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Issue: *The Esophagiome***Eosinophilic esophagitis: current perspectives from diagnosis to management**

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Eosinophilic esophagitis (EoE) is a chronic antigen-mediated immune disease of the esophagus characterized by symptoms related to esophageal dysfunction, as well as significant esophageal eosinophilia. Although dense eosinophilia is the hallmark of EoE, other characteristic histologic features have been described that may help distinguish EoE from other competing diagnoses, although none are specific to EoE. One or more foods and, at times, environmental allergens trigger EoE. Left untreated, esophageal inflammation in EoE may lead to esophageal remodeling and stricture formation. Symptoms in EoE vary with age, as they relate to the progression of the disease from an inflammatory to a fibrostenotic phenotype over time. There are currently no U.S. Food and Drug Administration–approved therapies for EoE. Current options include various dietary-restriction therapies, topical corticosteroids, and esophageal dilations. Several emerging therapies aiming at restoring the esophageal barrier function or targeting various inflammatory cells or their mediators are under investigation.

Keywords: eosinophilic esophagitis; esophagitis; eosinophilia; dysphagia; allergy; corticosteroids; dietary treatment; dilation

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated condition characterized by symptoms of esophageal dysfunction and the presence of esophageal inflammation.¹ It occurs in children and adults with different clinical presentations. Young children often have inflammatory features on endoscopy, whereas adults are more likely to have a combination of inflammation and fibrostenosis. EoE has a set of characteristic endoscopic and histologic features, which may vary depending on the stage and duration of disease.

Although not entirely diagnostic, a scoring system now exists for the endoscopic and histologic features of EoE. During the past 2 decades, research has led to a better understanding of the pathogenesis of EoE. We now know that EoE is primarily a T helper 2 (T_H2) inflammatory disease associated with allergic triggers, such as food and other environmental allergens. With a better understanding of the disease process, more questions arise. The role of proton pump inhibitors (PPIs) in the diagnosis and treatment of EoE has added another complex layer but also sheds exciting insight into its

pathogenesis.² Management options continue to be explored with high-quality studies, which currently comprise specialized diets, topical steroids, and dilation when fibrostenosis develops. Researchers are actively investigating novel treatments targeting inflammatory mediators and immune cells.

EoE features across ages

EoE can occur at any age, with its prevalence reported to be similar in children and adults (~ 0.5 – 1 cases/1000 persons).³ Both children and adults with EoE tend to have atopic histories, including asthma, allergic rhinitis, and/or atopic dermatitis.⁴ While the disease has similar histopathological features in all age groups, endoscopic features can vary, as the duration of disease tends to result in progressive esophageal remodeling,⁵ presumably secondary to ongoing esophageal inflammation,^{6,7} and is at least partially reversible with therapy.^{8–10} On endoscopy, children commonly present with inflammatory features, including esophageal white plaques and furrows, in contrast to adults and those with longer disease duration, who predominantly have fibrostenotic features consisting of fixed esophageal rings and strictures.^{5,10,11} This likely dictates symptom presentation, as more children present with nonspecific symptoms, such as abdominal pain, emesis, and gastroesophageal symptoms, while adults present with clear-cut symptoms of solid food dysphagia and esophageal food impactions.¹⁰ Symptoms are not mutually exclusive between children and adults, as it is likely that many children suffer from dysphagia as well but are less apt to describe their symptoms accurately. In all age groups, EoE patients often use behavioral adaptive-feeding practices to prevent dysphagia and food impactions, which need to be investigated during history taking in order to not miss the diagnosis.¹² While response to therapies, such as dietary restrictions and topical corticosteroids, is similar in children and adults, as described in more detail below, reversal of remodeling is more difficult to achieve in adults.^{8,9,13}

Histological features

EoE demonstrates a set of characteristic, although not entirely diagnostic, histological features and must be distinguished from reflux esophagitis (RE). EoE and RE demonstrate basal zone hyperplasia and papillary elongation (features of epithe-

lial hyperplasia), as well as spongiosis (dilated intercellular spaces). According to consensus criteria, a peak count of ≥ 15 eosinophils in at least one high-power microscopic field (hpf) is typically required for the diagnosis of EoE.¹ Although tissue eosinophilia is the histologic hallmark of EoE, the eosinophil is also often the principal inflammatory cell noted in biopsies of RE, and, as such, a peak count of ≥ 15 eosinophils is not pathognomonic for EoE.^{14,15} Compared with biopsies from patients with RE, biopsies from patients with EoE are more likely to demonstrate eosinophil surface layering and microabscess formation, the latter arbitrarily defined as clusters of four or more eosinophils.¹⁶ These features, which are often seen in association with desquamated and parakeratotic debris, likely account for the endoscopic white plaques typical of active EoE. Regarding the topography of inflammation, while eosinophilia in RE tends to be predominant in the distal esophagus, the number of eosinophils may be similar throughout the esophagus in EoE.^{17–19}

