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Translating New Developments in Eosinophilic Esophagitis Pathogenesis into Clinical Practice

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Opinion Statement

New developments in eosinophilic esophagitis pathogenesis are shaping our current therapeutic and management strategies. EoE is a chronic allergic inflammatory disease with progression to fibrostenotic disease. The disease warrants early diagnosis and long-term maintenance therapy. The diagnosis of EoE should be based on the concept of an allergy-mediated disease with esophageal dysfunction and esophageal eosinophilia. Recent findings suggest PPI-REE is likely a continuum of EoE or similar Th2-mediated allergic process. PPIs have therapeutic properties that can benefit both GERD and EoE. Therefore, PPIs should not be considered a diagnostic tool, but rather a therapeutic option for EoE. If patients are PPI-nonresponsive, then dietary therapy or steroid therapy should be considered. Dilation can be reserved as adjuvant therapy for severe fibrostenotic lesions.

Keywords

gastroesophageal reflux disease; eosinophilic esophagitis; proton pump inhibitors; PPI-responsive esophageal eosinophilia; topical steroids; dietary therapy

Introduction

Eosinophilic esophagitis (EoE) has emerged globally over the past two decades with increasing incidence. EoE is characterized as a chronic inflammatory disease incited by allergens resulting in esophageal eosinophilia and severe esophageal dysfunction [1]. This disease afflicts children and adults causing symptoms of dysphagia and abdominal pain. Over 20 years, great research effort has been made to elucidate the pathogenesis and natural progression of the disease in order to establish well-defined diagnostic criteria, develop

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Compliance with Ethics Guidelines

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.

Conflict of Interest

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therapeutic options, and generate strategies to monitor the disease. Experts reached a consensus defining EoE as an “immune/antigen-mediated” clinicopathologic disease requiring both esophageal dysfunction and eosinophilia (≥ 15 eos/hpf on 1 or more biopsy specimens) [1]. With the emergence of PPI-responsive esophageal eosinophilia (PPI-REE) and experts advocated the use of acid suppression as a diagnostic tool to exclude them from EoE. The recommended first-line therapies consisted of dietary therapy or corticosteroid therapy with the goal of attaining symptom resolution and maintaining histological remission. Several advances in elucidating EoE pathogenesis have now reshaped the landscape of EoE therapy. This paper will highlight recent findings in EoE pathogenesis and discuss current and investigational therapeutic options in light of current understanding of EoE.

EoE, PPI-Responsive Esophageal Eosinophilia, and GERD

The overlapping features of EoE and GERD pose several challenges in the diagnosis of EoE. Early authorities deemed it crucial to distinguish this disorder from GERD [2]. However, GERD and EoE are not mutually exclusive disorders [3]. First, GERD, in the absence of EoE, can have mild esophageal eosinophilia. Acid and bile can upregulate adhesion molecules and chemoattractants involved in eosinophil trafficking. Second, if GERD and EoE are unrelated, then the two diseases should coexist by chance alone given GERD prevalence of 10–20% [4]. Third, EoE might contribute to GERD. EoE inflammation and remodeling can alter esophageal motility, delay acid clearance, and reduce lower esophageal sphincter pressure. Disrupted barrier function and increased permeability due to EoE inflammation may render the epithelium susceptible and hypersensitive to acid reflux injury. In fact, vagal sensory neurons have enhanced acid responsiveness in EoE guinea pigs [5], and acid hypersensitivity has been described in EoE patients [6]. Conversely, GERD might contribute to EoE. Disrupted barrier function due to acid-related injury may increase epithelial permeability to allergens. In addition, refluxed gastric material induces mediators in the epithelium that can exacerbate immune activity [7].

