

# Eosinophilic Esophagitis: Current Treatment

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**Abstract** Eosinophilic esophagitis (EoE) is a relatively new entity with a significant amount of increased recognition over the last decade. The mainstay treatments of EoE are designed to eliminate the causative allergens or to reduce their effects on the esophageal mucosa. Common treatments include dietary modification, proton pump inhibitors, systemic and topical corticosteroids, and endoscopic treatments. As the pathogenesis of EoE is explored, new and novel treatments are being studied that target specific pathways and chemokines identified in as precipitating agents of EoE. This is a rapidly evolving field with significant ongoing research and clinical studies. Our review will therefore focus on current and novel treatment approaches to the disease.

**Keywords** Eosinophilic esophagitis · Allergens · Drug treatment · Elimination diets

## Introduction

Eosinophilic esophagitis (EoE) is a disease that has drawn increased attention over the past several years. First reported by Landres et al. in 1978 [1], EoE is a disease characterized by upper gastrointestinal (GI) symptoms associated with esophageal eosinophilia and basal cell hyperplasia. EoE is believed to have a strong association with atopy, and although seen in all races it is most common in Caucasians. The disease has been found to have a

3:1 male predominance among a vast age range from young children to the elderly [2, 3]. The majority of patients have a history of environmental and/or food allergies. Patients often have a personal or family history of allergic diseases, including asthma, eczema, allergic rhinitis, and food allergies [3].

The symptoms of EoE vary with age. The pediatric population present with vomiting (25–61 %), dysphagia (26–39 %), abdominal pain (25–34 %), feeding disorders (12–14 %), heartburn (14 %), and food impaction (7 %) [4, 5]. The most common presenting symptoms among teenage and adult patients are solid-food dysphagia (33–70 %), chest pain (25 %), gastroesophageal reflux disease (GERD)-like symptoms (23–27 %), and abdominal pain (25 %) [6]. Food impaction requiring endoscopic removal occurs in 33–54 % of adult EoE patients. Studies have shown that up to 15 % of all patients undergoing upper endoscopy for dysphagia have EoE [7–9].

The prevalence of EoE has increased significantly over the past several years. However, it is unclear whether the prevalence of EoE is truly increasing or if clinicians and pathologists are recognizing it more often. Several retrospective studies examining esophageal biopsies over extended time periods do suggest that the prevalence of EoE is increasing [10, 11], but this topic remains controversial as one large study suggests that increased recognition is responsible for the increased prevalence [12].

Several factors contribute to the development of EoE, including genetic predisposition, history of allergies, and presence of environmental and food allergens [13]. There is a strong correlation between EoE and other allergic conditions, such as asthma, environmental allergies, food allergies, and atopic dermatitis [14, 15]. Aeroallergens are thought to play an important role in the development of EoE. Experimental mice models have linked the

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development of EoE to respiratory antigens, but not to oral or intragastric allergens [16]. Initial studies linked a seasonal variation in presentation of EoE symptoms and diagnosis, supporting the theory that seasonal allergies have an effect on EoE development [10, 17–19]. However, a recent large retrospective analysis of 167 EoE patients showed that there was no seasonal variation in time of initial diagnosis [20]. Thus, the overall impact of seasonal allergies on EoE development remains unclear.

Dietary allergens have been shown to correlate with EoE in the pediatric population. This correlation has been demonstrated primarily in the significant improvements clinically and histologically with elimination diets [21]. A large retrospective study following 381 pediatric patients with EoE showed that 98 % had a significant improvement in clinical symptoms and histologic pathology over a 10-year period when they maintained a strict avoidance of dietary triggers [22].

The diagnosis of EoE is based on a combination of symptoms, endoscopic appearance, and histologic findings. A subset of patients may have co-existing GERD and will require treatment for both diseases. Several other diseases that cause esophageal eosinophilia include Celiac disease, Crohn's disease, infection, hypereosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, pemphigoid vegetans, connective tissue disease, and graft-versus-host disease [23].