EoE is an active chronic inflammatory condition. While the aforementioned histologic features are evidence of active inflammatory disease, chronic fibrostenotic disease manifests as lamina propria fibrosis, where the lamina propria takes on a distinctive hyalinized appearance. Lamina propria fibrosis is more frequently reported in EoE than in RE; and while in RE the lamina propria tends to contain a lymphocyte-predominant infiltrate, it may contain eosinophils in EoE.^{6,20–22}

Biopsy protocol

The 2013 American College of Gastroenterology EoE Clinical Guidelines recommend that two to four biopsies be obtained from both the proximal and distal esophagus from patients in whom EoE is a diagnostic consideration.¹ Furthermore, biopsies from the antrum and duodenum are recommended in all children and in adults with endoscopic abnormalities to rule out other causes of esophageal eosinophilia, such as eosinophilic gastroenteritis, Crohn's disease, and celiac disease.

Endoscopic-histological correlation

There are eight main endoscopic features described in EoE. These include fixed rings (corrugated esophagus, trachealization), transient rings (feline esophagus), linear furrows, white plaques or exudates,

edema (mucosal pallor), isolated stricture, diffuse narrowing (narrow-caliber esophagus), and lacerations induced by passage of the endoscope due to mucosal fragility (shearing or crepe paper esophagus).

Kim *et al.*²³ conducted a meta-analysis of the endoscopic features of EoE, which included 4678 patients and 2742 controls from 100 studies. The overall prevalence of these abnormalities in EoE patients ranged from 9% (diffuse narrowing) to 48% (linear furrows). In a subset of the analysis comparing the frequency of endoscopic abnormalities in children and adults, white plaques and edema were both more frequent in children (white plaques: 36% vs. 19%; edema: 58% vs. 18%) and rings and stricture were more common in adults (rings: 57% vs. 11%; stricture: 25% vs. 8%). Adults diagnosed with EoE may have had subclinical disease as younger individuals, and the median delay in the diagnosis of EoE was described as 6 years in one study.⁵ Thus, endoscopic features more common in children may be indicators of active inflammatory disease, while endoscopic features more common in adults may be indicators of chronic fibrostenotic disease.

Salek *et al.*²⁴ recently tested this hypothesis by conducting a detailed endoscopic–histological mapping in 10 EoE patients. The group performed 20–32 biopsies per patient according to a mapping protocol and recorded the endoscopic findings corresponding to each biopsy specimen (294 total biopsies). The patchy nature of the disease was confirmed, with only 111/294 (37.8%) biopsies containing a peak eosinophil count of > 15 per hpf. Somewhat surprisingly, peak counts were greater in the distal (defined as within 10 cm of the gastroesophageal junction) than in proximal biopsies (mean peak counts of 17 and 7 eosinophils per hpf, respectively). Mean peak eosinophil counts from biopsies of white plaques (20 eosinophils per hpf) and furrows (17 eosinophils per hpf) confirm these endoscopic findings as markers of active disease. In active disease, fixed rings more often occurred, along with other endoscopic abnormalities. Only one of nine (11%) biopsies from isolated fixed rings demonstrated a peak count of > 15 eosinophils per hpf. The results of these studies have implications for obtaining biopsies in patients with clinically suspected EoE, as endoscopists should target linear furrows and white plaques, which have the greatest likelihood of demonstrating EoE-range eosinophilia.

Histological reporting of biopsies

Histological reports should include an eosinophil peak count. They should also include descriptions of the degree of epithelial hyperplasia and spongiosis (e.g., mild, moderate, marked) and should note, if present, eosinophil surface layering and clustering and lamina propria fibrosis, if the lamina propria is present in the biopsies obtained. These reports not only support an initial diagnosis of EoE (or esophagitis with eosinophilia, depending on the relationship of the biopsy to PPI therapy), they also facilitate assessment of response to therapy on subsequent biopsies.

PPI response in esophageal eosinophilia

Several prospective studies have demonstrated that up to 50% of patients who met clinical, endoscopic, and histological criteria for EoE demonstrated response to PPI treatment.^{25–29} These patients were described to have PPI-responsive esophageal eosinophilia (PPI-REE) initially, to distinguish it from EoE, which is defined by its immune-mediated nature and its lack of response to PPIs.⁴ A recent meta-analysis of 33 studies demonstrated that PPIs achieve clinical and histologic response in 61% and 51% of patients with an EoE phenotype, respectively.³⁰ Efficacy tended to be higher when pathological pH monitoring was present; however, it was not significantly different compared with patients with normal esophageal acid exposure (65% vs. 49%).³⁰

