Curr Gastroenterol Rep (2010) 12:181–188
DOI 10.1007/s11894-010-0101-8

Approach to Dysphagia in the Young Patient in the Era of Eosinophilic Esophagitis

Nirmala Gonsalves

Published online: 30 April 2010
© Springer Science+Business Media, LLC 2010

Abstract Eosinophilic esophagitis (EoE) has emerged as an important cause of dysphagia and food impactions in young adults. Previously considered a rare condition, an increasing number of cases of EoE have been attributable to a rising incidence and a growing awareness of the condition. Typical endoscopic features include concentric mucosal rings, linear furrowing, white exudates, and a narrow caliber esophagus. Current consensus guidelines define EoE by 1) the presence of characteristic symptoms, especially dysphagia and food impactions in adults, 2)≥15 eosinophils per high power field in esophageal tissue, and 3) exclusion of other disorders with similar presentations (eg, gastroesophageal reflux disease). Current knowledge about the pathophysiology implicates food allergens, aeroallergens, and genetic factors. The main treatment options for EoE are proton pump inhibitors, dietary manipulation, and topical or oral glucocorticoids. Endoscopic dilation may be performed in patients who do not respond to medical therapy. This review highlights recent insights into the diagnosis and management of EoE in young adults.

Keywords Esophagus · Dysphagia · Stricture · Eosinophil · Ringed esophagus · Food impaction

Introduction

In previous years, patients with dysphagia were traditionally treated with endoscopic dilation of esophageal strictures. In cases where overt strictures were not visualized, empiric dilation of the entire esophagus was often performed. However, because eosinophilic esophagitis (EoE) has emerged as the most common cause of dysphagia and food impaction in young adults, the approach to dysphagia in these patients has been altered and is outlined in this review. EoE is a chronic condition characterized by increased esophageal eosinophils in the setting of esophageal symptoms. Although EoE may occur in conjunction with eosinophilic gastroenteritis, the increased number of cases of EoE is related to the variant with isolated esophageal eosinophilia [1]. Development of EoE is likely a result of the interplay of multiple factors, including esophageal acid exposure, food and environmental allergens, and genetic predisposition, and these factors are actively being investigated. This review highlights recent insights into the pathophysiology and treatment of EoE in adults and provides a suggested algorithm for management of these patients.

N. Gonsalves (✉)
Department of Medicine, Division of Gastroenterology,
Northwestern University, Feinberg School of Medicine,
676 St Clair St, Suite 1400,
Chicago, IL 60611-2951, USA
e-mail: n-gonsalves@northwestern.edu

Epidemiology

EoE has become a global epidemic both in children and adults with increasing reports from many continents including Europe, Asia, Australia, and North and South America [2–5]. Noel et al. [6] reported on the incidence of EoE in children residing in Hamilton County, Ohio; in 2000, the estimated incidence was 0.91 per 10,000 with a prevalence of 1 per 10,000 compared to 1.7 in 10,000 and a prevalence of 10.4 in 10,000 in 2007. Straumann et al. [7] reported an incidence of 0.15 cases per 10,000 and a prevalence of 3 per 10,000 among adults in Switzerland. In the United States, the incidence of adult cases in Olmsted County, Minnesota, has risen from 0.35 per 100,000 person-years in 1995 to 9.45 per 100,000 person-years in

2005 [8]. In an adult patient population presenting with dysphagia, incidence of EoE was found to be as high as 6.5% [9]. These numbers suggest that the incidence and prevalence of EoE is approximating that of other, more common, immunologic disorders (eg, inflammatory bowel disease) [10]. Furthermore, these estimates likely underestimate the true incidence and prevalence of EoE because the data are based on symptomatic patients presenting for endoscopy.

Clinical Features

Dysphagia, food impaction, heartburn, and chest pain are common presenting symptoms of adults with EoE [11••]. Up to 50% of adult food impaction cases encountered in an emergency department may be attributable to EoE, and therefore, esophageal biopsy performed at the time of a food impaction is advocated [12]. EoE tends to be a male-predominant disease in both the adult and pediatric populations. Among 323 adult patients in 13 reports, 76% were males with a mean age of 38 years (range 14–89). Among 754 pediatric patients in 16 reports, 66% were male with a mean age of 8.6 years (range 0.5–21.1) [11••]. Although reports also suggest a Caucasian predilection, EoE has been described in African Americans, Latin Americans, and Asians [13]

Historically, this diagnosis was often overlooked in young adults, with many patients undergoing repeated endoscopies and dilations with alternate diagnoses of gastroesophageal reflux disease (GERD) or a Schatzki ring. [14] . Another explanation for the delay in diagnosis of EoE is that eosinophilic infiltrate in the esophageal mucosa was previously equated with GERD with quantitative thresholds of eosinophilic infiltration making the distinction; lower counts were presumably related to GERD whereas higher counts were diagnostic for EoE [15]. A strict cut-off value can be problematic, however, because of the high prevalence of GERD in the adults and potential overlap between GERD and EoE. The potential interplay of acid exposure in the esophagus in patients with GERD and the development of EoE is incompletely understood at this time. Owing to this conundrum, current consensus guidelines have advocated that GERD should be adequately treated with acid suppression or ruled out with a pH monitoring study in the diagnostic workup for EoE. This is especially important because an increasing number of adults are manifesting with both GERD and EoE.