The consensus criteria for diagnosing EoE specify the presence of  $\geq 15$  esophageal eosinophils per high power field (HPF) in two to four biopsy samples from both the proximal and distal esophagus in the absence of GERD (Fig. 1). GERD is ruled out as a primary cause of eosinophilia through a clinical trial with proton pump inhibitors

(PPIs) or by pH-monitoring studies [2, 7, 25]. Patients with esophageal eosinophilia whose symptoms and pathology are entirely responsive to PPI therapy are not considered to have EoE, but rather “PPI-responsive esophageal eosinophilia” [24–26].

The treatment of EoE is varied as patients have a broad spectrum of presenting symptoms, and a varied response to therapy. Many patients present with solid-food dysphagia which may require endoscopic dilation. Others will have resolution of symptoms through medical and dietary therapy. The treatment options include PPIs, topical corticosteroids, systemic corticosteroids, and elimination diets (Table 1). The response to any one of these therapies depends in part on the degree of atopy, whether patients have additional causes of esophageal dysfunction (such as GERD), and compliance with treatment. Treatment goals are difficult to assign, and there are no current recommendations for how often patients should be re-biopsied. Repeat monitoring is not recommended if patients shown symptomatic improvement, as there are risks involved with upper endoscopy and anesthesia. The most common method of assessing treatment response is through the resolution of symptoms.

### Proton Pump Inhibitors

Proton pump inhibitors are recommended as part of the initial evaluation process for EoE and may be useful not only to differentiate EoE from GERD, but also as a co-therapy in patients with diagnosed EoE. They may also alleviate symptoms related to secondary GERD, which may be present with EoE [25, 27]. The recommended dosage is 20–40 mg once or twice daily for a period of 8–12 weeks for the adult population, and 1 mg/kg twice daily for 8–12 weeks in the pediatric population.

The entity known as “PPI-responsive EoE” is defined as patients manifesting the typical symptoms of EoE, without GERD, who achieve symptomatic and histologic improvement solely through the use of PPIs. The pathophysiology of PPI-responsive EoE is poorly understood.

It is hypothesized that acid suppression may have anti-inflammatory effects by decreasing the amount of eotaxin-3, leading to decreased eosinophils [28]. Pediatric studies have shown a dissociation between histologic findings and symptoms. One study based on findings from a questionnaire and pH study showed that both symptoms and eosinophilic infiltration improved when the patients were treated with either a PPI or steroid treatment, irregardless of whether or not they had documented GERD [29]. A recent series of case reports has shown that some patients may also show initial improvement with PPI therapy, with eventual symptomatic and histologic eosinophilia relapse

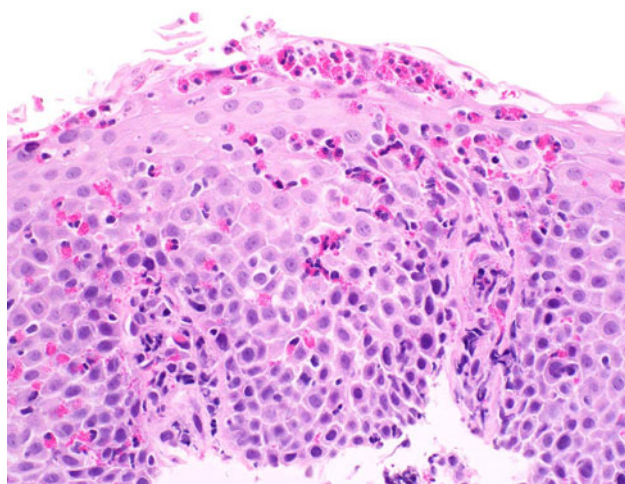


**Fig. 1** Mid-esophageal biopsy demonstrating stratified squamous epithelium with marked eosinophilia ( $>100$ /high power field) characterized by superficial layering and clustering, papillary elongation, spongiosis, and basilar hyperplasia

