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New Developments in the Diagnosis and Treatment of Eosinophilic Esophagitis

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Abstract

Purpose of Review: Eosinophilic esophagitis (EoE) is a chronic, allergen-driven, immune-mediated disease of the esophagus that progresses to esophageal fibrostenosis if left untreated. The aim of this review is to provide a concise update on recent clinically relevant advances in the development of diagnostic and therapeutic approaches for EoE.

Recent Findings—Current diagnostic and disease monitoring protocols for EoE rely on repetitive endoscopic evaluations and esophageal tissue acquisition for histopathologic analysis. Recent advancements in EoE diagnosis include endoscopic functional lumen imaging probe (FLIP), transnasal endoscopy (TNE), and the emergence of non-invasive diagnostic tools including cytosponge, esophageal string test, and mucosal impedance probe. Biomarkers for EoE have not yet proven their clinical utility. No Food and Drug Administration (FDA)-approved drugs currently exist for the treatment of EoE. Topical corticosteroid, proton-pump inhibitors (PPI), elimination diet, and dilation are the current treatment modalities for confirmed EoE. Promising results from clinical trials are emerging for biologic agents that target the interleukin (IL)-13 and the IL-4/IL-13 receptor, specifically, RPC4046 and dupilumab, respectively.

Summary—New diagnostic algorithms, non-invasive diagnostic strategies, and treatment modalities for EoE are emerging. Patients with EoE continue to require a multimodal and multi-disciplinary management approach.

Keywords

Eosinophilic esophagitis (EoE); Diagnosis; Treatment; Corticosteroids; elimination diet; biologic therapy

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, allergen-driven, immune-mediated disease of the esophagus [1, 2]. There is a male predominance, occurring at a male-to-female ratio of

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3:1. The incidence of EoE has been increasing [3, 4]. Persistent, sub-optimally controlled esophageal inflammation underlies a natural progression to fibrostenotic disease; during which esophageal dysmotility, tissue rigidity, reduced tissue compliance, and stricture formation often dictate the clinical presentations of dysphagia and food impactions [5–9].

EoE creates a significant healthcare burden and an impaired quality of life [10–14]. Children with EoE can exhibit failure to thrive with feeding difficulty, abdominal pain, food regurgitation, and, on rare occasions, esophageal food impaction [7, 15, 16]. Dysphagia and food impactions, however, are often the presenting symptoms in adult EoE patients [17]. The combination of abnormal feeding behaviors, feeding difficulty, food aversion, recurrent dysphagia, and food impaction likely contribute to failure to thrive in children and also to the lower body mass index in adults [18, 19]. However, children with uncomplicated EoE appear to have normal nutritional intake despite feeding behavior dysfunction [20].

Despite improvement in the understanding and recognition of EoE, there remains a significant delay to diagnosis from the time of symptom onset [21]. Such diagnostic delay is detrimental to the patient, since the risk of esophageal stricturing disease increases with each year of delayed diagnosis [7]. Nevertheless, care must be exercised to diagnose EoE accurately, as having the diagnosis can be life transforming and potentially raise life insurance premiums [22–24]. The aim of this review is to provide a concise update on recent advances in the development of diagnostic and therapeutic approaches of EoE that have contributed to our rapidly evolving understanding of EoE.

Diagnosis of EoE

EoE is currently defined as the presence of both clinical symptoms of esophageal dysfunction and histologic evidence of significant esophageal eosinophilic inflammation with 15 or more eosinophils per high-power field (hpf), although other infiltrating immune cells such as mast cells, lymphocytes, basophils, and innate lymphoid cells likely also contribute to disease pathogenesis [9, 25, 26]. The inflammation must be isolated to the esophagus and other causes of esophageal eosinophilia need to be excluded [26].

Emerging visual diagnostic tools—Direct visualization of the esophageal lumen and mucosa by upper endoscopy not only provides useful diagnostic information, but also provides the physician with the ability to immediately obtain esophageal biopsies for tissue diagnosis and disease stratification, *i.e.,* inflammatory stage, fibrostenotic disease, or mixed disease states. The EoE Endoscopic Reference Score (EREFS) classification is a validated tool to standardize quantification and reporting of endoscopic findings of disease severity: edema, rings, exudates, furrows, and strictures [27–29]. Since EoE is a patchy disease, 2 to 4 biopsies each in the distal and proximal halves or, occasionally the distal, middle, and proximal thirds, of the esophagus are typically obtained and put in separate biopsy jars [30, 26]. One emerging caveat of esophageal tissue acquisition is that esophageal biopsies often lack adequate lamina propria where subepithelial fibrosis occurs and thus may underestimate the severity of EoE, *i.e.,* pathologic remodeling and fibrostenotic disease, at the time of tissue acquisition for diagnosis. A recent analysis showed that adequate lamina propria was present in only 42% of esophageal biopsies [31]. Therefore, at least 7 biopsy specimens

from the middle-distal esophageal segment have been recently suggested to optimally detect EoE subepithelial fibrosis [31].