There are no clinical, endoscopic, or histological methods that can reliably distinguish PPI-REE from steroid-responsive EoE before initiation of therapy. Two groups of investigators attempted to identify any such factors by comparing clinical symptoms, endoscopic features, and histological findings.^{25,31} In both studies, EoE and PPI-REE patients were virtually identical. In one of these studies, PPI-REE patients were more likely to be older males and less likely to have typical findings of EoE; however, none of these factors was independently predictive of PPI-REE status on multivariate analysis.²⁵

Several studies have examined the pathogenesis of PPI-REE and the mechanisms behind PPI response. In a study comparing the gene expression in EoE and PPI-REE, PPIs significantly downregulated eotaxin-3, a chemoattractant that plays a major role in the pathogenesis of EoE. Similar downregulation

was exhibited by EoE patients treated with topical steroids.³² When comparing eotaxin-3 staining of esophageal biopsies among EoE, PPI-REE, and gastroesophageal reflux disease (GERD) patients, staining intensity was significantly higher in EoE compared with GERD but not different between EoE and PPI-REE.³³ From a molecular standpoint, the esophageal transcriptome of PPI-REE was within the same molecular spectrum as that of EoE. Specifically, 46 genes related to eosinophil chemotaxis, mast cell, epithelial barrier, T_H2 inflammation, and tissue fibrosis markers were similarly dysregulated.³⁴ Interestingly, PPIs reverted the genetic signature in PPI-REE, similar to what was seen in EoE patients after diet or steroid treatment.³⁵ These data suggest that EoE and PPI-REE share many pathophysiological features and appear to be part of the same disease spectrum. The question remains why only half of EoE patients respond to PPI.

Although the mechanism of action of PPIs in EoE patients is better understood, it is still not entirely clear. One hypothesis is that PPIs improve esophageal eosinophilia by reducing acid damage to the mucosa. A prospective study compared epithelial barrier integrity in PPI-REE and EoE, as measured by dilated intercellular spaces, electrical tissue impedance, and transepithelial electrical resistance and molecular flux.³⁶ PPIs restored barrier function in the PPI-REE group but not in patients unresponsive to acid suppressants. These data suggest that gastroesophageal reflux, even if not clinically apparent, could cause esophageal epithelial damage, allowing penetration of allergic antigens that trigger an eosinophilic response in the mucosa. PPIs are effective at restoring the epithelial barrier, similarly to what occurs in GERD. Another potential mechanism of action of PPIs is their direct anti-inflammatory effect, demonstrated both in EoE and in GERD esophageal squamous cell cultures in an experimental system devoid of acid.³⁷ In these studies, omeprazole reduced cellular eotaxin-3 secretion induced by interleukin (IL)-13 and IL-4.³⁸ However, the short half-life of PPIs makes it unclear if a sustained anti-inflammatory effect is maintained *in vivo*. A third possibility for responsiveness to PPIs in a subset of patients with esophageal eosinophilia is related to PPI metabolism. A recent study demonstrated that approximately one in four PPI-REE patients relapsed after decreasing their PPI dose and subsequently responded again after increasing the

dose. These patients had a rapid PPI-metabolism phenotype on CYP450 enzyme testing.³⁹ Despite persistent histologic inflammation, PPIs remain clinically useful in many EoE patients.^{28,40} Some EoE patients exhibit acid hypersensitivity, which has been demonstrated during an esophageal perfusion study independent of pathological acid reflux.⁴¹ An international task force recently proposed that PPIs not be used exclusively as a diagnostic tool, but rather as first-line treatment, before diet and steroids.²

Esophageal remodeling

EoE is a T_H2-mediated disease similar to asthma. Eosinophils are major effector cells in this inappropriate immune response, with IL-5 directly inducing tissue eosinophilia. Activated eosinophils release their cytotoxic contents, evolved to kill extracellular parasites, which leads to ongoing epithelial injury. Straumann *et al.*⁴² first described the natural history of EoE in 2003. In a cohort of 30 adult EoE patients followed for 7 years without antieosinophil treatment, dysphagia and esophageal eosinophilia persisted in all patients. As such, the authors concluded that EoE is a chronic disease. Several studies have since shown that long-standing untreated eosinophil-predominant esophageal inflammation leads to subepithelial fibrosis.^{6,13} This process is mediated by eosinophil secretion of profibrogenic cytokines, including transforming growth factor beta (TGF- β), fibroblast growth factor-9, and chemokine C-C motif ligand 18 (CCL18).^{43–48} Several of these cytokines are promising targets for directed biologic therapy.