**Table 1** Eosinophilic esophagitis: updated consensus treatment recommendations for children and adults (Liacouras et al. *J. Allergy Clin. Immunol.* [25])

| Therapy                                                                           | Consensus recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proton pump inhibitor (PPI) therapy                                               | <p>PPIs are useful in treating patients with EoE in whom GERD is a comorbid disease, and are useful to help eliminate GERD as a cause of esophageal eosinophilia</p> <p><i>Recommended dosing:</i></p> <p>Adults: 20–40 mg, once or twice daily for 8–12 weeks (depends on patient and chosen PPI)</p> <p>Children: 1 mg/kg per dose, twice daily for 8–12 weeks (for maximal dosing use adult recommendations)</p> <p>PPIs might also affect esophageal eosinophilia by means of other mechanisms and thus be helpful in a subset of patients described as having PPI-responsive esophageal eosinophilia</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Corticosteroids                                                                   | <p>Topical corticosteroid therapy should be considered in all children and adults given a diagnosis of EoE for both <i>initial and maintenance</i> therapy. The type and duration of steroid therapy may vary. Clinical experience and concern for ongoing symptoms, esophageal inflammation, and complications of untreated disease have led to the recommendation that after induction of clinicopathologic remission, topical corticosteroid therapy might need to be maintained; however, long-term therapy must be individualized for each patient</p> <p>When topical steroids are used chronically, in addition to observing for side effects, growth should be carefully monitored in children</p> <p><i>Recommended dosing:</i></p> <p>Topical swallowed corticosteroids</p> <p>Initial doses:</p> <p>Fluticasone (puffed and swallowed through a metered-dose inhaler)</p> <p>Adults: 440–880 mcg twice daily</p> <p>Children: 88–440 mcg twice to 4 times daily (to a maximal adult dose)</p> <p>Budesonide (as a viscous suspension)</p> <p>Children (&lt;10 years): 1 mg daily</p> <p>Older children and adults: 2 mg daily</p> <p>Systemic corticosteroids</p> <p>For severe cases (e.g. small-caliber esophagus, weight loss, and hospitalizations)</p> <p>Prednisone: 1–2 mg/kg</p> |
| Cromolyn sodium, leukotriene receptor antagonists, biologics, and other therapies | <p>Treatment of EoE with cromolyn sodium, leukotriene receptor antagonists, and immunosuppressive agents (azathioprine or 6-mercaptopurine) for the treatment of EoE is not recommended</p> <p>The lack of combined clinical and histologic benefit and potential side effects currently outweigh any potential benefit. <i>Biologic agents</i> await further clinical studies and <i>are not recommended</i> for routine use at the present time. Several additional studies on anti-interleukin-5, anti-immunoglobulin E therapy are pending</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Dietary therapy                                                                   | <p>Dietary therapy should be considered in all children given a diagnosis of EoE</p> <p>Preliminary observations suggest that dietary restriction should also be considered for motivated adult patients with EoE. When deciding on the use of a specific dietary therapy, the patient's lifestyle, adherence to therapy, and family resources need to be considered</p> <p>Consultation with a registered dietitian is strongly encouraged to ensure that proper calories, vitamins, and micronutrients are maintained</p> <p>The committee suggests that foods proved to cause EoE continue to be restricted from the diet, whereas those foods not definitively proved to be antigenic can be reintroduced systematically, with careful observation for recurrence of EoE</p> <p>Restriction of foods proved to trigger EoE might need to be continued indefinitely</p>                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Esophageal dilation                                                               | <p>Esophageal dilation with or without concomitant medical or dietary therapy can provide relief of dysphagia in selected patients with EoE</p> <p>In the absence of high-grade esophageal stenosis, <i>a trial of medical or dietary therapy before performance of esophageal dilation is reasonable</i></p> <p>For high-grade strictures, dilation before initiation of medical therapy has been well tolerated and effective. The risk of chest pain after dilation is significant and should be discussed with patients. The use of esophageal dilation as primary therapy without concomitant medical or dietary therapy does not address the underlying inflammatory process and has been inadequately studied. On the other hand, the degree to which esophageal strictures will reverse with medical or dietary therapy alone is uncertain</p>                                                                                                                                                                                                                                                                                                                                                                                                                                              |

EoE, Eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor

while on chronic PPI treatment. For this reason, it is recommended that patients who initially respond to PPI continue to be monitored closely for symptoms of relapse [30]. PPI use remains an essential initial step in both the diagnosis and treatment of EoE. PPI treatment can cause symptomatic improvement in patients with symptoms secondary to GERD and in patients with PPI-responsive EoE.

