and differentiate responders from non-responders. Seven patients with clinico-pathologic response were identified, two of whom re-developed esophageal eosinophilia within 1.5–2 years of treatment, and there were no clinical indicators to differentiate transient from long-term PPI responders. More importantly, 77 % of children showed no PPI response. The data from Schroeder et al. [29] emphasize the importance of the PPI trial, but also underscore that these patients need long-term follow-up given disease overlap and unclear differentiating factors between EoE and PPI-REE. These findings closely mirror work by Dohil, Newbury, and Aceves, who described transient response followed by recrudescence of esophageal eosinophilia in four children treated with (and remaining on) PPI, independent of seasonal variation. Dohil, Newbury, and Aceves caution against a quick diagnosis of PPI-REE, urge long-term follow-up of this approach, and caution reliance upon isolated acid reduction as the optimal long-term treatment strategy in this subset of subjects [27].

Adult studies have also supported the presence of PPI-REE. Moawad et al. [30] performed a randomized, controlled, single-blinded trial in 42 adult patients treated with topical fluticasone propionate versus esomeprazole and found no significant differences between the response rates to topical esophageal steroids or PPI. Symptom scores on the dysphagia questionnaire were significantly improved in the PPI-treated group, but this improvement was not related to the overall eosinophil count change, underscoring the disconnect that commonly occurs between symptoms and inflammation.

Dellon et al. conducted a large prospective study of an 8-week PPI trial in adults undergoing EGD, stratified by dysphagia ($n = 173$ with dysphagia and $n = 50$ without). Subjects with ≥ 15 eos/hpf on biopsy received a 2-month high-dose PPI trial (66/173 with dysphagia, 2/50 without dysphagia), followed by re-biopsy. Response was noted only in 24/66 total subjects with dysphagia, and these patients were indistinguishable by symptoms or endoscopic features from 40 subjects not responding to the PPI trial who were diagnosed with EoE [31•]. Vazquez-Elizondo et al. conducted an open label trial of an 8-week 20-mg twice-daily esomeprazole trial in 60 consecutive adult patients who had esophageal eosinophilia >15 eos/hpf. Using a remission cutoff of ≤ 5 eos/hpf and an improvement cutoff of 5–14 eos/hpf, 25 % achieved full remission, 56.6 % improved, and 71.6 % had symptomatic response. Decreases in eosinophil counts were noted more frequently (non-significantly) in those with more prominent distal

than proximal eosinophilia, and counts were significantly lower in those with evidence of GERD (e.g., heartburn/regurgitation by history). Molina-Infante et al. summarized the results of ten studies investigating PPI response in patients with suspected EoE, encompassing 152 children and 106 adults. Overall there was a symptom response to PPI in 78–86 % of children and 25–80 % of adults, and noted histologic remission in 23–40 % of children and 33–61 % of adults. Overall 50–85 % of subjects had symptom improvement without histologic remission, and 6 patients had relapse despite ongoing PPI therapy. PPI-REE was diagnosed with higher frequency in patients with pH probe-proven GERD [32].

New Insights into Dietary Therapy: Flexible Options Exist Allowing Tailoring

EoE is a chronic, antigen-driven disease that responds to dietary elimination. Evidence supporting a role for food antigen avoidance in treating EoE dates back to initial work by Kelly et al. and furthered by work from Markowitz et al. and Liacouras et al., demonstrating high rates of symptomatic response and histologic normalization with use of an exclusively elemental diet [10, 12, 33]. Targeted dietary elimination, first described by Spergel et al., identified the 13 most common pediatric food triggers through skin testing (PST) and atopy patch testing (APT), and provides an alternative that allows more selective exclusion of foods with nearly 80 % success in terms of symptomatic and histologic normalization [13•, 34–36]. However, other groups have described difficulty in replicating these data, highlighting food tests (milk, wheat) with poor reliability, as well as frustration regarding high variability in the APT process [2•, 16•]. A third strategy, empiric elimination, continues to grow in popularity. Kagalwala et al. showed that eliminating the six most common allergenic food groups in the US (6-food elimination diet [SFED], consisting of milk, egg, soy, wheat, peanut/tree nuts, and seafood), without allergy testing, resulted in similar rates of symptomatic and histologic remission to an elemental diet control group (74 % response for SFED versus 88 % response in the elemental control group) [14, 37].