The deposition of subepithelial fibrous tissue ultimately alters the anatomy of the esophageal wall and its mechanical properties, a process described as esophageal remodeling.⁴³ Remodeling processes can lead to formation of esophageal rings and strictures, seen on endoscopy. In a retrospective study of 200 untreated EoE patients from Switzerland, esophageal strictures, defined as esophageal diameter of ≤ 10 mm, were observed in one-third of patients after 10 years and in two-thirds of patients after 20 years of symptom onset.⁵ This study also demonstrated that eosinophil-driven inflammatory activity was not reduced over time; instead, fibrostenosis developed in addition to inflammatory alterations.⁵ These Swiss results were corroborated by a study originating in the United States.⁴⁹

Stricture formation is associated with dysphagia episodes and food bolus impactions that may necessitate endoscopic removal and carry the risk for subsequent esophageal perforations.⁵⁰ As such, therapeutic measures should be instituted to reduce esophageal remodeling processes.

Treatment end points

Disease activity of EoE can be measured in the domains of patient-reported outcomes (PROs), that is, symptoms and quality of life, and clinician-reported outcomes (ClinROs), which concern endoscopic, histologic, and biochemical activity.⁵¹ Until recently, no validated instruments were available to measure EoE activity in the different domains. Over the last couple of years, stakeholders (physicians, researchers, patients, regulatory authorities, and the pharmaceutical industry) have joined forces to develop and validate EoE-specific instruments to assess disease activity in the different domains.⁵² The development and validation of specific instruments to assess EoE activity are of major importance to standardize the way EoE activity is assessed, to define clinically meaningful end points for use in clinical trials, and to be able to compare the efficacies of different treatment modalities.⁵² In turn, this process will also help in developing therapeutic algorithms to provide EoE patients with much-needed appropriate therapy. At present, there are two validated instruments available to measure EoE symptom severity in adult patients: the Eosinophilic Esophagitis Activity Index (EEsAI) PRO instrument and the Dysphagia Symptom Questionnaire.^{12,53} Both instruments were developed following the PRO guidelines from regulatory authorities. Endoscopic severity of EoE-associated findings should be reported according to the EREFS grading system (exudates, rings, edema, furrows, strictures).⁵⁴

Assessment of histologic activity most often relies on reporting of the peak eosinophil count per hpf. An EoE-specific histology score has recently been published.⁵⁵ It acknowledges the patchy histologic nature of the disease and the limitations of relying solely on eosinophil peak count. In addition to eosinophil peak count, it includes many of the histologic features discussed above, including basal zone hyperplasia, eosinophil microabscess formation, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration (e.g., parakeratosis), dyskeratosis, and lamina propria

fibrosis. Each of these features is separately assigned a grade (severity) and stage (extent) along a 4-point scale. A composite histology score was more strongly associated with treatment status than eosinophil peak count alone.

There is an ongoing debate as to which treatment end points (symptoms, quality of life, endoscopic or histologic alterations) should be chosen for use in randomized clinical trials, for observational studies, and for daily clinical practice. In EoE, both PROs and ClinROs measure overall disease activity.⁵⁶ Untreated EoE results in esophageal remodeling processes, ultimately leading to stricture formation, and represents the main risk factor for food bolus impactions.^{5,43} EoE-related symptoms positively correlate with histologic and endoscopic activity.⁵⁷ However, the contribution of symptom severity, based on an EEsAI score, is only modest in predicting either endoscopic or histologic remission, defined as achievement of <20 eosinophils/hpf and improvement in EREFS score.⁵⁷ As such, physicians cannot rely purely on the absence of symptoms to predict either endoscopic or histologic lack of disease activity. Based on the above-mentioned findings, treatment end points at this time should include clinical, histologic, and endoscopic outcomes to assess overall EoE activity.

Current therapies for EoE

There are no U.S. Food and Drug Administration (FDA)-approved therapies yet for EoE. Current options for inducing clinical and histologic remission of EoE include specialized diets, topical steroids, and esophageal dilations (Fig. 1). In addition, researchers are investigating several emerging therapies, including biological agents.

Dietary therapy

Three main types of dietary-restriction therapies have been published in children and adults with EoE: elemental diet, test-directed elimination diet, and empiric elimination diets. An elemental dietary therapy consists of exclusive feeding with a hypoallergenic amino acid–based formula, at times modified with the addition of one to two solid foods to the diet for better acceptance. This diet is highly effective, with a histological remission rate of more than 90% described in both children and adults.^{58–60} Children with EoE also experience clinical improvement; however, symptom improvement in adults is