## Corticosteroids

### Topical Corticosteroids

Topical corticosteroids are considered to be the mainstay therapy for EoE and should be used to induce the initial remission of symptoms as well as for maintenance therapy. Swallowed fluticasone propionate and oral viscous budesonide have both been used as topical therapy for EoE. Fluticasone is used in a similar fashion as in reactive airway disease, but instead of the aerosolized solution being inhaled, as a treatment for EoE it is swallowed. This technique was first used by Faubion et al. [31] who described the treatment of four children with swallowed fluticasone and their subsequent symptomatic remission. Konikoff et al. confirmed this small study with the first randomized, placebo-controlled trial treating a group of children with fluticasone twice daily. The treatment group had a 50 % remission compared with 9 % seen in the placebo group. The standard recommended dose for adults is 440–880 mg twice daily and in children, 88–440 mg two to four times daily [32].

Viscous budesonide was originally tested in clinical trials on patients who had difficulty swallowing the inhaled fluticasone properly. Remission rates are as effective as those seen with fluticasone [33]. In addition to symptomatic improvement there is some evidence that budesonide may reverse esophageal fibrosis [34]. Recommended dosing is 2 mg daily in patients older than 10 years, and 1 mg daily for patients younger than 10 years.

Fluticasone and budesonide have been shown to result in clinical and histologic improvement in most patients; however, symptoms typically recur within 2–9 months when discontinued [22, 35, 37]. Helou et al. showed that in patients treated for 6 weeks, 91 % of patients reported recurrent symptoms within a mean of 8.8 months after treatment discontinuation. Daily maintenance therapy was not used in this study, but 47 % of patients reported using treatment as-needed for symptoms [36]. A recent case study demonstrated that topical ciclesonide, a corticosteroid with low systemic bioavailability, can potentially be used as an effective option for patients who are resistant to fluticasone and budesonide [36].

Topical corticosteroids are considered to be relatively safe compared with systemic corticosteroids. The main adverse effect observed are oral and esophageal candidiasis, which can be minimized by rinsing with water after each treatment. Although topical corticosteroid use is felt to be without significant complications, studies evaluating the long-term effects of inhaled corticosteroids are still needed.

### Systemic Corticosteroids

Systemic corticosteroids have been effectively utilized in the treatment of EoE, although they are not considered to be first line therapy due to the side effect profile associated with chronic use. In a pediatric study which compared swallowed fluticasone to oral prednisone, both treatment groups showed a rapid clinical and histologic response, with comparable outcomes [37]. The main differences between the groups were time to relapse and side effects. The average time to relapse among the patients treated with prednisone was 5.5 weeks compared with 8 weeks in the fluticasone group. Systemic adverse effects (hyperphagia, weight gain, and/or cushingoid features) were reported in 40 % of the prednisone group, whereas only 15 % of the fluticasone group developed esophageal candidiasis, with no report of systemic adverse effects [37]. Systemic steroids are effective in treating EoE, but they should be reserved for patients with severe dysphagia and weight loss. Recommended dosing is prednisone 1–2 mg/kg daily, which is to be continued until the symptoms improve. Systemic corticosteroids should not be used for maintenance therapy.

## Leukotriene Antagonists, Anti-Interleukin-5, Anti-Immunoglobulin E, and Anti-Tumor Necrosis Factor-Alpha

Montelukast, a leukotriene D4 receptor antagonist, has been studied in the treatment of EoE. Leukotriene D4 is produced by and serves as a chemotactic factor for eosinophils; therefore, theoretically, inhibition of the leukotriene D4 receptors would decrease the eosinophil over-expression seen in EoE. In a small trial involving eight patients using montelukast, seven showed significant symptomatic improvement, without histologic improvement, and all patients relapsed when montelukast was discontinued [38]. A recent study showed that Montelukast was not effective in maintaining the histopathological or clinical response achieved by topical steroids in adult EoE patients [39].

