

Eosinophilic Esophagitis in Adults: an Update on Medical Management

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Abstract Management of eosinophilic esophagitis (EoE) centers around the 3 Ds: diet, drug therapy, and dilation. Unfortunately, there is not a consistent relationship between symptom relief and resolution of mucosal eosinophilia. Elemental diets are very successful in children, but poorly tolerated by adults. The 6-food elimination diet is more attractive to adults, especially for those individuals with multiple food allergies. Steroids are the preferred anti-eosinophil drug for EoE. Oral prednisone is infrequently used because of side effects. Topical swallowed preparations (fluticasone, budesonide) are preferred for acute and possibly maintenance therapy. Relapses off steroids are frequent and dysphagia does not predictably improve. Esophageal dilation is key treatment for patients with the fibrostenotic phenotype of EoE. Long-term symptom relief for 1–2 years is common. Post-procedure chest pain is to be expected but perforation is very rare. A suggested algorithm for the treatment of EoE based on endoscopic phenotypes is outlined.

Keywords Eosinophilic esophagitis · Allergy testing · Elemental diet · 6-food elimination diet · Corticosteroids · Prednisone · Fluticasone · Budesonide · Proton pump inhibitors · Esophageal dilation

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Since originally described in 1978 [1], eosinophilic esophagitis (EoE) has evolved from sporadic case reports and case series to a major cause of morbidity in young people with an estimated prevalence of between 43 and 52/100,000 persons in the general population [2•]. From the newborn to the elderly, this disease can make its appearance at any time. In adults, the disease presents typically in young to middle-aged, white men with dysphagia for solids and recurrent food bolus impactions. In contrast, children tend to present with vague generalized symptoms including food intolerance, abdominal pain, vomiting, regurgitation, and failure to thrive. The majority of EoE patients have sensitization to food allergens, aeroallergens, or both [2•]. EoE is the subject of extensive research in order to understand its pathophysiology and factors contributing to its broad clinical presentations; however, many aspects of the disease are still a mystery. As such, significant heterogeneity in diagnosis and therapy remain. Being studied extensively by three specialties, allergists, gastroenterologists, and pediatricians, the amount of published literature on EoE has grown exponentially, especially in the past 5 years. Each of these specialties approach this condition with their own point of view, giving rise to wide variations in drug therapy and endoscopic treatments.

Recently redefined in 2011 by a multispecialty consensus group [2•], EoE is now described as “a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.” With few exceptions, 15 eosinophils/hpf are considered the minimum threshold for the diagnosis of EoE. Moreover, other causes of esophageal eosinophilia need to be excluded, specifically gastroesophageal reflux disease (GERD) and PPI-responsive esophageal eosinophilia. This update will focus primarily on the management of EoE in adults with only a brief review of pathophysiology and diagnosis. Key studies over the last 5 years will be highlighted.

Pathophysiology

As our knowledge about this enigmatic disease expands, more is known about its mechanisms and the key role that food and environmental allergens play. Foods and environmental antigens generate an inflammatory reaction by stimulating Th2 signaling. Th2 cells produce cytokines including IL-13, IL-5, and IL-9. IL-13 stimulates the production of eotaxin-3 and periostin in the esophageal mucosa from hyperplastic epithelial cells [3–6]. Eotaxin-3 is a strong chemoattractant responsible for recruitment and activation of eosinophils. Periostin, an extracellular matrix molecule, plays a significant role in EoE by regulating and promoting eosinophil adhesion and recruitment [3, 6, 7]. IL-5 has been implicated in EoE as a recruiter of eosinophils. IL-9 plays a significant role by promoting mastocytosis [3, 4]. Mast cells and eosinophils release transforming growth factor- β which can induce tissue remodeling, fibrosis, and further periostin expression, key processes in the development of EoE [3, 7].

Increased levels of all these cytokines as well as fibroblast growth factor 9, transforming growth factor- β , and other inflammatory mediators are found in biopsy specimens from patients with EoE [3]. Once the process of eosinophil infiltration and activation occurs in the esophageal mucosa, the degranulation cascade begins releasing a wide array of cytotoxic and proinflammatory proteins including major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. These proteins stimulate further eosinophil degranulation, thereby perpetuating the process of inflammation, epithelial growth, and, subsequently, fibrosis and tissue remodeling. This Th2 pathway appears critical in the development of EoE, as experimental studies show that T cell-deficient mice fail to develop antigen-induced EoE [3, 8]. Furthermore, studies in adults suggest that the degree of inflammation and tissue remodeling varies among individual patients, with some having a more “inflammatory phenotype” at endoscopy with minimal esophageal narrowing and others a more “fibrostenotic phenotype” with striking strictures and narrowed esophagus [9]. These phenotypes may require different therapeutic approaches to relieve the symptom of dysphagia and prevent further food impactions.

Gastroesophageal reflux can cause esophageal eosinophilia [2•, 10–12]; however, the relationship between GERD and EoE is rather complicated. For example, the frequent exposure of the esophageal mucosa to acid damages the tight junctions in the squamous cell layer, thereby increasing permeability, leading to the recruitment of inflammatory cells, including eosinophils, and possibly creating an entrance way for foods and aeroallergens into the systemic circulation [11, 12]. As this permeability increases, the gastric acid penetrates deeper leading to further injury and tissue damage leading to fibrosis [12]. The two diseases may also coexist together and contribute to

the other. For example, the cytokines released in EoE can impair esophageal motility and promote fibrosis, thereby impairing esophageal function and worsening GERD [2•].