Endoscopic Features

Reported endoscopic features in adult EoE include linear or longitudinal furrows (80%), concentric mucosal rings (64%), small caliber or narrow esophagus (28%), white plaques or exudates (16%), and strictures (12%) [12, 14]. Esophageal strictures and rings have also been identified on barium studies of patients with EoE [16]. Although routine barium studies are not necessary to diagnose EoE, in patients with severe dysphagia, radiographic characterization of the length and caliber of a stricture in EoE may be helpful prior to upper endoscopy by alerting the endoscopist to situations requiring added caution. In some cases, the endoscopic features of EoE may be subtle and overlooked at endoscopy. Case series reported as many as 8.8% of adult EoE patients and 30% of pediatric EoE patients had no apparent endoscopic abnormalities [12, 17]. Therefore, regardless of endoscopic findings, esophageal biopsies should be taken during a workup for unexplained dysphagia, refractory heartburn, or chest pain [11••].

Histologic Features

Although endoscopic features such as rings, furrows, and punctate exudates are highly suggestive of EoE, the diagnosis is established histologically. The pathologic criteria for EoE are increased esophageal intramucosal eosinophils without concomitant eosinophilic infiltration in the stomach or duodenum. Other major histologic features that may be seen include superficial layering of eosinophils, eosinophilic microabscesses (clusters of ≥4 eosinophils), intercellular edema or spongiosis, and degranulation of eosinophils. Other inflammatory cells such as lymphocytes, polymorphonuclear leukocytes, and mast cells may also be present [18]. Epithelial hyperplasia, also seen in reflux esophagitis, is defined by papillary height elongation and basal zone proliferation and is another common feature in EoE [18]. In some cases, subepithelial fibrosis may be present [19, 20].

Although other threshold values for the density of eosinophilic inflammation were used in previous studies, a recent consensus statement suggested a threshold value of ≥15 eosinophils per high power field to establish a diagnosis of EoE [11••]. Eosinophilic infiltration of the esophagus may be patchy within the esophagus; therefore, it is suggested that multiple biopsies be obtained. A retrospective study of adult EoE patients found that obtaining five biopsy specimens maximized diagnostic sensitivity using a diagnostic threshold of ≥15 eosinophils [14]. A follow-up pediatric study using the same diagnostic threshold demonstrated that three biopsy specimens yielded a diagnosis of EoE in 97% of patients [21]. In both series, biopsies restricted to only the proximal or distal esophagus were nondiagnostic in up to 20% of cases, emphasizing the patchy nature of the disease and the importance of obtaining biopsies from different locations.

In summary, recent consensus and expert opinion have led to the following definition of EoE. EoE is a clinicopathologic disease characterized by 1) the presence of symptoms including, but not limited to, dysphagia and food impaction in adults and feeding intolerance and GERD symptoms in children; 2) ≥15 eosinophils per high power field in the esophageal tissue; and 3) exclusion of other disorders associated with similar clinical, histologic, or endoscopic features (eg, GERD) with either the use of high-dose acid suppression prior to biopsy procurement or normal pH monitoring [11••]

Pathogenesis

Although the pathophysiology of EoE in adults is not clearly defined, a link to food and aeroallergens has been demonstrated. Mishra et al. [22] have induced esophageal eosinophilia in a mouse model after exposure to the allergen, *Aspergillus fumigates*. Also, a case report of an adult with allergic rhinoconjunctivitis and asthma demonstrated increased symptoms and esophageal eosinophilia during pollen seasons, whereas biopsies obtained during nonpollen months were normal [23]. Further supporting the existence of seasonal variation, a retrospective study of 234 children found that EoE was diagnosed less often in the winter months and that eosinophil levels tended to be higher in the summer and fall months when pollen was present [24].

Numerous clinical studies have demonstrated an association between food allergies and EoE. The first landmark study to implicate food as a trigger was conducted by Kelly et al. [25]. This group evaluated 10 pediatric patients with intractable GERD symptoms despite antireflux therapy who also had histologic changes of epithelial hyperplasia and eosinophilic infiltration in the esophagus [25]. After a dietary trial consisting of elemental formula, all 10 patients had a significant reduction in esophageal eosinophilia; five had complete resolution of esophageal eosinophilia, and six had resolution of endoscopic abnormalities. Reintroduction of the culprit foods resulted in symptom relapse in 9 of the 10 children, with a median delay of only 1 h (0.5–8 h) after the food trigger, lending further support to this association. Specific food triggers in this group were cow's milk in seven patients, soy protein in four, wheat in two, peanut in two, and egg in one. Studies have also demonstrated improvement in EoE after treatment with an empiric six-food elimination diet in children and adults and a targeted elimination diet based on allergy testing in children [26–28].