Previously, experts proposed using a PPI trial to distinguish GERD from EoE [2]. This proposal was based on the assumption that acid suppression is the only therapeutic effect of PPIs, and therefore only GERD can respond to PPIs. The assumption has several flaws. First, there are multiple mechanisms whereby EoE patients might benefit from PPI-induced acid suppression (see below). Second, PPIs have acid-independent, anti-inflammatory effects that might be benefit both GERD and EoE patients (see below). Indeed, this assumption was questioned as emerging reports described patients with PPI-REE [1,8–11]. These patients have clinical and histological findings consistent with EoE yet achieve clinicohistological remission on PPIs. Prospective studies estimated 33–74% of patients with esophageal eosinophilia responded to PPIs [8–11]. Two randomized controlled trials (RCT) compared esomeprazole 40mg daily to fluticasone 440μg twice daily and found no differences in remission rates [8,10]. No clinical features, endoscopic features, nor inflammatory markers (eotaxin-3, major basic protein, tryptase) can distinguish PPI-REE patients from EoE patients [11,12]. Most recently, genetic transcriptome analysis of PPI-REE patients and EoE patients revealed remarkable overlapping molecular signature [13].

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Taken together, patients with PPI-REE might indeed have EoE or the same allergy-mediated process that responds to therapeutic effects of PPIs.

PPI as a Therapeutic Option for EoE

There are multiple plausible mechanisms whereby EoE patients benefit from PPI-induced acid suppression [3]. Reducing acid exposure might decrease acid injury-related cytokines, pain, and esophageal permeability. In fact, mucosal integrity, determined by electrical tissue impedance and transepithelial electrical resistance, was impaired in both EoE and PPI-REE patients [14]. Treatment with high-dose PPI partially restored mucosal integrity in the PPI-REE group. The investigators speculated that acid reflux might exacerbate mucosal permeability facilitating allergen entry.

EoE patients might benefit from PPIs through mechanisms that are independent of acid suppression. PPIs can inhibit Th2 cytokine-induced eotaxin-3 secretion in esophageal epithelial cell, potentially reducing eosinophil recruitment [15,16]. The effect was achieved with physiological doses of omeprazole [16]. More recently, the eotaxin-3 expression by epithelial cells in the esophageal biopsies of children with esophageal eosinophilia was examined before and after PPI therapy [17]. After PPI therapy, eotaxin-3 expression decreased in the proximal esophagus where reflux is unlikely to occur suggesting that anti-inflammatory effects rather than acid suppression are the reason for the decrease [17]. PPIs can also exhibit anti-oxidant properties, inhibit certain functions of immune cells, and decrease expression of adhesion molecules and inflammatory cytokines [3]. Lastly, the timely transcriptome analysis of PPI-REE patients showed reversion of classic allergic inflammation gene expression including eosinophilia, mastocytosis, tissue remodeling, and impaired barrier function after PPI therapy providing compelling evidence that PPIs have therapeutic properties directed at allergic inflammation [13]. Furthermore, the study identified candidate genes that may predict PPI-responsiveness in EoE patients.

The diagnosis of EoE should be based on the conceptual definition that the patient has an “immune/antigen-mediated” disease. PPIs have multiple effects that might provide benefit in both an allergic disease like EoE and a peptic-acid disorder like GERD. Thus, for any patient who has esophageal symptoms and esophageal eosinophilia, a clinical and/or histological response to PPIs does not rule in GERD nor does it not rule out EoE. Therefore, a trial of PPI therapy might not be suitable for diagnostic purposes. Assessing for the presence of GERD in a patient with esophageal eosinophilia may require further diagnostic studies such as esophageal pH/impedance monitoring. Diagnostic approaches such as an allergy evaluation, novel gene profiling [13], or additional immunostaining for inflammatory biomarkers [18,19]might help discern the presence of an allergy-mediated process in a patient with esophageal eosinophilia. In light of recent developments, updates to current guidelines will likely soon follow. Until then, PPI therapy should be regarded largely as a therapeutic option rather than a diagnostic tactic, and high-dose PPI therapy is a reasonable initial option for EoE patients. (Figure 1).

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Allergens and Dietary Therapy

EoE is an allergic disorder [1]. EoE has been tied to atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis. The link between EoE and food allergens was clearly recognized after Kelly and colleagues documented disease remission in children prescribed an elemental diet and disease recrudescence following food reintroduction [20]. Animal studies have employed intraesophageal ovalbumin [21,22] or peanut extract [23] challenges in mice to induce EoE emphasizing the role of food allergen. Seasonal variations associated with diagnosis suggest a role for aeroallergens. Recent human data suggest that aeroallergens might be more relevant in adults and older children documenting 89% of EoE adults having aeroallergen sensitization [24] and children aeroallergen sensitization increasing with age [25]. However, there are some conflicting epidemiological data disputing the seasonal trend in EoE incidence [26,27].