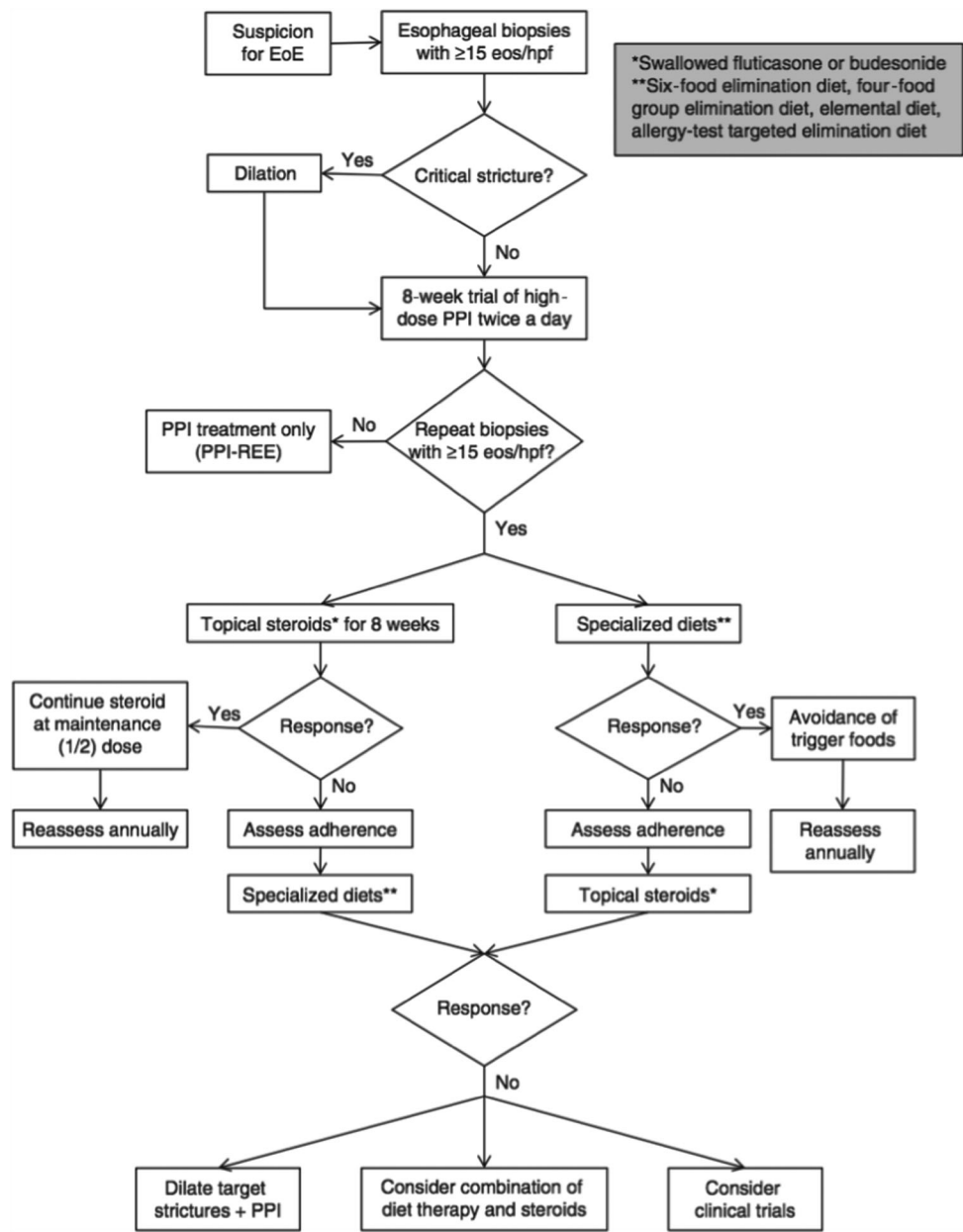


Figure 1. Current options for inducing clinical and histologic remission of EoE include specialized diets, topical steroids, and esophageal dilations.

less clear owing to a paucity of data.^{59,60} This diet is particularly useful in children with multiple preexisting IgE-mediated food allergies, failure to thrive, and feeding difficulties, as it provides them with complete nutrition while the various symptoms and feeding difficulties are being managed. Its disadvantages include the cost of the formula, the occasional

need for gastric tube placement to accommodate the large volumes of formula needed for adequate nutrition, and the social isolation that this very restrictive diet can create. In fact, few adults with EoE accept this dietary treatment modality.⁶⁰

The second dietary elimination therapy, referred to as test-directed elimination diet, consists of

avoidance of foods that test positive by skin prick and/or patch tests. It is the least effective, with an overall reported histological remission rate of 48% in children and 32% in adults.⁵⁸ Spergel *et al.*⁶¹ reported histological response as high as 77% in children with milk avoidance when combined with foods that tested positive by skin prick and patch tests. Common foods that tested positive in that group's experience were milk, wheat, egg, soy, nuts, seafood, corn, and chicken, among others.⁶² Advantages of the test-directed elimination diet include its reasonable efficacy in children and its less restrictive nature than an elemental diet, rendering it more socially acceptable. However, it involves extensive tests, some of which have not yet been validated. Better testing is needed to identify triggers for EoE in order to tailor dietary elimination accordingly.