Transnasal endoscopy (TNE) is a recent diagnostic tool that may potentially become widely adapted by clinicians given its safety, cost effectiveness, feasibility, and high patient preference [32]. TNE is performed in an unsedated patient, and while using only topical anesthetics, TNE is able to provide histologic tissue of the proximal esophagus. In the study performed in pediatric patients with EoE, the total surface area from mucosal biopsies was not significantly different when compared with the same subjects undergoing upper endoscopy using standard endoscopy forceps [32]. More than half the patients and the majority of the parents preferred this approach over standard endoscopy with sedation. Further validation in larger cohorts is needed.

Upper gastrointestinal (GI) esophagram double-contrast protocol, which includes swallowing a 12.5-mm barium tablet, was recently proposed as a complementary study to upper endoscopy to detect fibrostenotic changes in EoE [33]. However, the need for specialized radiographic interpretation capability may restrict its use to only a few select centers.

Endoscopic functional lumen imaging probe (FLIP) is a novel and widely accepted endoscopic method to assess esophageal caliber and distensibility in EoE patients. FLIP uses high-resolution impedance planimetry during volume-controlled distention to determine variations in luminal pressure and geometry in a cross-sectional area of the esophagus along an axial plane [34, 35]. FLIP studies in EoE patients have demonstrated reduced esophageal distensibility [8], which is associated with increased food impactions and the need for esophageal dilation [36–38]. Esophageal narrowing and reduced esophageal distensibility are features also observed in pediatric EoE [8], suggesting that early diagnosis of EoE and timely treatment to prevent pathologic tissue remodeling are required. FLIP has established its importance in EoE severity assessment, disease stratification, and assessment of treatment response.

Emerging non-invasive diagnostic tools—Due to the invasive nature of repetitive endoscopic evaluations with multiple biopsies, minimally invasive methods to diagnose EoE and to assess disease activity have been proposed. Cytosponge, a string-tethered spherical mesh sponge that is compressed in a dissolvable gelatin capsule, is swallowed by an unsedated patient and retrieved by withdrawing the string through the mouth [39]. The cytosponge is safe, well tolerated, and the esophageal tissue specimen obtained by this method appears adequate for histopathologic analysis. The sensitivity and specificity of the cytosponge to assess EoE histologic activity are 75% and 86%, respectively [39, 40]. Similarly, the esophageal string test captures adherent luminal secretions containing eosinophil-derived proteins that reflect mucosal inflammation in EoE [41]. Other approaches similar to the cytosponge and esophageal string test methods, such as endoscopic esophageal brushings and blind esophageal brushings via a nasogastric tube, have been recently proposed [42, 43]. Extending the analysis of esophageal brushings to include esophageal levels of eosinophil-derived neurotoxin (EDN), which is highly expressed in the EoE esophagus [44], appears to improve EoE detection and disease monitoring [43]. Further

investigation, optimization and validation of these emerging non-invasive diagnostic tools in larger patient cohort remain to be established.

Measurement of electrical impedance at the esophageal mucosal surface is another emerging modality to assess disease activity in EoE [45–48]. The mucosal impedance probe detects changes in the electrical impedance, thought to be related to a defect in the esophageal barrier function. Real-time mucosal impedance measurements correlate inversely with esophageal eosinophil counts and spongiosis severity in EoE, allowing the ability to quickly determine and monitor EoE disease activity [49]. However, upper endoscopy is still required to introduce the mucosal impedance probe into the esophagus.

Potential biomarkers—Measurement of serum levels of select panels of EoE-related cytokines, chemokines, and serum proteins has not yet proven their clinical utility as serologic biomarkers for EoE [50–52]. However, EoE patients have increased mean peripheral blood absolute eosinophil counts (AEC) [53–55]. Normalized serum eosinophil peroxidase levels, the ratio of serum eosinophil peroxidase levels to AEC, are lower in EoE patients and have an inverse correlation with esophageal eosinophil density; and thus, are being evaluated as a potential biomarker for EoE [53]. The presence of multiple food-specific serum IgE antibodies correlates with esophageal eosinophilia in children with nonspecific gastrointestinal symptoms, which can be useful in stratifying potential EoE patients [56]. Esophageal and plasma food antigen- specific IgG4 antibodies are elevated in EoE [57–60]. Furthermore, serum epithelial-specific autoantibodies, specifically, anti-desmoglein 3 (DSG3) IgG4 and anti-collagen XVII (NC16A) IgG4, are elevated in EoE. Serum anti-NC16A IgG4, but not IgG1, levels are significantly elevated in EoE patients and decrease after topical corticosteroid treatment in histologic responders [61]. While promising, additional investigation and validation are required.