A dietary approach is a widely accepted form of therapy for EoE. There are three general approaches to the dietary therapy: (1) elemental diet, (2) empirical elimination diet, and (3) directed elimination diet. The elemental diet, comprised of an exclusive amino acid-based formula, is the most restrictive approach but highly effective with a 90% remission rate [28]. The empirical elimination diet strategically excludes food commonly associated with food allergy such as cow's milk protein, wheat, egg, soy, nuts, and fish and demonstrated 72% efficacy [28]. The directed elimination diet is based on allergy testing (skin prick testing and/or atopic patch testing). However, current allergic testing methods have limitations and are not reliable in identifying food triggers, and the directed elimination diet approach was less successful at 45% efficacy [28].

There are three stages to the dietary therapy [29]. The first stage achieves disease remission 6–8 weeks after initiating the diet. The second stage reintroduces previously excluded foods in a step-wise fashion to identify trigger food(s) with endoscopy and histology. Patients typically have 1 or 2 culprits identified through this process. The third stage establishes a maintenance regimen that excludes identified trigger food(s) long-term in order to maintain remission.

Overall, dietary therapy offers EoE patients a relatively safe, long-term option. However, there are several potential challenges that need to be considered. All diets are restrictive and require close monitoring for nutritional deficiencies. Patients require education in food labels and cross-contamination. Factors such as lifestyle restrictions, enteral feeding tube requirement, dietary costs, endoscopic procedural costs, and tedious reintroduction stage can potentially detract from patient adherence to therapy. For these reasons, dietary therapy should be offered in highly motivated patients with preference to SFED, then directed elimination diet, and reserving the elemental diet for severe or refractory cases (Figure 1).

Th2 cytokines (IL-5, IL-13, and IL-4)

EoE is considered a hypersensitivity to allergens. The disease tends to fall in the spectrum of T-cell –mediated hypersensitivity as opposed to IgE-mediated hypersensitivity, although both mechanisms are likely involved. In T-cell-mediated hypersensitivity, antigen-presenting cells and antigen-specific T cells activate a Th2-predominant inflammatory

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response. Dendritic cells [30], epithelial cells [31], and eosinophils [32] are all presumed to function in some capacity as antigen-presenting cells in EoE. Straumann and colleagues first discovered that Th2-mediated allergic inflammation was involved in EoE [33]; several studies followed reflecting elevated expression of Th2 cytokines (IL-5, IL-13, and IL-4) in the esophagus and serum [34–36]. These Th2 cytokines are responsible for the recruitment and activation of eosinophils, mast cells, and basophils.

IL-5, in particular, is known to promote eosinophil proliferation in the bone marrow and to prime eosinophils for cytokine stimulation. Early murine studies established that eosinophil trafficking is IL-5 dependent [37]. IL-5 also led to esophageal remodeling and fibrosis in the mice [38–40]. A few clinical studies have targeted IL-5 with humanized monoclonal antibodies, mepolizumab and reslizumab. Despite a reduction in peripheral eosinophilia or esophageal eosinophilia, the anti-IL-5 therapies did not attain symptomatic resolution [41–44]. Recent subanalysis of pediatric mepolizumab study, described a reduction in esophageal mast cells and eosinophil-mast cell couplets in responders [45]. Thus, IL-5 holds a central role in eosinophil and mast cell function in EoE, and continues to be a viable therapeutic target.