Diagnosis

EoE is suspected by symptoms of esophageal dysfunction, primarily dysphagia, food impaction, heartburn, or chest pain. This presentation must be accompanied by pathologic findings of at least one biopsy specimen showing 15 or more eosinophils/hpf as the minimum threshold for the diagnosing of EoE [2•]. Several other histologic findings support the diagnosis, including eosinophil microabscesses, superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, elongation of rete peg, and subepithelial lamina propria fibrosis. As already known, esophageal eosinophilia is not pathognomonic for this disease, hence the need to exclude other causes of esophageal eosinophilia, specifically GERD and PPI-responsive esophageal eosinophilia. In addition, these microscopic changes may be patchy in nature; thus, multiple tissue samples are recommended. The consensus paper of 2011 [2•] recommends at least 2–4 biopsies from both the proximal and distal esophagus.

The typical endoscopic findings of EoE include: whitish plaques or exudates, fixed (“trachealization”) or transient (“felinisation”) rings, longitudinal furrows, mucosal edema, pallor or congestion, diffuse esophageal narrowing, and friable or “crepe paper” mucosa. However, up to 10 % of individuals with EoE have a normal appearing esophagus [2•]. Thus, all patients with suspected EoE need endoscopy to look for the classic endoscopic features, take multiple biopsies, define the two possible phenotypes, and assess for possible esophageal dilation.

Allergy testing plays a role in the workup of this antigen-driven disease. Multiple studies report that up to 60 % of patients with EoE have a prior history of atopy [2•, 13–15]. The majority of EoE patients have sensitization to food or aeroallergens based on skin prick testing or serum-specific IgE testing. The rates of concurrent asthma, allergic rhinitis, eczema, and food allergy are high. Therefore, a thorough evaluation by an allergist is strongly recommended.

In recent years, studies have focused on the differentiating of GERD from EoE, but clinical features and some histopathologic findings are nonspecific and frequently overlap. To complicate this scenario, the response to PPIs and results of pH monitoring tests may not accurately distinguish GERD and EoE [16•]. Evidence of this is the recently described “PPI-responsive esophageal eosinophilia” describing a subgroup of patients with typical symptoms of EoE, having GERD excluded by pH testing and responding to PPI therapy alone with resolution of the mucosal eosinophilia. Multiple theories

explaining the response to PPI have surfaced, including potential anti-inflammatory properties for PPIs [17, 18] such as blocking eotaxin expression and down-regulating IL4 and 13. Therefore, a 2-month trial of 20–40 mg twice daily of any PPI followed by endoscopic evaluation with biopsies is the currently accepted method for ruling out PPI-responsive esophageal eosinophilia [2•].

Management

The ideal management of EoE is one individualized to improve the patient's symptoms and quality of life. Several potential endpoints (dysphagia resolution, decrease stricture size, and/or decrease mucosal eosinophilia) have been studied, but whether these endpoints translate into benefits for patients remains controversial [19]. Although multiple studies have addressed the management of EoE, significant heterogeneity in therapy approaches still remain. Moreover, a prospective study among academic and community gastroenterologists in 2010 showed significant variability in practice patterns for both the diagnosis and treatment of eosinophilic esophagitis [20]. Nevertheless, there are three main aspects involved in the management of EoE: the three “Ds”—diet modification, drugs, and esophageal dilation.

Diet

Recent studies showing successful treatment of EoE with elimination diet further support the pivotal role of foods as triggering factors [5]. Hence, the enthusiasm for diet modifications as a therapeutic approach remains attractive, particularly in children where it has proven most successful. There are three dietary regimens effective in treating EoE: elemental diet, dietary restriction based on multimodality allergy testing, and dietary restriction based on eliminating the most likely food antigens (6-food elimination diet).

The elemental diet, a strictly amino acid-based formula, was initially used successfully in children with esophageal eosinophilia attributed to GERD but not responsive to antacids [21]. Several studies followed in EoE patients further confirming the effectiveness of this diet particularly in children where it plays a major role in treatment [22, 23]. The biggest limitations to an elemental diet are the poor taste of the formulations, often requiring tube feedings, and elimination of the regular diet, which translates into poor patient compliance. This is particularly evident in adults, where studies have demonstrated significant issues with diet adherence [24]. However, it is the most effective dietary therapy when compared to other diet modification regimens in relieving symptoms and reducing eosinophilia [2•]. The average time for clinical improvement is 8.5 days [23]. The diet should be maintained for 6–12 months before

reintroducing regular foods, usually based on prior skin tests and patient desires starting with less allergic food products.

The second regimen consists of dietary restrictions based on multimodality allergy testing. Food allergens identified are removed from the diet. Initial studies with positive results were performed in children but more recent reports also showed efficacy in adults. Response rates to selective dietary restriction have been reported in the 70 % range [25, 26]. This dietary approach is the least disruptive for the patient as it represents a targeted therapy where only identified food allergens are removed while allowing all other solid and liquid foods. Milk, soy, wheat, chicken, and beef are the foods most frequently identified by skin prick and patch tests. However, a limitation of this approach is the low sensitivity of skin prick and patch tests to accurately identify food allergens causing esophageal inflammation [27].