Treatment of EoE

There are currently no drugs approved by the Food and Drug Administration (FDA) for the treatment of EoE. The complexity of current EoE management requires a multimodal, multi-disciplinary approach that includes chronic corticosteroid treatment, proton-pump inhibitors (PPI), dietary antigen restriction, lifestyle modification, and repeated endoscopic diagnostic and therapeutic evaluations [25, 62]. Several biologic agents are being investigated for the management of EoE. A paradigm-shifting advancement is the recent orphan designation of dupilumab, a monoclonal antibody that targets the α-chain of interleukin (IL)-13 and IL-4 receptor [63]. Prior to dupilumab's orphan status for EoE, efforts in the management of EoE have focused on: 1) controlling inflammation and tissue remodeling with corticosteroids, proton-pump inhibitors (PPI), and various investigative biologic agents; 2) the exclusion of antigenic stimulation via elimination diet; and 3) endoscopic dilation of the symptomatic, fibrostenotic esophagus if uncontrolled by medical and dietary therapies [64]. Data have emerged to suggest that in adult EoE patients, controlling esophageal inflammation may decrease the need for subsequent esophageal dilation [38, 65].

Topical Corticosteroids—Controlling inflammation with swallowed topical corticosteroids is a mainstay of EoE treatment [25]. Emerging proprietary and non-

proprietary corticosteroid formulations that improve bioavailability and treatment efficacy should increase available treatment options [66–68]. In the United States, fluticasone administered as an aerosolized and swallowed formulation and oral viscous preparations of budesonide are the two most frequently used topical corticosteroids for EoE [69, 70]. Clinical trials in Europe have demonstrated successful use of an effervescent budesonide tablet in EoE [68]. In a recent study, oral dispersible budesonide induced histologic remission in 87% at 12 weeks in adults with EoE [71]. Topical corticosteroid dampens EoE-associated esophageal inflammation, improves mucosal barrier integrity and histologic remodeling, resulting in improvement of esophageal diameter, distensibility, and in the rates of food impaction [72–75, 38]. Oral viscous budesonide therapy achieves better endoscopic and histologic improvement, compared to fluticasone propionate in pediatric and adolescent EoE; this is likely due to oral viscous corticosteroid preparations achieving better esophageal mucosal deposition [76, 66]. Oral viscous budesonide (OVB) can also be compounded by specialty pharmacy. In a retrospective analysis of a cohort of 48 children and adult EoE patients who received compounded OVB at 2.4 mg mean initial dose (range 1 – 6 mg per day) either once daily or twice daily, there was a significant, durable symptomatic, endoscopic, and histologic response after a mean follow-up period of 17 months [77]. In children with EoE, long-term maintenance dosing of aerosolized and swallowed fluticasone was found to be safe and achieved improvement in histologic inflammation, lamina propria fibrosis, endoscopic features and clinical symptoms [75].

Recently, an induction-maintenance corticosteroid protocol was proposed for EoE management [78]. In this protocol for adult EoE patients, induction corticosteroid therapy with 1 mg twice daily of budesonide is initiated for 2 to 4 weeks to reach clinical response, followed by maintenance therapy with 0.25 mg twice daily that can then be rescued with 1 mg twice daily dosing for 7 to 15 days during EoE flares. Corticosteroids are discontinued if patient maintains ≥6 months of deep remission – a combination of clinical symptom improvement; endoscopic inflammatory remission with complete absence of white exudates, furrows, and edema; and histological inflammatory remission with peak eosinophil count less than 5 eosinophils per high-power field. Using this protocol, deep remission was achieved at 89 weeks in 9.4% of adult EoE patients. Corticosteroid discontinuation occurred at 104.7 weeks, with 81.8% experiencing EoE clinical relapse after a median of 22.4 weeks. In another study, budesonide maintenance dosing at once every other day in adult EoE patients was not effective [79]. These studies suggest that a higher daily budesonide maintenance dose is necessary to potentially achieve complete histologic and endoscopic remission.