In the last year, two large retrospective case series from prominent university referral centers were published, attempting to contrast efficacy of the three main dietary strategies. Henderson et al. [16•] compared remission rates among three cohorts of patients undergoing an elemental diet, classic SFED, or tailored elimination diet in 98 pediatric patients on PPI therapy. All three diets showed successful peak eosinophil count reduction. The elemental diet produced a peak count reduction from 51 to 1 eos/hpf, SFED from 76.5 to 2.5 eos/hpf, and tailored diet from 38 to

Table 1 Comparison of benefits and detriments of the three dietary management styles

Approach	Definition	Pros	Cons
Elemental diet	Diet exclusively consisting of amino acid-based formula	Hypoallergenic Nutritionally comprehensive Reduces symptoms and eosinophil counts	Taste (may require feeding tube) Expense Age appropriateness Excludes all food May have adverse impact on quality of life
Empiric diet	Diet that eliminates the major food allergens from the diet (typically milk, egg, wheat, soy, peanut/tree nut, and fish/shellfish, though variants exist)	Allergy testing not required Studied across all ages Reduces symptoms and eosinophil counts	Some avoidance may be unnecessary Only 4 foods may be necessary Expense May be nutritionally incomplete
Targeted diet	Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)	Most specific therapy Can preserve diet Established sensitivity, specificity, and NLR/PLR to assist with add-back Reduces symptoms and eosinophil counts	Testing precision and technique is inconsistent across centers Milk testing precision very poor when negative Empiric milk elimination as an addition greatly improves response Some avoidance may be unnecessary (sensitization without clinical allergy)
	Re-introduction strategy	Pediatric	Adult
	Suggested order ^a	Fish/shellfish Peanut/tree nut Soy Wheat Egg Milk	Fish/shellfish Egg Peanut/tree nut Soy Milk Wheat

NLR/PLR negative/positive likelihood ratio

^a Data are best established for classic SFED but may be applicable to both elemental and targeted diets

7 eos/hpf. There were no significant proportional differences in the number of patients achieving remission (<15 eos/hpf). There were significant differences in the odds of remission between elemental and SFED, and elemental and tailored elimination therapy, but not between the tailored and the SFED diet. Henderson et al. [16•] noted poor NPVs for the four most commonly introduced foods (milk, egg, soy, and wheat), ranging from 40 to 67 % based on PST and APT. However, it clearly demonstrates the potential for multiple successful dietary management strategies.

In a similar study, Spergel et al. reported retrospective data on 7 dietary styles in 941 pediatric EoE patients evaluated between 2000 and 2011 [14]. The diets evaluated included empiric milk avoidance; empiric milk, egg, and wheat avoidance; classic SFED; tailored elimination; tailored elimination plus empiric milk elimination; empiric milk, egg, wheat, soy, and meat avoidance; and a vegan diet. A causative food, defined as histologic disease recurrence on food re-introduction, was identified in 319 patients, most commonly milk, followed by egg, wheat,

beef, soy, and chicken. Remission rates (<1 eos/hpf) were nearly identical for both targeted elimination and SFED (53 %), 47 % for empiric milk/egg/wheat, and 30 % with just empiric milk elimination alone. The highest observed remission rates were with targeted elimination combined with an empiric milk elimination and empiric milk/egg/wheat/soy/meat elimination diet, which both had a 77 % response rate. Together these studies confirm that there is potential for multiple successful dietary management strategies that include allergy testing-based diets in children [13•, 16•]. Table 1 reviews the pros and cons of the three major dietary strategies.