The third dietary elimination therapy is purely empiric, consisting of avoidance of foods known to be common allergens. Varieties on this diet, including a six-food elimination diet (avoidance of milk, wheat, egg, soy, nuts, and seafood)^{63,64} and a four-food elimination diet (avoidance of milk, wheat, egg, and legumes),⁶⁵ have been reported with an overall histological remission rate of 73% in children and 71% in adults.⁵⁸ While an empiric elimination diet is reasonably effective in both children and adults, is more socially acceptable than an elemental diet and eliminates the need for testing, it can be overwhelming for some patients given the number of foods simultaneously being avoided. Given that milk was found to be by far the most common trigger of EoE, a much less extensive dietary therapy, consisting of milk avoidance alone, was conducted in children with EoE, and resulted in histological remission in 65% of the patients.^{66,67}

While all the above-mentioned diets have been described in short-term efficacy trials, with up to 2-month follow-up, little is known regarding their utility as long-term maintenance therapies. A common goal with long-term care of patients with EoE on dietary elimination therapy is to narrow the list of foods being removed over time. This will ensure increasing dietary choices over time, hence better chronic adherence to the diet, and the potential for avoidance of the risk of a *de novo* immediate IgE-mediated clinical reactivity to a food following its prolonged avoidance, although the latter is very rarely reported.⁶⁸ Diet liberalization is commonly done by reintroduction of one food at a time,

followed by clinical and histological evaluation.^{65,69} The challenge with reintroduction of foods is its trial-and-error nature, with the process often resulting in multiple endoscopies with biopsies before a final list of food triggers is identified for long-term avoidance.

With any chosen dietary therapy, close evaluation and follow-up by a dietitian with some experience in food allergy is highly recommended, to ensure that the dietary restriction is safe and effective while minimizing interference with the quality of life of patients with EoE and their families.

Corticosteroid therapy

Topical steroids are the other option for first-line treatment. They have been shown to induce histological remission in EoE in a dose-dependent manner.^{70,71} Two formulations currently exist, fluticasone and budesonide.¹ Both medications are commonly used to treat pulmonary disorders and were not originally intended to treat esophageal conditions. There are three randomized, placebo-controlled trials demonstrating the efficacy of aerosolized, swallowed fluticasone.^{72–74} In a study of 50 EoE children, fluticasone 440 µg administered twice daily induced remission in 50% of patients, compared with 10% placebo response.⁷⁴ In 42 adults with EoE, fluticasone administered at 880 µg twice daily induced response in 62% of patients, whereas response to placebo was 0%.⁷² Most recently, in a study of a mixed population of 42 children and adults, fluticasone at 880 µg twice daily was efficacious in 65% of the population versus 0% efficacy in the placebo arm.⁷³ One noteworthy finding of this study was that extension of high-dose steroid treatment in fluticasone nonresponders for an additional 3 months did not yield improved efficacy. Furthermore, nonresponsive patients had a different gene expression profile than responders. In studies utilizing higher dosages of fluticasone, the development of esophageal candidiasis increased.^{72,73}

The second topical steroid formulation used in the management of EoE is budesonide, which can be administered in a viscous suspension or via a nebulizer. Several controlled trials have demonstrated an efficacy in inducing histologic remission ranging from 27% to 87%, depending on the dose used, vehicle to administer the drug, patient population, and treatment end point.^{9,13,71,75,76} In 20 children with EoE treated with a viscous slurry of budesonide

created by using a sugar substitute, 80% achieved complete histologic response.⁷⁶ Similar response was noted with the use of a budesonide oral suspension (70%) and an effervescent tablet (83%).^{70,71} In one controlled trial using a nebulized form of oral budesonide in which patients continuously swallowed the accumulated fluid twice daily for 15 days, 86% of adults with EoE achieved histologic response.¹³ Collectively, the studies using budesonide appear to have a better response compared with fluticasone, although the two medications have never been compared head to head. A recent retrospective study did not find a significant difference between EoE patients treated with fluticasone versus budesonide.⁷⁷ An open-label randomized trial of 25 EoE patients compared the efficacy of nebulized budesonide to viscous budesonide and used nuclear scintigraphy to assess mucosal contact time between the two preparations.⁷⁸ Patients randomized to viscous budesonide had a higher histologic response compared with nebulized budesonide, although it was not statistically significant (64% vs. 27%, $P = 0.09$). A higher medication contact time in the esophagus was a likely explanation for the better response to viscous budesonide.