The EoE transcriptome determined by genome-wide microarray discovered many IL-13-inducible genes responsible for pathogenesis [34,46]. IL-13 can induce esophageal epithelial cells to express eotaxin-3, a strong chemoattractanct for eosinophils. Remarkably, eotaxin-3 is the most highly-upregulated gene (53-fold increase) in the EoE transcriptome [46]. This study also identified a single nucleotide polymorphism (SNP) in the eotaxin-3 gene that is associated with disease susceptibility. Recent studies elaborated how epigenetic DNA methylation might mediate eotaxin-3 regulation [47]. As previously stated, PPI can decrease IL-13-induced-eotaxin-3 expression in esophageal epithelial cells [15,16]. Mice with genetic deletion of the eotaxin-3 receptor were protected from allergen-induced EoE [46]. Previous animal studies confirmed that IL-13 facilitates eosinophil recruitment [48], however recent studies concluded IL-13 is not critical, as deletion of IL-13 did not abolish eosinophilia [49]. IL-13 can potentially disrupt the integrity of the epithelial barrier by downregulating epithelial cell differentiation genes such as filaggrin, involucrin, and desmoglein-1 [50,51]. Periostin, an extracellular matrix protein involved in both fibrogenesis and eosinophil trafficking, is markedly upregulated in esophageal specimens and regulated by IL-13 as well [52]. IL-13 overexpression in mice induced features of esophageal remodeling [53]. Overall, compelling evidence underscore the prominent effect IL-13 has on disease progression. A RCT tested QAX576, a monoclonal antibody against IL-13, with promising results [54]. QAX576 was well tolerated and reduced intraepithelial eosinophil by 60%. Expression of EoE transcripts improved. Presently, a phase II, double-blind, RCT (NCT02098473 clinicaltrials.gov) is evaluating the efficacy and safety of the anti-IL-13 monoclonal antibody RPC4046 in EoE adults.

Although esophageal IL-4 expression is higher in EoE patients [35,36], it is still unclear what specific effects are commanded by IL-4. In other allergic disorders, IL-4 induces naive T cells to differentiate to Th2 cells. IL-4 also facilitates B cell class switching to IgE. In esophageal epithelial cells, IL-4 stimulates eotaxin-3 secretion [15]. Currently, the anti-IL-4

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monoclonal antibody dupilumab is already being examined in other conditions, like asthma and atopic dermatitis, and preparations for a clinical trial in EoE are underway.

Eosinophils

Eosinophils do not normally reside in the esophagus. Eosinophils derive from the bone marrow where systemic cytokines, such as IL-5, stimulate proliferation. The peripheral eosinophils are then primed for systemic and local chemokine that ultimately direct eosinophils to the esophagus. Peripheral eosinophils from EoE patients are primed for recruitment with enhanced expression of CRTH2 (receptor for chemoattractant prostaglandin D2)[55], adhesion molecule ICAM-1 [55,56], and CCR3 (receptor for eotaxin-3)[57]. In the esophagus, local cytokines activate eosinophils to release eosinophil granule proteins such as major basic protein-1, eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase by cytolytic degranulation [58]. These eosinophil granule proteins injure the esophageal mucosa and can be detected with a novel esophageal string device to assess mucosal inflammation [59].

Therapies aimed to prevent eosinophil recruitment seem promising. A RCT utilized OC000459 to selectively inhibit CRTH2, the receptor for prostaglandin D2 in adults with corticosteroid-refractory EoE [60]. The drug was well tolerated and achieved reduction in esophageal eosinophilia and symptoms. Administration of an antibody to Siglec-F, an eosinophil receptor, decreased eosinophils and remodeling in the esophagus of allergen-induced EoE mice [61]. Anti-Siglec-therapies are being investigated in other human diseases, but currently none are used in EoE.

Thymic Stromal Lymphopoietin and Basophils

Thymic stromal lymphopoietin (TSLP) was brought to the forefront by genome-wide association study (GWAS) [62,63] and candidate gene profiling [64] as SNPs associated with EoE were identified at the gene. TSLP, an epithelial-derived cytokine, is speculated to drive allergic inflammation by expanding a distinct basophil population that promotes Th2-mediated inflammation [65]. Noti and colleagues developed an allergen-induced EoE mouse model that delineated a TSLP-basophil axis in which eosinophilic inflammation was dependent on both TSLP and basophils [23]. The investigators also provided translational data correlating TSLP genetic variants to increased basophil numbers in EoE subjects [23]. In another study, the population of basophils isolated from blood of EoE patients expressed distinct Th2-related functional profile [65]. Additional TSLP studies identified a SNP for the TSLP receptor located on Xp22.3 and Yp11.3 and may account for the male predilection in EoE [64].