Humanized antibodies to interleukin-5 (IL-5) were originally used to treat hypereosinophilic disorders such as asthma. As IL-5 appears to play a significant role in EoE,

treatment modalities involving IL-5 have been studied in EoE patients. A small study of four patients treated with mepolizumab infusions in addition to their current therapies showed significant improvement in peripheral and esophageal eosinophilia, symptoms, and quality of life [40]. In a follow-up study consisting of 11 patients with EoE who were unresponsive or dependent on systemic corticosteroids, the five patients who were treated with mepolizumab showed significant reduction in esophageal eosinophilia compared to those receiving placebo. There was a modest improvement in symptoms as well, but it was not statistically significant when compared to placebo [41]. In another study, reslizumab, another anti-IL-5, was given to 226 patients in varying doses. Although the reduction in esophageal eosinophils was statistically significant, the improvements in symptoms were observed among both groups, and the difference was not statistically significant [42].

A single small study evaluating treatment with infliximab, an anti-tumor necrosis factor- $\alpha$  agent, showed little improvement in symptoms and no histologic benefit in terms of EoE treatment [43].

Omaliuzumab is an anti-immunoglobulin E (IgE) antibody which has been used in the treatment of severe atopic asthma and allergic rhinitis. It has been shown to decrease eosinophil counts in the blood and lungs of patients [44]. Omaliuzumab could have a role in future therapy for the treatment of EoE; however, no randomized clinical studies have been initiated at this time.

Chemoattractant receptor homologous molecule expressed on T-helper type 2 cells (CRTH2) is a G protein-coupled receptor expressed by Th2 lymphocytes and eosinophils that mediates prostaglandin D<sub>2</sub>-driven chemotaxis which in turn appears to inhibit allergic inflammation in asthma. It is postulated that a CRTH2 receptor antagonist could function as a potential therapy for EoE. An orally available CRTH2 antagonist (OC000459) was utilized as a monotherapy in a study of 26 adult patients with EoE. When compared to placebo, there was a reduction in esophageal eosinophils (114.7–74.2 vs. 102.8–99.4 eos/HPF), but the reduction in symptoms assessment scores among the treatment and placebo groups were similar (16.5–8.8 vs. 16.7–9.8 points) [45].

Prospective treatments with other anti-inflammatory agents are currently being studied to determine the efficacy and safety of these future therapies.

## Elimination Diets

Eosinophilic esophagitis is believed to be a reaction to ingested allergens, and dietary therapy has therefore been a successfully utilized treatment option. Several different

approaches have been tested in clinical trials, ranging from elemental diets to elimination diets. The majority of the research in dietary modification has been done among the pediatric population. Adult trials have been difficult to conduct due to a poor tolerance to restrictive diets. The rationale behind dietary therapy is that the removal of specific food antigens will eliminate the allergic process causing EoE. There are several different methods of addressing these food allergies. The most restrictive dietary approach is an amino acid-based formula. A second approach is the six-food elimination diet. The third option is a diet tailored specifically to the patient's known allergens based on clinical history and allergy testing. All of these methods are very effective when done correctly. Selection of the appropriate diet is based on patient preference, severity of disease, and resources.

### Amino-Acid Based Formula

The amino acid-based formula is considered the gold standard in elimination diets as it limits the intake of possible ingested allergens. It consists of liquid preparations composed of elemental amino acids. This method is reserved for patients who do not respond to other less restrictive options as it is difficult to follow due to the dietary formulas being of poor palatability and the general requirement of a nasogastric or gastrostomy tube. All studies involving the efficacy of elemental diets have been performed in pediatric patients. A retrospective pediatric study of 381 patients over a 10-year period showed a 98 % improvement in clinical symptoms and esophageal histology when patients followed an elemental diet. When the patients were switched to an elemental diet, their symptoms resolved within 7–10 days and histologic resolution was evident by 4–5 weeks. Many patients were then able to slowly reintroduce foods, starting with the least allergenic foods [22].