On the other hand, dietary studies that have focused exclusively on adult patients have provided conflicting data as to the efficacy of allergen testing-based diets. Gonsalves et al. conducted a prospective, non-randomized, uncontrolled study of an SFED in 50 adult EoE patients, noting 94 % had symptom improvement, 74 % responded, and 64 % achieved remission [15]. However, isolated PST-based allergy testing predicted a trigger in just 13 % [15]. In a 6-week, prospective, uncontrolled study of 67 adults,

Lucendo et al. conducted a prospective 6-week SFED variant (avoidance of cereal grains, dairy, egg, seafood, legumes, nut/seed, and soy) and noted 75.5 % achieving counts <5/hpf, but this was poorly concordant with allergy testing results. However, 15 of the 49 patients who maintained the diet for 2 years remained in histologic remission [38]. Lastly, Molina-Infante et al. noted minimal effect of a 6-week testing based targeted elimination diet in an uncontrolled, non-randomized adult cohort of 22 patients, noting 10/15 had no histologic change [39]. It remains unclear whether a particular dietary approach is more effective in certain age ranges, and additional adult studies are warranted.

One other study of interest deals with the concept of epitope specificity in the recognition of food allergen triggers in EoE. In IgE-mediated food allergy certain major food epitopes are conformational and therefore labile with extensive heat and tolerated by many allergic individuals who have immediate hypersensitivity to food antigens [40]. Specifically this has been identified with both cow's milk and hen's egg, and between 70 and 80 % of milk/egg allergic individuals may tolerate "baked" forms of these product (e.g., extensively heated for >30 min at a temperature >350 °F), which also may be associated with phenotype of faster overall allergy resolution [41]. It has been unclear whether these foods are safe for individuals with milk-triggered EoE. In a case series of 15 patients with confirmed milk-triggered EoE, Leung et al. showed that 11/15 patients remained in remission after 6 weeks of baked milk ingestion [42•].

New Pathophysiologic Insights Have Potential Therapeutic Value

In 2010, genome-wide array screening of children with EoE identified a gain of function mutation associated with a loci of interest on gene 5q22, encoding thymic stromal lymphopoietin (TSLP), a master Th2 cytokine essential for allergic development [43]. However it was unclear exactly how this mediated disease. Recently, study by Noti et al. [8•] discovered that TSLP and basophils are crucial mediators in an IgE-independent experimental murine model of EoE, which may indicate a new potential therapeutic target.

In a murine model established through epicutaneous food sensitization on an atopic dermatitis-like skin lesion, mice developed EoE-like disease with expansion of systemic basophil production and a trend towards higher TSLP expression compared to control mice. TSLP-deficient mice treated with a TSLP-blocking antibody were protected from experimental EoE, as were mice treated with basophil depletion. Importantly, the mice in this

model system developed food impactions, the rates of which were significantly diminished when TSLP or basophils were decreased. These investigators further established IgE independence of EoE in this system. In translational studies, biopsy samples with EoE showed higher immunohistochemical staining of TSLP or basophil markers, and the basophil staining correlated with increasing eosinophil counts; peripheral blood mononuclear cells from subjects with active or inactive EoE that expressed the gain-of-function TSLP polymorphism were noted to have higher numbers of basophils [8•].

Other murine model systems demonstrated that eosinophils are important for esophageal strictures, fibrosis, and certain histological features such as basal zone hyperplasia. In addition, interleukins such as IL-13 were demonstrated to cause strictures that were independent of eosinophilia [44, 45]. However, other functional and histologic features such as those dependent on esophageal smooth muscle appear to be independent of eosinophils. Both increased smooth muscle contraction and decreased smooth muscle relaxation were independent of eosinophilia, and smooth muscle hypertrophy and hyperplasia relied on esophageal mastocytosis [45, 46]. With regard to fibrosis, CCL18 has been found to be elevated in EoE [47]. Studies by the Luster laboratory identified CCR8 as the CCL18 receptor, and both were found to be elevated in active EoE biopsies [48]. Together, these studies have translational implications for both anti-eosinophil strategies using biologics that provide siglec-8, IL-13, CCR8, and/or mast cell blockade.

Data for anti-IL-5 as treatment for EoE have been largely disappointing in controlled trials [1•, 2•]. However, investigation has focused on the eosinophil response. Both Aboonia et al. [50] and Aceves et al. [49] have indicated that the mast cell, and not the eosinophil, may play a more important role in EoE. Mast cells outnumber eosinophils in the smooth muscle of affected esophageal tissue, and tryptase-secreting mast cells can associate with dysphagia and greater levels of TGFβ1 (which may mediate esophageal smooth muscle contractility) [49]. Using nested biopsy samples from a prior anti-IL-5 clinical trial, Otani et al. [51•] noted that mast cell numbers decreased in 77 % of anti-IL-5 treated subjects, which correlated to decreased eosinophil counts, and that responders had significantly larger mast cell decreases than non-responders. IL-9, a key mast cell growth factor, was noted to be produced from the esophageal eosinophils, and was also decreased after treatment [51•]. It is potentially notable that while eosinophil decreases did not correlate with symptom changes, mast cell decreases did associate with symptom response in this study.