So far, anti-TSLP therapy and anti-basophil therapy have been examined only in murine models [23]. Treatment of allergen-induced EoE mice with either an anti-TSLP monoclonal antibody or a basophil-depleting CD200R3-specific monoclonal antibody reduced esophageal eosinophilia. The incidence of food impaction in the mice decreased when blocking either TSLP or basophils.

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Invariant Natural Killer T Cells

The role of invariant natural killer T (iNKT) cells has been of particular interest. iNKT cells are a subset of T cells responsive to sphingolipid antigens when presented by CD1d surface molecule. A dietary sphingolipid, such as cow's milk-derived sphingomyelin, when loaded onto a CD1d molecule, induced iNKT cell proliferation and profound Th2 cytokine secretion [66]. Furthermore, mice deficient in CD1d were protected from the allergen-induced EoE [67]. Esophageal biopsies of EoE patients contained high levels of iNKT cells [68,69]. iNKT cells from active EoE patients produced more Th2 cytokines when activated by milk-derived sphingomyelin compared to iNKT cells isolated from control or inactive EoE subjects [68]. Collectively these data support a prominent role for iNKT cells in driving Th2-mediated inflammation.

iNKT cells may have an etiological role in EoE. Lexmond and colleagues provide compelling evidence proposing iNKT cells may have an early role in the process of allergic sensitization [70]. In early life, iNKT cells respond to microbial lipid antigens. When early life microbial signals are not present, expression of iNKT cell chemokine CXCL16 is increased causing persistent accumulation of iNKT cells in the colon and lungs. As a result, these mucosal tissues become susceptible to allergic sensitization as the iNKT cells anticipate lipid antigen presentation. The investigators detected high mRNA levels of CXCL16, iNKT cell markers, and CD1d in esophageal biopsies of early-onset (age <6years at diagnosis) EoE subjects who were highly sensitized to food antigens [70]. Indeed, early life exposure such as antibiotic use in infancy was associated with 6 times the odds of having EoE [71] and might have sufficiently attenuated early life microbial signals.

As for therapy, Lexmond and colleagues demonstrated that dietary therapy normalized markers of the CXCL16-iNKT-CD1d axis [70]. CD1d-deficient mice were protected from allergen-induce EoE [67]. Neutralizing anti-CD1d antibody or anti-human Vα24Jα18 (iNKT cell receptor chain) antibody prevented allergen-induced EoE in mice [69]. Thus, the iNKT cell pathway proves to be a promising novel pathway to target.

Mast Cells

Mast cells, similar to eosinophils, contain inflammatory mediators (TGFβ1, IL-4, IL-13, histamine, leukotrienes, tryptase, chymase, and carboxypeptidase A3) that can contribute to EoE pathogenesis and fibrogenesis. Mast cell activation can be initiated in many ways with the most common being antigen cross-linking of IgE and the high affinity receptor FcεRI. Both human and animal studies recognize congruencies between eosinophils and mast cells in EoE [72–77]. A recent study, involving a guinea pig model of EoE, demonstrated that the mast cell mediator prostaglandin D2 induces eosinophil trafficking via D-type prostanoid receptor 2 [77]. Immunostaining for tryptase and IgE illustrated that IgE-bearing mast cells are increased in the epithelium and lamina propria of EoE patients [78]. Mast cell containing tryptase were increased in the esophageal smooth muscle layer [73]. These mast cells were also expressing TGFβ1, which can induce smooth muscle cell contraction, suggesting mast cells might mediate esophageal contraction. In animal counterparts, mast cells are localized in the lamina propria and muscularis mucosa of allergen-induced EoE mice, further

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supporting the idea that mast cells promote smooth muscle hypertrophy and govern esophageal function [75].

Previous experiences involving mast cell stabilizer cromolyn sodium have been rather unsuccessful [1]. Results with leukotriene receptor antagonist montelukast have been equivocal [1], and there are upcoming trials on montelukast (NCT00511316, NCT01458418, clinicaltrials.gov). Both topical steroid therapy and dietary therapy have modulated mast cells and mast-cell associated genes [76]. As mentioned previously, the anti-IL-5 monoclonal antibody mepolizumab decreased mast cells and eosinophil-mast cell couplets in the esophagus of responders underscoring the intimate relationship between eosinophils and mast cells [45].