### Six-Food Elimination Diet

The six-food elimination diet is based on removing those foods groups with the most allergenic potential, namely, milk, eggs, soy, wheat, nuts, and seafood.

This diet is less restrictive than elemental diets and does not require the in-depth allergy testing necessary in specific food elimination diets. Studies in adults have shown varied results, which are likely associated with the degree of compliance to the diet itself. In one study of 35 patients with EoE, 74 % of the patients showed improvements both clinically and histologically [46]. Once patients achieve symptomatic improvement on the six-food diet, they can slowly reintroduce food groups in an effort to localize those food groups responsible for their symptoms.

A recent cohort study of patients with celiac disease found a higher incidence of EoE among these patients than in the general population [47], suggesting that gluten may play a pivotal role in the development of EoE. Thus, further investigations evaluating the specific effects of gluten on EoE development are required. It has often been hypothesized that cow's milk also plays an important role in EoE development, although no studies have been carried out to substantiate this finding.

### Specific Food Elimination

In the specific food elimination diet, allergy testing is performed on individual patients to help predict which foods are responsible for the allergic reactions precipitating EoE. Diagnostic tests consist of radioallergosorbent testing (RAST) and the IgE skin prick test. Allergy testing can be very beneficial in localizing food allergies; however, the tests can be expensive and are time-consuming. Atopy patch testing (APT) is also being used in combination with the skin prick test. The latter isolates IgE-mediated reactions, whereas APT isolates non-IgE mediated reactions where T cells play an important role, such as in contact dermatitis. The combination of these two tests is more effective than either APT or skin prick testing alone because it enables both IgE cell-mediated and non-IgE cell-mediated causes of allergic reactions to be detected. A study utilizing both skin prick testing and APT in 146

patients showed that 77 % had clinical and histologic improvement within 6 weeks of dietary changes [48].

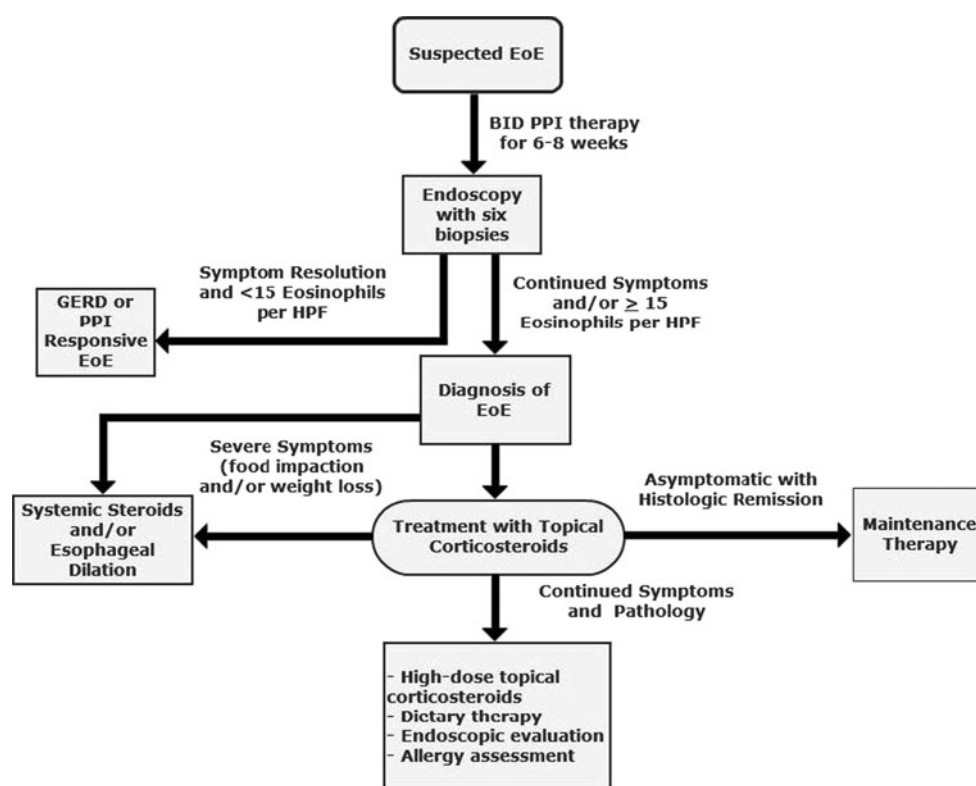
A recent study of adult patients demonstrated that an elimination diet is able to significantly improve symptoms and reduce endoscopic and histopathologic features of EoE [49]. Among these patients, the re-introduction of certain foods caused relapse of symptoms. This study emphasizes the role of food allergens in the development of EoE. Foods responsible for relapse were identified through systematic reintroduction, but the skin prick test did not accurately identify the causative food allergens [49].