Krishnamurthy et al., building on data that PARP14 acts as a transcription cofactor for STAT-6 (critical for eotaxin-3 expression), found PARP14 and PARP1 gene expression was upregulated in esophageal biopsies of children with

EoE versus controls, and PARP14 RNA was also upregulated [52]. Using biopsies from two clinical populations, PARP14 and eotaxin-3 expressions were strongly correlated. Transfecting an esophageal cell line with PARP14 in the presence of STAT-6 increased eotaxin-3 promoter activity, and IL-4 and IL-13-induced expression of eotaxin-3 mRNA was attenuated by PARP inhibition [52]. This is preliminary work, but may be a future pathway for therapeutic exploitation.

Update on a New Diagnostic Modalities and Natural History

Diagnosing and monitoring of EoE are heavily dependent on obtaining an esophageal biopsy. Non-invasive methods based on symptom algorithms are poorly predictive eosinophil counts [1•, 2•]. Furuta et al. [53•] recently described an effective, minimally invasive monitoring technique. Using a modified capsule and 90-cm string (Enterotest, Pilpitas, CA), patients swallowed a capsule, and the proximal end of the string was used to assess esophageal luminal secretions for the presence of eosinophil secondary granule proteins ([ESGP] MBP-1, EPX, EDN, ECP, and CLC/Gal-10). Children with active EoE, EoE in remission, GERD, and with no esophageal disease swallowed the capsule/string and were monitored for 24 h followed by string removal, upper endoscopy with biopsy, and analysis of the biopsy and string for ESGPs. ESGP levels from both the string and the mucosal biopsy were able to differentiate those with active EoE from those in remission, with GERD, or with no esophageal disease, and there was significantly strong correlation between biopsy and ESGP findings. Indeed, statistical analysis revealed high receiver-operator characteristic scores, an indicator of accuracy and precision, for the ability of the string test to predict EoE [53•]. Though this technique requires further study, it is an exceptionally promising diagnostic modality.

Similarly, an adult study demonstrated that the use of a test that quantifies esophageal compliance, endoFLIP, predicted the risk of future food impaction based on esophageal rigidity [54•]. Although not yet reported in children, this test may provide a powerful tool for the assessment of esophageal function and remodeling. Indeed, esophageal tissue remodeling with resultant fibrosis, angiogenesis, and smooth muscle hypertrophy appears to underlie the major EoE complications of food impactions and stricture as well as the predominant EoE symptom of dysphagia [55–57]. Underscoring the importance of tissue remodeling, pivotal adult studies have demonstrated that long-standing, untreated EoE progresses almost uniformly to esophageal stricture [58•, 59•]. These studies have important implications for pediatric practitioners since the

hope is that the control of inflammation and remodeling will translate into the control of potential stricture formation.

Lastly, 2013 also saw the first implementation of molecular diagnostics to EoE with the use of the EoE diagnostic panel (EDP), a fluidic gene microarray applicable to fresh and paraffin-embedded esophageal biopsy specimens. The EDP demonstrated 98 % specificity and 96 % sensitivity for distinguishing a diagnosis of EoE in children. This molecular tool described by the Rothenberg laboratory could have a significant impact on EoE and, if combined with less invasive methods, could revolutionize the field of EoE diagnostics [60•].

Conclusion

There continue to be breakthroughs in the understanding of the underlying pathophysiology of EoE, how to diagnose EoE, and how to most effectively treat EoE. Significant progress has been made in the past 12–15 months. However, many barriers remain, including poor differentiation of EoE from other diseases with esophageal eosinophilia, reliance on biopsy for diagnosis, unclear superiority of several treatment approaches, and lack of an effective biologic treatment. Future work aimed at addressing these issues will undoubtedly have important implications for our understanding and care of EoE.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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