EoE and IgE-mediated Allergy

Although EoE is considered a food allergy, the relationship between EoE and IgE-mediated food allergy is confounding. To briefly review, IgE-mediated hypersensitivity requires Th2 cells to signal B cell class switching to generate antigen-specific IgE. Cross-linking of antigen, antigen-specific IgE, and Fc receptors on mast cells or basophils activate the release of mediators such as histamine, tryptase, and leukotrienes. IgE-mediated food allergy has been observed in the range of 15 – 43% in EoE patients [1]. Food-specific IgE has been detected by skin prick test with some success in children [79], but with less success in adults [80]. Furthermore, specific IgE to plant allergen, such as birch pollen or profilin, can cross-react with food components in EoE adults [81,82]. Certainly, IgE-bearing mast cells and B cells are detected at elevated levels in the esophageal biopsies of EoE patients [83]. However, EoE is not dependent on IgE-mediated inflammation as IgE-deficient and B cell-deficient mice continue to have esophageal inflammation [23,84]. In addition, anti-IgE monoclonal antibody omalizumab was ineffective in treating EoE subjects [85,86].

Interestingly, reports describing the EoE development after oral immunotherapy for IgE-mediated food allergy in up to 2.7% of patients have called for a deeper evaluation between the pathophysiology of IgE-mediated allergy and EoE [87,88]. Although the mechanism of oral immunotherapy is not completely understood, it is speculated that desensitization is achieved by evoking suppressor T cell activity, decrease specific IgE levels, while increasing specific IgG4 levels [89]. A recent study implicates IgG4 involvement in EoE pathogenesis [85]. Patients with EoE had increased total serum level of IgG4, and the specific-food IgG4 detected reacted with common EoE triggers (milk, wheat, eggs, and nuts). Levels of IgG4 were 45-fold higher in esophageal tissue of EoE patients, and dense IgG4 plasma cell infiltration was depicted in the lamina propria. Currently, the study implies that EoE may be an IgG4-associated disease, but further studies are needed to delineate relationship between IgG4 and EoE

Epithelial Barrier Function

The esophageal epithelium is composed of stratified squamous epithelial cells that form a barrier during health. How allergens reach to the esophagus is unknown; epithelial barrier dysfunction poses a reasonable susceptibility for allergens to enter the esophageal epithelium. In active EoE, histological findings of spongiosis or dilated intercellular spaces

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indicate impairment in epithelial barrier [1]. Baseline intraluminal impedance measurement, a marker of mucosal integrity, was lower in EoE patients [90]. Indeed, measurements of permeability and transepithelial electrical resistance on *ex vivo* tissue biopsies also confirmed barrier dysfunction [51]. Expression of cell junction and adhesion proteins such as E-cadherin, claudin-1, zonula occludens-3, and desmoglein-1 were diminished in biopsies [51,91,92]. Genes associated with epithelial differentiation and barrier function such as involucrin, small proline-rich protein, and filaggrin were downregulated [50]. However, filaggrin protein expression in epithelia cells increased after steroid therapy in children [93] and adults [92] with EoE. Lastly, treatment with high-dose esomeprazole improved mucosal integrity in PPI-REE patients [14]. Restoring epithelial barrier function seem to be an appropriate therapeutic parameter to achieve, however it is still not clear if there is an intrinsic barrier dysfunction in EoE patients that precedes inflammation.

Steroid Therapy

Both topical and systemic corticosteroids are considered effective therapies for inducing and maintaining remission in EoE, and several controlled trials have been conducted in both children and adults [94]. However, the mechanism of action of steroids is not entirely understood in EoE. As highlighted throughout this review, corticosteroids have pleiotropic effects on immune cells, esophageal cells, and mediators relevant to EoE pathogenesis. The IL-13-induced transcriptome in EoE was reversed with steroid treatment [34]. Steroid treatment downregulated IL-5 gene expression in the human esophagus [95] and attenuated IL-5-induced esophageal inflammation in mice [40]. After steroid therapy, eosinophils from EoE patients had decreased surface marker CD18 which might impair cell adhesion [56]. Expression of mast cell-associated genes were significantly decreased after steroid treatment in EoE patients [76]. Potential indicators that might determine steroid responsiveness include FK506 binding protein 51 gene expression, TGFβ1 genetic polymorphisms, esophageal tryptase, and esophageal eotaxin-3 [96–98].