The third approach consists of eliminating the most likely food antigens. Also called the 6-food elimination diet (SFED), this diet removes the 6 most common food allergens: cow's milk protein, soy, wheat, egg, nuts, fish/shellfish. This regimen was validated by a prospective study in 2011 by Gonsalves et al. [28•] in which 50 adult patients were subjected to SFED for 6 weeks. Nearly 95 % had symptom improvement and a complete histologic response (< 5 eosinophils/hpf) was identified in 64 %. A subset of 20 patients with symptomatic improvement and histologic remission completed the “reintroduction phase”. One food group was introduced every 2 weeks. The order of food reintroduction was individualized based on allergy testing or patient preference. Upper endoscopy with biopsies was repeated 4 weeks after the reintroduction of 2 food groups or earlier if symptoms developed. The causative food was found in all 20 patients, with median time to symptom recurrence of 3 days. The foods most frequently associated with EoE relapse were wheat (60 %) and milk (50 %) followed by soy (10 %), nuts (10 %), and egg (5 %). Skin prick testing predicted only 13 % of foods associated with EoE exacerbations, further validating the limitations of skin tests to identify food allergens. Thus, the 6-food elimination diet may be the preferred dietary approach in adults, but requires the assistance of a dietician to help identify proper food selection.

Medications

Corticosteroids

The main pathophysiologic process in EoE involves chronic inflammation of the esophageal mucosa. Corticosteroids are powerful anti-inflammatory drugs acting on eosinophils by inducing apoptosis, down-regulating chemoattractants, and inhibiting pro-inflammatory mediators [6]. Multiple studies have evaluated steroids in various preparations including

topical (aerosolized or viscous preparations which are swallowed) and systemic oral tablets for EoE.

Oral methylprednisolone was the first corticosteroid used for treating EoE. In a pediatric case series, Liacouras et al. treated 20 patients with 1.5 ml/kg daily divided in two doses [29]. Nineteen patients showed histological improvement (mean esophageal eosinophil count decreased from 34 to 2 per hpf), 9 became asymptomatic, and 6 markedly improved after an average of 8 days of therapy. Unfortunately, 9 patients had symptomatic relapses when the steroids were stopped. Concerns for side effects of systemic steroids (especially growth abnormalities and adrenal insufficiency), as well as disease relapse after stopping the drug, have restricted their use and led to studies involving other forms of steroid therapy. Today, oral steroids are reserved for use in an emergency setting when patients may present with severe dysphagia, weight loss, and hospitalization [2•].

Most of the experience with topical steroid therapy in EoE is derived from the pediatric population. Konikoff et al. conducted a randomized, double-blind, placebo-controlled trial of swallowed fluticasone propionate in patients (average age 8 years) with active eosinophilic esophagitis [30]. Thirty-six children were randomly assigned to receive either 880 mcg of fluticasone (21 patients) or placebo (15 patients) divided twice daily for 3 months. The primary endpoint was histologic remission (peak esophageal eosinophil count ≤ 1 eosinophil) in both the proximal and distal esophagus. Fifty percent of patients treated with fluticasone achieved histologic remission. As a secondary endpoint, the group reported resolution of vomiting more frequently with fluticasone therapy than placebo (67 % pretreatment vs. 27 % post-treatment; $p=.04$) which was a common complaint among young children (15/28, 54 %).

To compare the effectiveness of oral vs swallowed therapy, Schaefer et al. performed a prospective randomized trial of oral prednisone versus swallowed fluticasone for histologic and clinical response in EoE [31]. Eighty children were randomized to receive prednisone (1 mg/kg/dose twice a day; maximum 30 mg twice a day) or swallowed fluticasone by metered dose inhaler (110 mcg per puff for ages 1–10 years and 220 mcg per puff for ages 11 years or older) for 4 weeks, followed by an 8-week weaning protocol. Esophageal histology was evaluated at baseline and after 4 weeks of therapy. Histologic improvement was seen in 30 of 32 patients in the prednisone group and 34 of 36 patients in the fluticasone group. All patients on the prednisone arm and 35/36 patients on fluticasone arm were free of presenting symptoms at week 4. Symptom relapse was seen in 45 % of patients by week 24 with no significant difference in time to relapse between groups. Adverse side effects (hyperphagia, weight gain, and/or cushingoid features) were noted in 16 (40 %) patients on prednisone and none receiving fluticasone. This pivotal study bolstered the primary use

of swallowed steroids in EoE and raised the first concerns about the need for maintenance therapy.

Additional studies have followed in the adult population involving fluticasone and budesonide in the treatment of EoE [32, 33•, 34]. A seminal study was the randomized, double-blind, placebo-controlled trial by Straumann et al., where the effect of oral budesonide (1 mg twice daily for 15 days) in 36 adult patients with active EoE was evaluated [32]. Pre-treatment and post-treatment disease activity was assessed clinically, endoscopically, and histologically. The primary endpoint was reduced mean numbers of eosinophils in the esophageal epithelium. A 15-day course of therapy significantly decreased the number of eosinophils in the esophageal epithelium in patients given budesonide (68.2 to 5.5 eosinophils/hpf; $p<.001$) but not in the placebo group (62.3 to 56.5 eosinophils/hpf; $p=0.5$). Dysphagia scores significantly improved in patients receiving budesonide compared with placebo (5.61 vs. 2.22; $p<.001$). No serious adverse events were observed, proving that a 15-day course of budesonide was well tolerated and highly effective in inducing histologic and clinical remission of EoE.