Although data exist for induction with topical steroids, data for maintenance therapy are scarce. In an extension of the trial by Straumann *et al.*⁹ using a reduced dose of budesonide at 0.25 mg twice daily for 1 year, the median time to clinical relapse appeared longer for budesonide compared with placebo, although this was not statistically significant. Since EoE is a chronic inflammatory condition and there are indirect data suggesting that fibrostenosis develops in virtually all EoE patients over time, maintenance therapy is a recommended strategy.⁵ One commonly used maintenance regimen is half of the induction dose, which is a total of 880 µg of fluticasone or 1 mg of budesonide daily. Further studies are needed to determine the appropriate dose needed to keep EoE patients in remission and delay or prevent development of fibrostenotic features.¹⁰ Topical steroids are safe medications, although esophageal candidiasis may occur following treatment.¹

Esophageal dilation

The third therapy option used in the management of EoE is dilation. Dilation does not affect the underlying pathogenesis of the disease, but is effica-

cious in improving clinical symptoms, particularly in patients with a narrow stricture or a diffusely narrow esophagus.⁷⁹ There are three techniques for dilation: bougie, wire guided, and controlled radial expansion balloons. All methods have been used successfully, and the choice of dilator depends on institutional experience and the endoscopist's preference. The goal of dilation is to achieve an esophageal diameter of at least 15 mm and preferably 18 mm, which may require several sessions, depending on the initial caliber of the esophagus. However, this is mostly anecdotal, and there are no controlled trials to date describing the critical threshold of clinical response. Moreover, not all dysphagia in EoE is due to stricture; poor esophageal compliance may be a contributing factor.⁸⁰

Several studies have confirmed the clinical efficacy of esophageal dilation, which appears to last approximately 1–2 years.^{49,81} In one study of 13 EoE patients followed for a median of 14 years and only maintained with a PPI, clinical response was achieved with dilation performed every other year once a diameter of 15 mm was achieved.⁴⁹ Although there were initial concerns of increased risks of dilation in EoE patients, one meta-analysis of nine studies including 860 patients who had undergone 992 dilations demonstrated a risk of hemorrhage of 0.1% and a risk of perforation of 0.3%.⁷⁹ EoE patients undergoing dilation should be counseled about developing postprocedural chest pain, which is most often self-limited but at times requires pain control.

Emerging therapies for EoE

As the pathophysiology of EoE involves disturbances in the epithelial barrier, immune effector cells, and inflammatory mediators and cytokines, emerging therapies are directed to these areas.

Targeting the esophageal epithelial barrier

Disturbances in the epithelial barrier might allow allergens to permeate the epithelium, initiating allergic inflammation. Impairment of the epithelial barrier has been implicated in EoE on the basis of decreased intraluminal impedance measurements, decreased transepithelial electrical resistance, dilated intercellular spaces, and downregulation of adhesion proteins, such as desmoglein-1, in EoE patients.^{4,82–85} Investigators are examining the effect of sucralfate slurry, a medication

originally developed for mucosal ulceration, on dilated intercellular spaces, tight junctions, mucosal impedance, and mucosal activity in patients with EoE (NCT02353078 www.clinicaltrials.gov).

Targeting inflammatory mediators and immune effector cells

IL-5 promotes eosinophil proliferation in the bone marrow and primes eosinophils for biological activation. EoE murine studies established that eosinophil trafficking is IL-5 dependent and drives esophageal remodeling.^{86–89} Mepolizumab, an anti-IL-5 monoclonal antibody, in a randomized controlled trial with adult EoE patients, decreased eosinophil numbers in esophageal tissue, although there was minimal symptom improvement.⁹⁰ Mepolizumab, in pediatric EoE subjects, reduced mast cells, IL-9 cells, and mast cell–eosinophil couplets, but again did not improve symptoms.⁹¹ Similarly, reslizumab, another anti-IL-5 monoclonal antibody, decreased esophageal eosinophilia but did not improve symptoms.⁹² The data thus far suggest that anti-IL-5 is more impressive in reducing eosinophilia but not as much for clinical symptoms.

IL-13 likely activates local tissue inflammatory response in EoE, since gene transcriptome analysis identified many IL-13–inducible genes responsible for pathogenesis, and elevated IL-13 mRNA levels are detected in esophageal tissue.^{44,93,94} Murine studies demonstrated that IL-13 was responsible for eosinophil recruitment and esophageal remodeling.^{95,96} A randomized controlled trial with QAX576, a monoclonal antibody against IL-13, revealed a 60% reduction in esophageal intraepithelial eosinophils and some symptom improvement.⁹⁷ The treatment modified genetic markers of EoE inflammation, including eotaxin-3, periostin, mast cell markers, and improvement in barrier function. Overall, there appears to be improvement in both clinical and histologic outcomes, at least in one small study. A large double-blind, multicenter, randomized controlled trial is currently evaluating the efficacy and safety of the anti-IL-13 monoclonal antibody RPC4046 in EoE adults (NCT02098473 www.clinicaltrials.gov).