Asymptomatic esophageal candidiasis and herpes esophagitis have been observed with swallowed, topical corticosteroid therapy [80, 75]. In clinical trials, asymptomatic esophageal candidiasis occurred in approximately 20% (0% - 26%) of topical corticosteroid-treated EoE patients [81]. Adrenal insufficiency of unclear clinical significance has been reported in children on high-dose swallowed topical fluticasone propionate or oral viscous budesonide [82, 83].

Proton-pump inhibitor (PPI) therapy for EoE—High-dose PPI therapy is no longer a diagnostic agent, but is now widely accepted as a first-line therapeutic modality for EoE,

based on our evolving understanding of PPI-responsive esophageal eosinophilia (PPI-REE) being in the EoE continuum [84–88, 26]. Treatment with PPI modulates esophageal inflammation beyond suppression of the acidic environment [89, 90]. A recent meta-analysis of 33 studies, comprising 619 patients with symptomatic esophageal eosinophilia, demonstrated that PPI therapy induced clinical response and histologic remission in 60.8% and 50.5% of patients, respectively [91]. On PPI maintenance, sustained remission has been observed in 73–86% of pediatric and adult PPI-REE patients [92]. Low-dose PPI maintenance with esomeprazole at 1 mg/kg (maximum of 40 mg) daily dosing in 57 EoE children, who responded initially to an 8-week esomeprazole trial at 1 mg/kg dose (maximum of 40 mg) twice daily, achieved clinical response in 86% and histologic remission in 70.1% of these children at 1 year with an adequate safety profile [93]. Complete histologic response, defined as ≤5 eosinophils/hpf, to the 8-week PPI induction phase resulted in better histologic control on the low-dose PPI maintenance. Histologic remission was sustained at 2 years in 11 of 12 children (91.6%) from the same cohort who underwent further esomeprazole maintenance dose reduction to 0.5 mg/kg once daily in the second 12-month period. Although PPI adverse effects, *i.e.,* diarrhea, abdominal pain, headache, and urticaria, are mild and infrequent [93], high-dose induction therapy is likely required to achieve therapeutic benefits of inflammation modulation and mucosal barrier restoration; thus, tapering the maintenance dose to the lowest effective dose should remain a treatment goal to minimize adverse drug outcomes.

Elimination diets in EoE—Dietary modification to exclude food-derived antigenic stimulation is effective in achieving histologic and clinical remission in EoE patients [94–96]. Elemental diet remains the most effective strategy; however, therapy compliance is a significant challenge. Four weeks of elemental diet improves clinical symptoms in 88% and achieves histologic response in 71% of patients, with an improvement in mucosal barrier integrity and a significant reduction in gene expression of key cytokines such as IL-13, IL-5, and thymic stromal lymphopoietin (TSLP) [97, 98]. Esophageal inflammation is improved in 88% of EoE patients by elemental diet therapy; in 74% by six-food-elimination diet (SFED) excluding cow milk, wheat, egg, soy, peanut and seafood; and in 64% by a four-food elimination diet (FFED) strategy excluding only milk, wheat, egg, and soy [99, 100]. Antigenic exclusion can also improve esophageal distensibility [38]. A meta-analysis of 33 studies on 1128 children and 189 adult EoE patients shows that elemental diets are effective for 90.8% of cases, SFED for 72.1%, and allergy testing-directed elimination diet for 45.5% of cases [96]. However, allergy testing-directed selective elimination diet by way of skin prick tests and atopy patch testing has been shown to have suboptimal efficacy in adult EoE and thus is generally not recommended [101, 102]. More recently, esophageal prick test (EPT) with food antigens was proposed a potential novel safe and feasible method to guide elimination diets [103], however, EPT remains to be further evaluated and validated.

While effective, empiric food elimination by way of elemental diet, SFED, or FFED may cause unnecessary dietary restriction. A novel step-up food elimination strategy was recently proposed. In a multicenter, prospective clinical trial, a 2–4-6 step-up elimination diet strategy in EoE patients achieved clinicohistologic response and identified food triggers of EoE early, and thus avoided unnecessary dietary restriction [104]. Briefly, patients were