Other adult studies were not as encouraging. For example, Alexander et al. performed a double-blind, randomized, placebo-controlled trial of fluticasone in 42 adult patients with a new diagnosis of EoE [33•]. Patients in the treatment arm swallowed 880 mcg of aerosolized fluticasone (4 puffs) twice daily for 6 weeks. Endpoints were symptomatic and histologic response. They reported complete histologic response (>90 % decrease in mean eosinophil count) in 11/15 (62 %) patients receiving 6 weeks of fluticasone compared with none of 15 patients receiving placebo ($p<.001$), based on intention-to-treat analysis. Histologic responses (a decrease in eosinophil count >50 %) were observed in 68 % of patients on fluticasone (13 of 19) compared with none on placebo (0 of 15) by per-protocol analysis ($p<.001$). Dysphagia was reduced in 57 % of patients receiving fluticasone compared to 33 % receiving placebo therapy ($p=0.22$) by intention-to-treat analysis and 63 % of the fluticasone patients (12 of 19) versus 47 % on placebo (7 of 15) ($p=0.49$) based on per-protocol analysis. Esophageal candidiasis developed in 26 % of patients receiving fluticasone. Based on these results, the group concluded that aerosolized, swallowed fluticasone leads to a histologic but not a predictable symptomatic response in adults with EoE.

In an attempt to identify which topical steroid therapy is better for EoE, Dellon et al. performed a randomized trial comparing nebulized and viscous topical steroid preparations [34]. Subjects received budesonide 1 mg twice daily, either nebulized and then swallowed or as an oral viscous slurry for a total of 8 weeks. Measurements included dysphagia improvement, reduction in eosinophil counts, and the mucosal medication contact time. The latter was measured with scintigraphy after tagging the budesonide with

radiocontrast. Esophageal mucosa contact time was greater with the swallowed slurry, while most of the nebulized drug remained in the mouth or inadvertently was inhaled into the lungs. The authors concluded that viscous topical steroid therapy in the form of a swallowed slurry was more effective than the nebulized preparation in reducing numbers of esophageal eosinophils in patients with EoE, while both groups had a similar degree of dysphagia improvement.

Thus, topical steroids are very effective in decreasing the eosinophil count in EoE subjects, but symptom response is more unpredictable. Furthermore, symptom recurrence after stopping the medication is well documented (35 % to 88% between 3 and 12 months of stopping the drug) and remains a dilemma. Therefore, steroids may need to be used more chronically as in inflammatory bowel disease. To address this issue, Straumann et al., performed a randomized, double-blind, placebo-controlled, 50-week trial, evaluating the efficacy of twice-daily swallowed budesonide (0.25 mg each) to maintain remission in 28 patients [35•]. Pre- and post-treatment activity was assessed clinically, endoscopically, histologically, immunohistologically, and by endosonography. The primary therapeutic endpoint was maintenance of EoE in histologic remission. In patients given low-dose budesonide for 50 weeks, on maintenance therapy, the esophageal eosinophils increased from 0.4 to 31.8 eos/hpf ($p=.017$) which was significantly less than the patients on placebo (0.7 to 65.0 eos/hpf with $p=0.001$). At baseline, the symptom score was comparable in the 2 groups. With placebo, the score increased significantly to 4.00 ± 2.18 points ($p<0.001$), whereas with budesonide the increase to 2.29 ± 2.43 was not significant ($p=.08$). At week 50, 64 % of patients receiving budesonide versus 35 % of placebo were in clinical remission ($p=0.26$). The median time to relapse was more than 125 days in the budesonide group and 95 days in the placebo group. Furthermore, only budesonide reduced non-eosinophilic markers of inflammation, epithelial cell apoptosis, and remodeling events, and was associated with a significant reduction in overall mucosal thickness (0.75 to 0.45 mm; $p=.025$) as measured by endoscopic ultrasound. No serious adverse events occurred. This study demonstrated the efficacy of topical steroid therapy as maintenance therapy for EoE patients and suggested a potential role in decreasing fibrotic scar tissue.

Despite some limitations, topical steroids are currently the mainstay therapy for adult treatment of EoE. We recommend the following regimen: 220 mcg two to four puffs swallowed (not inhaled) twice daily (after breakfast and before bedtime) or budesonide slurry swallowed 1 mg BID. Patients are instructed to rinse their mouth with water but not swallow to decrease the risk of oral thrush. It is recommended that patients do not eat or drink for 1–2 h after ingestion to maximize the esophageal contact time. The

duration of acute therapy is unknown ranging from 2 weeks to 3–4 months with some suggesting as-needed therapy until symptoms resolve. The role of maintenance therapy still is not defined.

Anti-IL and Montelukast

Multiple cytokines are involved in the pathophysiology of EoE. As a result, several anti-IL drugs have been studied in EoE with mixed results.

IL-5 stimulates eosinophil mobilization and recruitment. Stein et al. performed a small, open label trial of mepolizumab, an anti-IL5 drug, in 4 adults with EoE and longstanding dysphagia and strictures [36]. Patients received 3 infusions of anti-IL-5 (750 mg intravenously monthly) without change in their current therapy. Peripheral blood eosinophilia, percent of CCR3+ cells, and esophageal eosinophilia decreased at one month from baseline after anti-IL-5 treatment. Patients also reported less dysphagia and improved quality of life. Although limited to only 4 patients, these results positioned anti-IL-5 drugs as a promising therapeutic intervention for EoE.