On a molecular level, several studies have investigated the role of cytokines in this inflammatory response using interleukin-5 (IL-5) and eotaxin knockout mice [29]. They demonstrated decreased esophageal eosinophilia after aeroallergen exposure in eotaxin knockout mice and the complete absence of esophageal eosinophilia in IL-5 knockout mice [30]. IL-5 also appears to mediate eosinophil-induced esophageal remodeling [31]. Eosinophil recruitment in affected patients appear to be confined to the esophagus, driven mainly by an IL-5–selective T-helper cell (Th2) response [32]. Further supporting the concept that EoE is Th2-mediated is the high incidence of other atopic diseases such as allergic rhinitis, atopic dermatitis, and asthma in EoE patients [33].

Several studies have also implicated a genetic predisposition for developing EoE. Familial clustering has been recognized in adults and children, first suggesting a genetic predisposition [34–36]. In a case series of 381 pediatric patients with EoE, 5% had siblings with EoE and 7% had a parent with either an esophageal stricture or known EoE [17]. The basis for this genetic predisposition to EoE continues to be investigated. Eotaxin-3, a gene encoding an eosinophil-specific chemoattractant, has recently been identified as the most highly induced gene in pediatric EoE patients [37•]. Treatment with topical corticosteroids downregulated esophageal eotaxin-3 levels, suggesting the change to be reversible [38]. Although formal gene analysis has not yet been pursued in adults, immunohistochemical staining for eotaxin-3 in esophageal tissue of adult patients with EoE was significantly increased compared to patients with reflux, suggesting a similar trend to the pediatric data [39].

Natural History

Although defining the natural history and progression of EoE is critical in developing goals of treatment, limited natural history data exist to help guide current recommendations. Given the increased morbidity that can be associated with complications of EoE (eg, food impactions), a key goal of management is to prevent disease recurrence and complications. In the longest available natural history study, Straumann et al. [3] followed 30 medically untreated adult patients for an average of 7.2 years. During this time, 97% experienced continued dysphagia and one third had undergone esophageal dilation. Although EoE persisted, interestingly, levels declined in most patients during the follow-up period. Barrett's metaplasia has been reported in patients with EoE, but it is unclear whether or not this is a causal relationship [40]. Esophageal malignancy related to EoE has not been reported; however, limited long-term data are available.

Treatment

Because the natural history of the disease is not clearly defined, controversy exists regarding the optimal goals of

treatment. Some advocate eradication of all eosinophils from the esophageal mucosa, but others believe symptom resolution or even reduction of eosinophilia is a reasonable endpoint. Based on expert opinion, reasonable goals include eradication of esophageal eosinophilia and symptom resolution. The main treatments studied in EoE include proton pump inhibitors, systemic or topical corticosteroids, montelukast, immunomodulators, dietary therapy, and endoscopic dilation of strictures. Available treatment data for each are summarized below.

Proton Pump Inhibitors

EoE initially was reported to be a manifestation of GERD; since then, it has become evident that EoE and GERD can coexist and overlap to some degree. Patients exist with symptoms and endoscopic features consistent with EoE, who are completely responsive to GERD therapy. Among 100 patients in nine adult EoE studies who underwent pH monitoring, 18% had abnormal results [11••]. Three recent studies, one adult and two pediatric, report normalization of symptoms and tissue eosinophilia after proton pump inhibitor therapy [41–43]. Consequently, recent consensus guidelines suggest that the evaluation of GERD as a potential contributor to esophageal eosinophilia is an important element of the diagnosis and management of EoE [11••]. If EoE is suspected, a treatment course of acid suppression for about 4 to 6 weeks followed by repeat endoscopy with biopsy is recommended. If the patient has resolution of symptoms and EoE, continued acid suppression is advocated.

Oral Corticosteroids

Oral corticosteroids were one of the first effective treatments identified for EoE. Liacouras et al. [44] treated 21 children with methylprednisolone, 1.5 mg/kg/d, for 4 weeks, and reported that 65% were asymptomatic and 30% had marked improvement after treatment. All patients had histologic resolution of eosinophilia; however, esophageal biopsies taken 6 months after discontinuation of steroids demonstrated recurrence of esophageal eosinophilia to near pretreatment levels. Subsequently, given the temporary nature of the response and the well-known side effect profile of oral corticosteroids, this treatment is generally reserved for very severe cases of EoE.