In the clinical setting, topical steroids are preferred given a favorable safety profile, while systemic steroids are generally reserved for severe cases. The most common ways of administering corticosteroids topically to the esophagus are swallowed aerosolized fluticasone and oral viscous budesonide. For fluticasone, patients are instructed to hold their breath, puff the inhaler, and then swallow. For oral viscous budesonide, patients are directed to mix the contents of the budesonide respule (0.5mg/2ml) with sucralose to create a slurry. In addition, there have been both formal and anecdotal reports of other various viscous agents such as honey, apple sauce, amino acid-based semisolid, and food thickeners [94]. In general, after topical steroid application, patients are not to eat or drink for 30 minutes and then asked to rinse the medication from the mouth to prevent oral candidiasis. With the exception of esophageal candidiasis and herpes esophagitis, topical steroids are generally well tolerated and less prohibitive on life style. Short-term data have not observed adrenal suppression. However, due to necessary maintenance therapy, long-term safety data on bone health, growth, and adrenal suppression are needed. The therapeutic effects of topical steroids are largely limited by uneven delivery and penetration to the affected areas of the esophagus. Current and future clinical studies aim to optimize dose, frequency, formulation, and delivery of corticosteroids in both the induction and maintenance of remission in EoE.

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Remodeling, Fibrogenesis, and Epithelial Mesenchymal Transition

The chronic inflammatory nature of EoE will progress to a fibrostenotic disease the longer the disease is left untreated [99,100]. Outcomes such as food impactions, fibrotic strictures, esophageal narrowing, mucosal tears, and transmural perforations are all due to esophageal remodeling and fibrosis [1,101,102]. Fibrogenesis is part of normal repair response to epithelial injury, where activated fibroblasts synthesize and organize extracellular matrix (ECM) proteins such as collagen, fibronectin, and tenascin-C [103]. Once inflammation has subsided and the tissue is repaired, fibroblasts will reorganize the fibrous tissue to restore normal tissue. However with unrelenting inflammation, excessive deposition of ECM proteins creates fibrosis. Challenges to understanding EoE remodeling are largely due to limitation in diagnostic tools to assess the deeper layers of the human esophagus where subepithelial fibrosis [74], smooth muscle hypertrophy, and angiogenesis [104] occur. Several mediators and cells involved in Th2 inflammation will facilitate fibrogenesis. IL-5 promoted collagen deposition [39] and IL-13 overexpression generated features of esophageal remodeling, strictures, and dysmotility in mice [38,53]. In humans, eosinophils are located throughout the entire thickness of the esophagus including the muscle layers, and exposure to their products caused esophageal fibroblasts and smooth muscle cells to secrete ECM proteins, collagen I and fibronectin [105]. Mast cells residing in the lamina propria and smooth muscle layer likely contribute to smooth muscle dysfunction. [73,76]. Both eosinophils and mast cells are potential cellular sources for TGFβ1 a well-known fibrogenic agent.

Epithelial cells have also acquired means to drive fibrogenesis. Epithelial-mesenchymal transition (EMT) is the process by which epithelial cells lose their epithelial characteristics and gain mesenchymal features of a fibroblast. Staining for vimentin (mesenchymal marker) and cytokeratin (epithelial marker) revealed evidence of EMT in the EoE epithelium [106]. TGFβ1 induced EMT by upregulating mesenchymal markers such as N-cadherin, vimentin, and fibronectin [106]. TNFα and IL-1β can also induce EMT changes including acquisition of αSMA and loss of E-cadherin [107]. Epithelial cells that have undergone EMT can signal to nearby fibroblasts to secrete fibrogenic cytokines, which likely precipitate the subepithelial fibrosis seen in EoE [108]. Features of EMT resolved after patients were treated with elemental diet, SFED, or topical steroids [106].