initiated on a 2-food elimination diet (TFED) excluding milk and gluten-containing cereals first. Non-responders were stepped up sequentially to FFED, with the additional exclusion of egg and legumes; and ultimately to SFED, with the elimination of nuts and fish/seafood. Each elimination diet step lasted 6 weeks. Overall, EoE remission was achieved in 43% of the TFED group, in 60% of patients receiving both TFED and FFED, and in 79% of patients receiving all three tiers of elimination diet therapy. Patients who failed any elimination diet therapy were rescued with 8 weeks of swallowed topical steroids – viscous oral budesonide 2 mg twice daily in adults and 1 mg twice daily in children, or swallowed fluticasone 800 μg twice daily. Histologic remission occurred in 79% of patients who underwent corticosteroid rescue therapy following a failed step-up antigen elimination protocol [104]. This strategy reduced the number of endoscopies when compared to a traditional six-food elimination diet. However, declaring elimination diet failure after 6-week trial was recently suggested to be premature, with histologic resolution eventually observed when the elimination diet therapy was extended for an additional 5 to 22 weeks or a mean of 10 weeks [105]. The duration of elimination diet, goal-directed therapy will likely need to be revisited in a larger study.

Relevant biologic therapies—Targeting TNF-αwith infliximab or IgE with omalizumab has not been shown to be effective in treating EoE [25]. An anti-IL-13 monoclonal antibody, QAX576, reduced esophageal eosinophilia and EoE-related gene expression, but did not significantly improve clinical symptoms [25]. Another anti-IL- 13 monoclonal antibody, RPC4046, however, reduced esophageal eosinophilia, but also improved endoscopic features and dysphagia in EoE patients, particularly in steroid-refractory EoE patients [25]. Dupilumab, an antibody that targets the common α-chain of the IL-13 and IL-4 receptor, recently achieved an orphan designation for the treatment of EoE. In a 12-week phase II, randomized, double-blind, placebo-controlled clinical trial in 47 adult patients with active, moderate-to-severe EoE, dupilumab at 600 mg subcutaneous loading dose, followed by 300 mg subcutaneous injection once weekly, achieved clinical response with a 3-point reduction (45% improvement) in Straumann Dysphagia Instrument score at week 10 of dupilumab *versus* 1.3-point reduction (19% improvement) for placebo; histologic remission with overall peak intraepithelial eosinophil count reduced by 93% from baseline for dupilumab *versus* an increase in 14% from baseline for placebo; and endoscopic and esophageal distensibility improvement [63].

Dilation Therapy for EoE—The narrowed, fibrostenotic, symptomatic EoE-associated esophagus can be rescued with dilation in a slow, deliberate, and graduate manner to improve dysphagia [106, 107]. In a recent study of 509 EoE patients, esophageal dilation was well tolerated [108]. Mucosal tear is expected and is a dilation success rather than a complication [106, 109]. Traditionally a procedure usually performed in adult EoE patients, dilation in EoE children was shown recently to be safe, with pain being a commonly reported post-procedure complaint [110]. Overall, the risk of esophageal perforation due to dilation is less than 1% [109]. In a meta-analysis of 845 children and adults with EoE undergoing 1820 dilations, the pooled clinic response was 95% with a very low complication rate (perforation in 0.38%, hemorrhage in 0.05%, and hospitalization in

0.67%) [111]. The predictor of repeated, multiple dilations was a smaller baseline esophageal diameter, with the second dilation typically occurring within 1 year [108].

CONCLUSION

Recent advances in EoE are improving our diagnostic and therapeutic approaches. Current diagnostic strategy still relies on endoscopic evaluation with esophageal biopsies for tissue acquisition and histopathologic analysis. Although endoscopic biopsies potentially require deeper tissue penetration to include the lamina propria to more accurately characterize EoE severity, up-and-coming investigative diagnostic approaches are shifting toward non-invasive modalities. Current treatment strategies available to EoE patients center on monotherapy or combination therapy, utilizing dietary modification to exclude antigenic stimulation and corticosteroids and PPI to control tissue inflammation and pathologic tissue remodeling. Dilation therapy for the narrowed, fibrostenotic, symptomatic esophagus can potentially be avoided with optimal medical and elimination diet therapies, although may be required for severe fibrostenotic strictures as an adjunct therapy. Dupilumab is an emerging promising treatment for EoE that has gained orphan drug status. Given the complexity of the treatment regimens and frequent follow ups, optimal care of EoE patients requires a multimodal, multi-disciplinary management approach.

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Abbreviations:

AEC	absolute eosinophil count
EoE	eosinophilic esophagitis
FLIP	functional lumen imaging probe
FFED	four-food elimination diet
hpf	high-power field
PPI	proton-pump inhibitor
PPI- REE	PPI-responsive esophageal eosinophilia
SFED	six-food elimination diet

TFED	two-food elimination diet
TNE	transnasal endoscopy

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