Unfortunately, placebo-controlled trials followed with conflicting results [6, 37]. For example, a randomized, double-blind, placebo-controlled trial by Spergel et al. evaluated the effect of reslizumab, a neutralizing antibody against IL-5, in 226 children and adolescents with EoE [37]. All treatment groups, including the placebo arm, showed improvements in physician's global assessment scores; hence, differences between reslizumab and placebo were not statistically significant. Reslizumab did significantly reduce esophageal eosinophil counts; however, symptom improvement could not be correlated with these changes. Adverse events in the reslizumab groups included headache, cough, nasal congestion, and upper respiratory tract infection. These agents remain under study, but are not currently recommended for the treatment of EoE.

Similarly, montelukast, a selective leukotriene receptor antagonist, widely used in the treatment of asthma and allergic rhinitis, has been studied in the EoE population. However, results have shown ineffectiveness in maintaining the histopathological or clinical response among patients previously treated with topical steroids [38]. Therefore, these agents are not recommended for EoE.

Proton Pump Inhibitors

Acid suppression therapy plays an important role in the management of eosinophilic esophagitis. As discussed previously, the relationship between GERD and EoE is complex. GERD can cause esophageal eosinophilia by itself, and both conditions can coexist. The picture was further complicated by the recently described syndrome of "PPI-responsive esophageal eosinophilia" [16•]. In a prospective

study from Spain, 26 of 35 (75 %) patients with mucosal eosinophilia achieved clinicopathological remission with rabeprazole 20 mg dosed twice daily. Of these 26 patients, 17 had a GERD-like picture with erosive esophagitis and/or positive pH testing with a 100 % response to PPIs. Nine had an EoE profile with dysphagia and typical endoscopic findings representing a 50 % response to PPIs for those with classical EoE profile. Reflux testing and absolute eosinophil counts did not accurately identify the PPI responsive group—in fact, one patient with an eosinophil count of 150/hpf normalized on PPI therapy [16•].

The currently accepted method for ruling out GERD and PPI-responsive esophageal eosinophilia is a 2-month trial of 20–40 mg twice daily of any PPI followed by endoscopy evaluation with biopsies. If the patients are on PPIs at the time of first endoscopy, then biopsies can be obtained. If not, then patients should ideally be treated with PPIs and wait for 2 months for an upper endoscopic examination so as to appropriately categorize the patient. Overall, there appears to be little role for esophageal pH testing unless antireflux surgery is being considered. However, apart from their role in the diagnosis, PPIs have proven useful as co-therapy in the management of EoE. They may relieve reflux symptoms and potentially decrease the recruitment of inflammatory cells in the esophagus by their intrinsic anti-inflammatory mechanisms as well as preventing acid damage to the tight junctions in the esophageal mucosa [2•, 10, 17, 18]. PPIs are well tolerated with few side effects.

Endoscopic Dilation

For years, endoscopic dilation played an important role in the management of EoE. Adults with EoE tend to have significant deposition of fibrous tissue and consequently esophageal rings, strictures, and narrowed esophagus. These patients have the fibrostenotic phenotypes for EoE and account for over 60 % of patients seen in our practice. Numerous studies have addressed the safety and efficacy of endoscopic dilation in EoE. The main concern is the risk of perforation, since the esophageal wall has decreased compliance from the extensive deposition of collagen making it fragile and prone to deep tears and possibly perforation.

The first published case series addressing dilation of EoE was in 2001 by Morrow et al. involving a retrospective review of 19 patients diagnosed with ‘ringed oesophagus’ treated with serial esophageal dilations [39]. Of these patients, 11 reported heartburn, 17 had food impactions, and 11 had erosive esophagitis. The characteristic endoscopic appearance was a poorly distensible esophagus with multiple concentric rings causing significant stenosis. Esophageal biopsies showed extensive mucosal eosinophilia with basal cell hyperplasia and prolongation of rete pegs. Patients

underwent several dilation sessions with Savary bougies gradually increasing dilator size to a goal diameter of 14–15 mm. No perforations occurred. Follow-up was performed on average 19 months later with 16 (84 %) patients reporting that their dysphagia improved dramatically from on average daily to only once/twice a month. After the initial series of dilations and PPI therapy, only one patient required frequent dilations and subsequently improved with oral prednisone.