It is clear that TGFβ1 plays a central role in fibrogenesis and EMT, thus interrupting TGFβ1 signaling is an attractive therapeutic strategy. Silencing TGFβ1 signaling targets such as phospholamban [109] and Smad3 [21] have diminished the contraction *in vitro* and abrogated fibrosis and angiogenesis in mice. There is an ongoing phase II trial looking at the effectiveness of losartan, an angiotensin II receptor blocker that might reduce TGFβ1, in patients with EoE (NCT01808196 www.clinicaltrials.gov).

Dilation for Fibrostenosis

As previously discussed, PPIs, steroids, and dietary therapies can attenuate esophageal inflammation, thereby preventing further fibrogenesis and remodeling while esophageal tissue restores to normal. The ability for any of these therapies to reverse long-term

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remodeling is arguable and has not been unequivocally demonstrated. Although it is reasonable to first try medical therapy, an esophageal dilation procedure remains the only effective means to mechanically obliterate high-grade fibrostenotic lesions and provide symptomatic relief. Initially, higher complication rates with esophageal dilation procedures in EoE patients were reported, but with increased recognition and experience a recent meta-analysis reports complication rate of <1% [110]. Although dilation does not achieve histological improvement nor addresses the underlying inflammatory process [111], clinical improvement is achieved in 75% of cases [110]. Without concurrent medical therapy to address the inflammatory process, patients will need repeat dilations. Thus, dilation should probably be considered an adjuvant therapy to a medical therapy (Figure 1).

Conclusions

New developments in EoE pathogenesis are refining our current therapeutic and management strategies. EoE is now recognized as a chronic allergic inflammatory disease with progression to fibrostenotic disease. The disease warrants early proper diagnosis and long-term maintenance therapy. The diagnosis of EoE should be based on the concept of an allergy-mediated disease with esophageal dysfunction and esophageal eosinophilia (≥ 15 eos/hpf). PPI-REE is likely a continuum of EoE or similar Th2-mediated allergic process. Thus, PPIs should be considered a therapeutic option for EoE. If patients are PPI-nonresponsive, then dietary therapy or steroid therapy could be offered. Dilation should be reserved for severe fibrostenotic lesions. New investigational drugs are on the horizon. Development of genetic markers and biomarkers will help predict responsiveness to treatment and individualize therapy.

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* Of importance

** Of most importance

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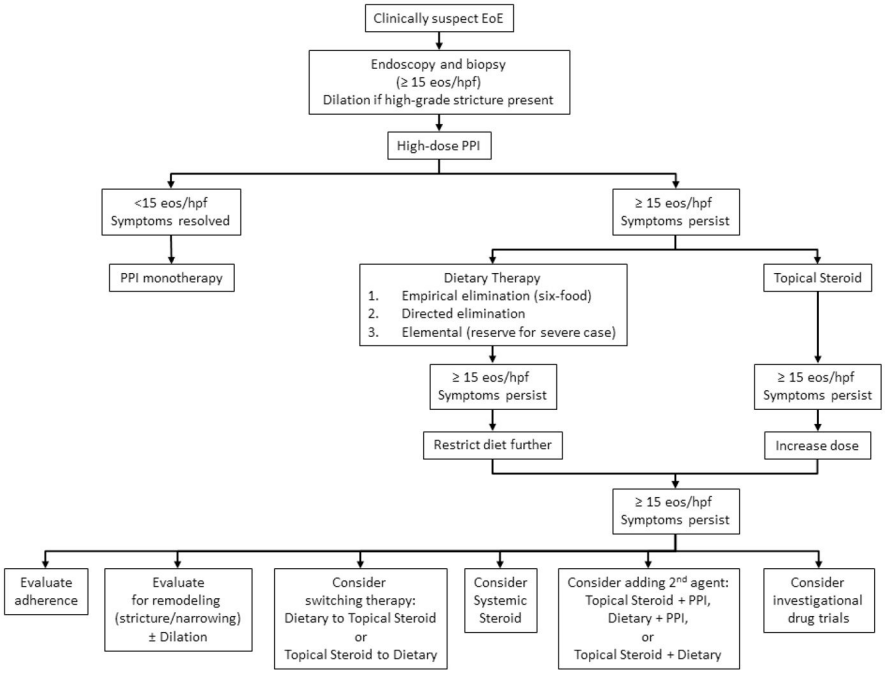

Figure 1.
Algorithm for current therapeutic options in EoE.