IL-4 and IL-13 often share similar downstream effects, and while the role of IL-4 has not been clearly delineated in EoE, it is detected at higher levels in the esophagus of EoE patients.^{37,46,98,99} Dupilumab, a human monoclonal antibody that tar-

gets the IL-4 receptor α subunit, a component of IL-4 receptor types I and II, as well as the IL-13 receptor system, was demonstrated to be therapeutically effective in patients with asthma and atopic dermatitis.^{100,101} A randomized controlled trial will assess the clinical efficacy of repeat subcutaneous doses of dupilumab to relieve symptoms in adult patients with active, moderate-to-severe EoE (NCT02379052 www.clinicaltrials.gov).

The prevalence of IgE-mediated food allergies in EoE is 15–43%.⁴ Skin-prick testing has detected food-specific IgE in children.^{61,102} IgE-bearing mast cells and B cells are present in EoE esophageal biopsies.⁹⁴ An open-label study using omalizumab, an anti-IgE monoclonal antibody, in primarily adolescent EoE subjects showed significant reduction in esophageal tissue IgE levels. Thirty-three percent of the subjects demonstrated complete clinical and histological remission. The responders had low peripheral blood eosinophil counts, suggesting that IgE might play a role in the pathophysiology in a subset of EoE patients.¹⁰³ However, in a prospective trial, omalizumab was ineffective in reducing symptoms and esophageal eosinophilia in patients with EoE.¹⁰⁴

Chemoattractant receptor–homologous molecule expressed on T_H2 cells (CRTH2) is expressed by T_H2 lymphocytes, eosinophils, and basophils.¹⁰⁵ CRTH2 antagonists interfere with the prostaglandin pathway, blocking the prostaglandin D₂ receptor, subsequently preventing the activation and recruitment of CRTH2-expressing inflammatory cells. A randomized controlled trial using OC000459, a selective CRTH2 antagonist that is orally bioavailable, demonstrated a modest improvement in eosinophilic inflammation and symptoms in severe, steroid-refractory EoE adults.¹⁰⁶

Mast cells release numerous inflammatory mediators contributing independently or in tandem with eosinophils to esophageal inflammation.^{6,107–111} IgE-bearing mast cells are increased in the esophageal mucosa and the smooth muscle layer of EoE patients.^{108,112} While earlier small case series demonstrated unsuccessful results with the mast cell stabilizer cromolyn sodium,^{4,113} there is an ongoing double-blind, randomized controlled study examining the safety and efficacy of cromolyn sodium in EoE (NCT02371941 www.clinicaltrials.gov).

Cysteinyl leukotrienes are best known for their pathophysiologic role in asthma, and their effects

are mediated through the CysLT₁ receptor, which is expressed by eosinophils, basophils, mast cells, T cells, smooth muscle cells, fibroblasts, and vascular endothelial cells. Montelukast is a CysLT₁ receptor antagonist. A few case series have demonstrated symptomatic relief in EoE patients, but histological response to montelukast could not be verified.^{114,115} In a prospective study, montelukast failed to maintain steroid-induced remission in adult EoE subjects.¹¹⁶ A recently completed randomized controlled study evaluated the efficacy of montelukast compared to placebo on prevention of dysphagia and food impaction in EoE subjects (NCT00511316, www.clinicaltrials.gov); however, the results of the study are not yet available. Another study will compare response to treatment of EoE with montelukast compared with topical fluticasone therapy (NCT01702701, www.clinicaltrials.gov).

TGF- β 1 is directly involved in esophageal fibrous remodeling in both pediatric and adult patients.^{7,47} Mast cells infiltrating the esophageal smooth muscle layer of EoE patients express TGF- β 1.¹⁰⁸ Angiotensin II receptor blockers inhibit TGF- β and have been studied in connective tissue diseases, such as Marfan's syndrome, in which there is excessive TGF- β production.¹¹⁷ An open-label trial of losartan, an angiotensin II receptor blocker, in EoE subjects with or without a connective tissue disorder will measure histologic improvement, symptomatic improvement, reduction in TGF- β , and drug safety (NCT01808196 www.clinicaltrials.gov).

Conclusions

EoE is a chronic antigen-mediated allergic disease for which tremendous discoveries have been made, and continue to be made, since it was first described only four decades ago. In terms of diagnosis, collaborative efforts are ongoing to better define symptoms, endoscopic findings, and histological features, and established objective criteria now exist for scoring several of these features. This will help optimize follow-up of patients with EoE and facilitate conduct of therapeutic trials for patients with this disease. While an FDA-approved therapy for EoE does not yet exist, multiple therapies, including dietary restrictions, topical corticosteroids, and esophageal dilations, are currently being used, and continue to be refined through several studies. In addition, multiple new therapies are currently underway, which will help better manage patients with EoE, and will

shed more light into the pathogenesis of this chronic disease.

Conflicts of interest

The authors declare no conflicts of interest.

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