Several publications have followed over the last 10 years providing reassurance about the efficacy and safety of endoscopic dilation. These consisted mostly of retrospective series and case studies involving different dilation techniques, including Savary dilators, bougie dilators, and through-the-scope (TTS) balloons [40, 41•, 42, 43]. Meanwhile, other studies usually including only single case reports raised concerns for serious complications such as perforation [44–52]. The study by Schoepfer et al. provides the most realistic picture of the potential risks and benefits associated with the usage of esophageal dilation [41•]. The authors performed a retrospective review from a combined database (Switzerland and Chicago) including 681 EoE patients divided into two cohorts. Cohort 1 consisted of patients treated with dilation alone, and cohort 2 included patients treated with a combination of dilation and topical steroid medications. From these two cohorts, a total of 207 EoE patients were treated with esophageal dilation, 63 in cohort 1 and 144 in cohort 2. Endoscopic dilation led to a significant increase in esophageal diameter as well as improvement in dysphagia in both cohorts ($p < 0.001$). Importantly, the average length of dysphagia relief was 23 months in cohort 1 and 20 months in cohort 2 ($p = \text{NS}$). No esophageal perforations occurred. Among the patients surveyed, 74 % reported retrosternal pain after dilation usually lasting from 1 to 7 days; however, all agreed to have a repeat dilation if required. The authors concluded that esophageal dilation, despite not changing the inflammatory response, significantly improved symptoms thereby identifying tissue remodeling rather than inflammation as the key cause of most EoE complaints in adults. In the cohort on anti-inflammatory drugs, the dilation seemed to give more benefit than medications.

Dellon et al. performed a single-center, retrospective study on safety, clinical response and complications of EoE patients treated with endoscopic dilation (either Savary or TTS balloons) [43]. Of 130 EoE cases, 70 dilations (12 Savary, 58 balloon) were performed in 36 patients. Esophageal size improved from 12 to 16 mm ($p < .001$), with an overall symptom response rate of 83 %. The only predictor of clinical response was final dilation diameter. There were 5 complications (7 %): 2 deep mucosal rents and 3 episodes of chest pain; no perforations were reported. All complications occurred in patients receiving topical steroids, who underwent balloon dilation.

Complications were associated with younger age (23 vs. 42; $p=.02$) and more dilations (4 vs. 1.7; $p=.009$). This study suggests not using steroids during the time period that dilations are being performed.

Over the last several years, large retrospective studies and two systematic reviews have addressed the efficacy and safety of dilation in EoE. Almost 500 patients involving nearly 1,000 dilations were treated with 3 esophageal perforations—a rate of 0.3 % and similar to dilation in a non-EoE population [6]. Furthermore, the rare isolated reports of esophageal perforation were usually treated conservatively. Of clinical importance, 92 % of patients treated with dilation had improvement in their dysphagia symptoms for an average 1–2 years. Therefore, esophageal dilation is a viable option in the healthy adult not desiring to take steroids or an elimination diet [9•].

There are currently no guidelines for esophageal dilation in EoE. However, based on the published literature and the senior author's experience, the following recommendations are made [9•]. Dilations are performed only after endoscopy has identified the areas of maximum narrowing and approximate size of the esophageal lumen diameter. The basic rule is to start with a small diameter

dilator, progress slowly and dilate to a diameter of 15–18 mm to achieve symptom relief. Savary and Maloney bougies are the preferred dilators, since the esophageal lumen can be narrowed or strictured in more than one location. Also, these dilators provide a better sense of the force applied against the fibrotic esophageal wall. In contrast, TTS balloons are more expensive as they are not reusable, and more time consuming since they likely need repositioning throughout the esophageal lumen. A lumen diameter of 15 mm will allow patients to eat a modified regular diet, and a diameter of 18 mm will allow a full regular meal [53]. For severe narrowing not allowing passage of the standard 9-mm endoscope, multiple dilation sessions, usually spaced over 3–4 weeks, will be required to achieve these luminal diameters. The progression of diameter per session remains controversial; however a cautious approach is recommended. Repeat endoscopy after dilation is not required, as it will only provide a visual reassurance of the mucosal changes post-dilation. All patients should be made aware that pain is an expected side effect which may persist for several days, but typically responds well to analgesics with infrequent need for narcotics.