### Endoscopic Treatment

Eosinophilic esophagitis patients often present with symptoms of dysphagia or even food impaction. The role of endoscopic dilation in these patients has been controversial. Early EoE dilation studies estimated the rate of perforation following dilatation to be as high as 5 % [50]. Several subsequent retrospective studies determined that these initial studies overestimated the rate of complications, suggesting that the perforation risk was <1 %, although up to 5 % of patients developed chest pain [51, 52].

A recent retrospective analysis from 2006 to 2010 evaluated 54 patients who underwent 66 total dilations [53]. None of the patients suffered perforation or hemorrhage or required hospitalization; two patients (4 %) had

**Fig. 2** Suggested treatment algorithm for eosinophilic esophagitis (EoE). GERD Gastroesophageal reflux disease, PPI proton pump inhibitor, HPF high power field



chest pain. There were no endoscopic features (rings, furrows, plaques) associated with any complication. The type of dilator, size of dilator, number of prior dilations, and age of patient were also not associated with complications. The authors of this study concluded that endoscopic dilation using a variety of dilators can be safely performed with minimal complications in patients with EoE [53].

Physicians should consider a primary radiological assessment of an esophageal stricture and choose the appropriate procedure and dilator size. It is important to remember that dilation does not treat the underlying cause of EoE, nor does it replace medical or dietary therapy.

## Conclusion

Eosinophilic esophagitis is a clinicopathologic disease which has received increased recognition over the past several years. The underlying mechanism causing EoE is probably food allergies and aeroallergens. Based on current literature, the management of EoE should follow a common algorithm. Patients presenting with symptoms of EoE should be started on a twice daily dose of PPI for 6–8 weeks. Following this treatment period, an upper endoscopy should be performed that includes a total of  $\geq 6$  esophageal biopsies (2 proximal, 2 mid, and 2 distal). Patients showing symptom resolution and normal histology are diagnosed with GERD or PPI-responsive EoE, and treatment with PPIs should be continued. Patients who continue to have symptoms and found to have  $\geq 15$  eosinophils per HPF are diagnosed with EoE and should be started on topical corticosteroids. Patients who respond well to the topical corticosteroid should be continued on a maintenance dose. If the patient continues to have symptoms, then a repeat biopsy should be considered. In the absence of histologic improvement, additional therapies should be pursued. These patients may benefit from consultation with an allergy specialist to determine further allergic evaluation. Patients who at any time during the treatment process have worsening dysphagia, food sticking, or weight loss should be treated with systemic corticosteroids and evaluated endoscopically for the presence of a stricture. Endoscopic dilation using a variety of dilators can be safely performed with minimal complications. This treatment plan will need to be individualized for each patient, and the risks and benefits of repeat esophageal biopsies will need to be weighed. Ongoing research is exploring additional treatment options that will address the underlying allergic response. Consequently, the treatment of EoE will continue to evolve over the next several years (Fig. 2).

**Conflict of interest** None.

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