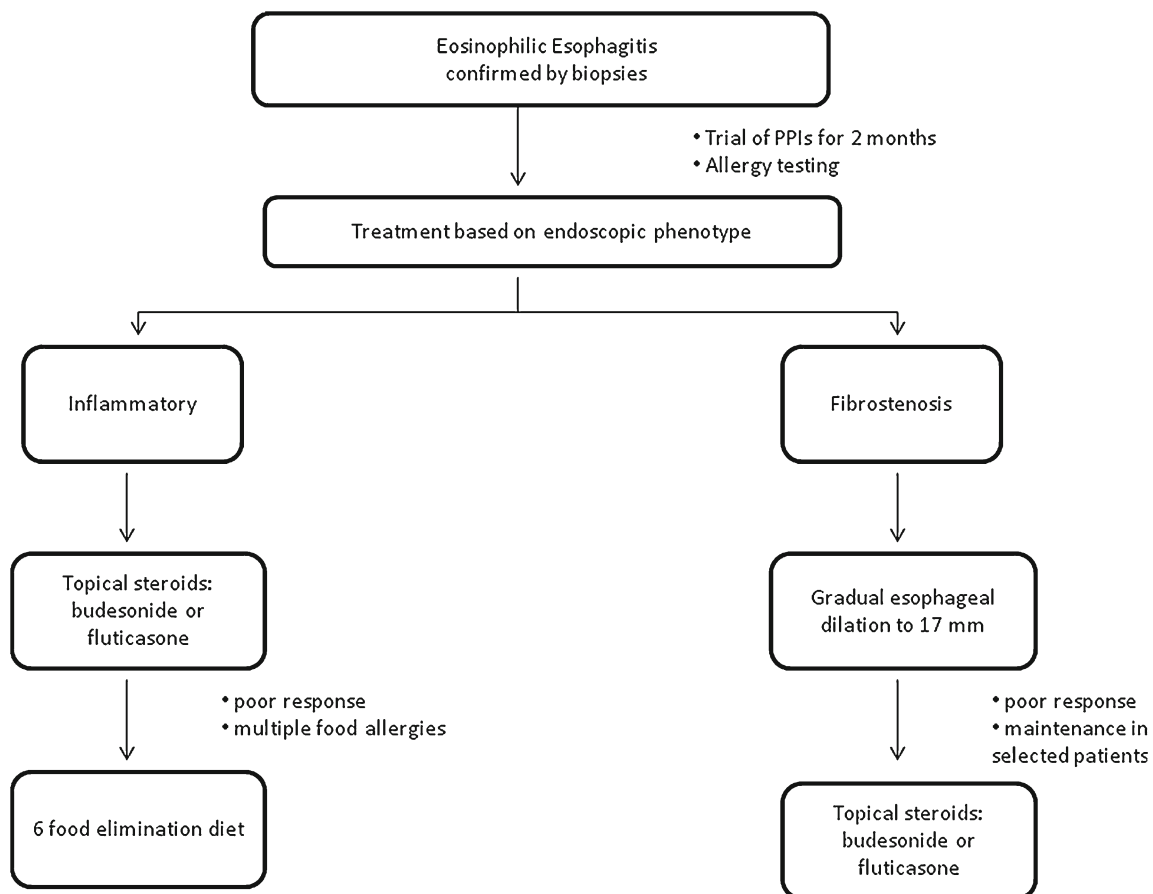


Fig. 1 Algorithm for the treatment of eosinophilic esophagitis

Practical Clinical Algorithm for the Treatment of Eosinophilic Esophagitis

There are no society or consensus group algorithms for treating EoE. In our Esophageal Center, we are now using the algorithm outlined in Fig. 1 with two potential treatment pathways depending on the endoscopic phenotype of the esophagus. Patients with the “inflammatory phenotype”, characterized by furrows, exudates but minimal fibrosis allowing passage up to a 17-mm bougie at one session, are most likely to benefit first from topical steroids, either fluticasone or budesonide. Patients are treated for 3–6 months, and endoscopy with biopsies repeated to assess improvement in mucosal eosinophilia. Patients with persistent symptoms or multiple food allergies are offered a 6-food elimination diet. In contrast, patients with a “fibrostenotic phenotype” have endoscopic evidence of lumen obstruction associated with rings, strictures, or generalized narrowing. These patients require gradual esophageal dilation over 2–4 sessions to a diameter of 17–18 mm. Symptom relief is predictable because dilation directly expands the esophageal lumen with some pain as an expected side effect. Depending on the degree of inflammation (arbitrarily eosinophils >40 per hpf), topical steroids can be added. Endoscopy with biopsies is repeated in 1 year as needed (usually every 2–3 years) based on recurrence of dysphagia. Whether to use maintenance anti inflammatory therapy in either of these phenotypes is unknown at this time.

Conflict of Interest Ricardo Prieto declares that he has no conflict of interest.

Joel E. Richter declares that he has no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology*. 1978;74:1298–301.
2. •• Liacouras CA et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3–20. *State-of-the-art review on eosinophilic esophagitis*.
3. Rothenberg ME. Biology and treatment of Eosinophilic esophagitis. *Gastroenterology*. 2009;137(4):1238–49.
4. Abonia JP, Rothenberg ME. Eosinophilic esophagitis: rapidly advancing insights. *Annu Rev Med*. 2012;63:421–34.
5. Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2012;10(10):1066–78.
6. Blanchard C, Mingler MK, McBride M, et al. Periostin facilitates eosinophil tissue infiltration in allergic lung and esophageal responses. *Mucosal Immunol*. 2008;1:289–96.
7. Abonia JP, Franciosi JP, Rothenberg ME. TGF-beta1: mediator of a feedback loop in eosinophilic esophagitis—or should we really say mastocytic esophagitis? *J. Allergy Clin Immunol* 126:1205–7
8. Mishra A, Scholtman J, Wang M, et al. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. *J Leukoc Biol*. 2007;81:916–24.
9. • Bohm ME, Richter JE. Oesophageal dilation in adults with eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2011;33:748–57. *Critical systematic review of the efficacy and safety of esophageal dilation in EoE*.
10. Tobey NA, Carson JL, Alkiek RA, Orlando RC. Dilated intercellular spaces: a morphological feature of acid refluxdamaged human esophageal epithelium. *Gastroenterology*. 1996;111:1200–5.
11. Barlow WJ, Orlando RC. The pathogenesis of heartburn in non-erosive disease: a unifying hypothesis. *Gastroenterology*. 2005;128:771–8.
12. Dellon ES et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2009;7(12):1305–13.
13. Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009;7:1055–61.
14. Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, DeVault KR, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2009;104:828–33.
15. Chehade M. IgE and non-IgE-mediated food allergy: treatment in 2007. *Curr Opin Allergy Clin Immunol*. 2007;7:264–8.
16. • Molina-Infante J, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol*. 2011;9:110–7. *Study highlights the complex relationship of GERD and mucosal eosinophilia and helps identify the subset of PPI responsive EoE*.
17. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci*. 2009;54:2312–7.
18. Cheng E, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, Spechler SJ, Souza RF. Omeprazole blocks eotaxin 3 expression by oesophageal squamous cells from patients with eosinophilic esophagitis and GORD. *Gut* 2012.
19. Hirano I. Therapeutic End Points in Eosinophilic Esophagitis: Is Elimination of Esophageal Eosinophils Enough? *Clin Gastroenterol Hepatol* 2012
20. Peery AF, Shaheen NJ, Dellon ES. Practice patterns for the evaluation and treatment of eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2010;32:1373–83.
21. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503–12.
22. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective way treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98:777–82.
23. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*. 2005;3:1198–206.
24. Peterson K, Clayton F, Vinson LA, Fang JC, Boynton KK, Gleich GJ, et al. Utility of an elemental diet in adult with eosinophilic esophagitis. *Gastroenterology*. 2011;140.
25. Molina-Infante J et al. Efficacy of elimination diet based on food sensitization skin testing for adult eosinophilic esophagitis. *Gastroenterology*. 2012;142 suppl 2:abstract.
26. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol*. 2005;95:336–43.

27. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2002;109:363–8.
28. • Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults: food reintroduction identifies causative factors. *Gastroenterology*. 2012;142(7):1451–9. *Reviews the impact of the 6-food elimination diet in adults with EoE.*
29. Liacouras C, Wenner W, Brown K, et al. Primary eosinophilic esophagitis in children: Successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr*. 1998;26:380–5.
30. Kornikoff MR et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterol*. 2006;131:1381–91.
31. Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfeifferkorn M, Corkins MR, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: A randomized trial in children. *Clin Gastroenterol Hepatol*. 2008;6:165–73.
32. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology*. 2010;139:1526–37.
33. • Alexander JA, Jung KW, Arora AS, Enders F, Katzka DA, Kephart GM, Kita H, Kryzer LA, Romero Y, Smyrk TC, Talley NJ. Swallowed Fluticasone Improves Histologic but Not Symptomatic Responses of Adults with Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol* 2012. *Study highlights the inconsistent improvement of EoE symptoms in patients treated with topical steroids. Authors could not explain the dichotomy as eosinophilia was nearly eradicated.*
34. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012;143:321–324.
35. • Straumann A, Conus S, Degen L, Frei C, Bussman C, Beglinger C, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2011;9:400–9. *Maintenance budesonide keeps some patients with EoE in symptomatic remission for up to a year with evidence of resolving esophageal fibrosis.*
36. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006;118:1312–9.
37. Spergel JM, Rothenberg ME, Collins MH, Futura GT, Markowitz JE, Fuchs 3rd G, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129(2):456–63. 463.e1–3.
38. Lucendo AJ, De Rezende LC, Jimenez-Contreras S, Yague-Compadre JL, Gonzalez-Cervera J, Mota-Huertas T, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci*. 2011;56:3551–8.
39. Morrow JB, Vargo JJ, Goldblum JR, Richter JE. The ringed esophagus: histological features of GORD. *Am J Gastroenterol*. 2001;96:984–9.
40. Potter JW, Saeian K, Staff D, et al. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. *Gastrointest Endosc*. 2004;59:355–61.
41. • Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol*. 2010;105:1062–70. *Important study identifying the trade-offs of esophageal dilation in adults with EoE – “no pain, no gain”.*
42. Bohm M, Richter JE, Kelsen SG, Thomas R. Esophageal dilation: a simple and effective treatment for adults with eosinophilic oesophagitis and oesophageal rings and narrowing. *Dis Esophagus*. 2010;23:377–85.
43. Dellon E, Wood G, Rubinas T. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. *Clin Endosc*. 2010;71:706–12.
44. Riou PJ, Nicholson AG, Pastorino U. Esophageal rupture in a patient with idiopathic eosinophilic esophagitis. *Ann Thorac Surg*. 1996;62:1854–6.
45. Kaplan M, Mutlu EA, Jakate S, Bruning K, Losurdo K, Losurdo J. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. *Clin Gastroenterol Hepatol*. 2003;1:433–7.
46. Prasad GA, Arora AS. Spontaneous perforation in ringed esophagus. *Dis Esophagus*. 2005;18:406–9.
47. Liguori G, Cortale M, Cimino F, Sozzi M. Circumferential mucosal dissection and esophageal perforation in a patient with eosinophilic esophagitis. *World J Gastroenterol*. 2008;14:803–4.
48. Cohen MS, Kaufman AB, Palazzo JP, Nevin D, Dimarino AJ, Cohen S. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2007;5:1149–53.
49. Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol*. 2008;6:598–600.
50. Giles H, Smith L, Tolosa D. Eosinophilic esophagitis: a rare case of esophageal rupture in children. *Am Surg*. 2008;74:750–2.
51. Robles-Medrand C, Villard F, Bouvier R. Spontaneous esophageal perforation in eosinophilic esophagitis in children. *Endoscopy*. 2008;40 Suppl 2:E171.
52. Quiroga J, Prim JM, Moldes M, Ledo R. Spontaneous circumferential esophageal dissection in a young man with eosinophilic esophagitis. *Internet Cardiovasc Thoracic Surg*. 2009;9:1040–2.
53. Goldschmid S, Boyce Jr HW, Brown JI, Brady PG, Nord HJ, Cyman GH. A new objective measurement of esophageal lumen patency. *Am J Gastroenterol*. 1989;84:1255–8.

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