Topical Corticosteroids

Swallowed topical corticosteroids have a low systemic bioavailability and have been extensively used in treatment of adult EoE. Fluticasone propionate has been most extensively studied and has demonstrated efficacy in several adult series. A retrospective study reported resolution of dysphagia in 21 adults treated with fluticasone for 4 months [45]. In a prospective study,19 adult patients were treated with fluticasone, 500 μg, twice daily for 4 weeks; 60% of patients had resolution of EoE along with marked reduction in both proximal and distal esophageal eosinophilia [46]. Side effects were rare; however, three patients developed asymptomatic esophageal candidiasis and 66% experienced recurrent symptoms within 3 months of discontinuing therapy. In addition to symptoms, endoscopic features of EoE have also been shown to improve with long-term treatment of fluticasone [47]. In the first randomized, placebo-controlled trial of fluticasone, Konikoff et al. [48] administered fluticasone propionate, 880 μg/d, for 3 months to 36 children with EoE. Treatment with fluticasone induced histologic remission in 50% of patients compared to 9% with placebo. Of note, nonallergic individuals had a better response than did allergic individuals.

Although fluticasone may be effective, swallowing an aerosolized inhaler may be difficult for some patients; therefore, other delivery mechanisms have been studied. A retrospective study by Aceves et al. [49] of 20 children treated with oral budesonide suspension, 1 to 2 mg daily, reported symptomatic, endoscopic, and histologic improvement. Straumann et al. [50] recently reported a randomized, double-blind, placebo-controlled trial of swallowed budesonide, 1 mg nebulized, twice daily, in 36 adults with EoE. Esophageal eosinophilia decreased from 62 per high power field at baseline to 4 per high power field after only 15 days of budesonide; no change was observed after placebo. Symptoms improved in 84% of patients receiving budesonide compared to 33% receiving placebo.

In summary, topical corticosteroids have demonstrated treatment efficacy after short courses of therapy ranging from 15 days to 3 months. However, it has been documented that symptoms and esophageal eosinophilia return within 3 to 6 months after discontinuation of steroids. Although the safety and effectiveness of topical steroids have made them a popular therapy in adults, the optimal duration of treatment and maintenance strategy remain to be defined. Expert opinion suggests continuing patients on a maintenance regimen of this therapy.

Montelukast

Montelukast, a leukotriene D4 receptor antagonist indicated for the treatment of asthma and allergic rhinitis, has been studied in a small case series. Attwood et al. [51] treated eight adult patients with EoE with montelukast, initially starting at a dose of 10 mg daily and escalating the dose until symptomatic improvement was achieved. Seven patients were reported to show symptom improvement

however high doses were needed. Unfortunately, six of the seven responders had recurrence of symptoms within 3 weeks of discontinuing therapy or dose reduction, and there was no reduction in the density of esophageal eosinophilia. Therefore, consensus guidelines have suggested that the use of montelukast for the treatment of EoE is not supported by the current literature [11••].

Immunomodulators

Interleukin-5, a cytokine produced by Th2 lymphocytes, regulates the proliferation, maturation, and release of eosinophils from the bone marrow and exhibits increased expression in the esophageal epithelium of patients with EoE [1]. Mepolizumab is a fully humanized monoclonal IgG antibody that selectively binds and inactivates IL-5. An open-label trial was reported using mepolizumab in four adult patients with EoE, three of whom had severe disease [52]. Maximum esophageal eosinophilia diminished from 153 to 28 per high power field after 4 weeks of therapy. Patients reported improvement in symptoms and quality of life, and mepolizumab was generally well tolerated. A recent randomized, placebo-controlled trial of 11 adults with EoE, who were either unresponsive or dependent on corticosteroids, demonstrated less encouraging results [53]. Mepolizumab, administered once every 4 weeks for 12 weeks, significantly reduced both peripheral blood and esophageal eosinophilia. However, remission (defined as ≤5 eosinophils per high power field in the esophageal mucosa) was not achieved in this study.

Anti-IgE therapy with omalizumab was used in an open-label trial of nine adults with eosinophilic gastroenteritis, seven of whom had concomitant EoE [54]. Significant decreases in symptoms, IgE levels (79% reduction), and peripheral eosinophilia (34% reduction) were reported along with a decrease in esophageal (but not gastric or duodenal) eosinophilia.

Another biologic immunomodulator that was studied in EoE is infliximab, a tumor necrosis factor (TNF)-α monoclonal antibody typically used in the induction of remission and maintenance therapy of inflammatory bowel disease. TNF-α expression is increased in patients with EoE. In an open-label trial, treatment of three patients with two doses of infliximab, 5 mg/kg, at weeks 4 and 6 did not result in symptom improvement, reduction of esophageal eosinophilia, or reduced tissue expression of TNF-α [55].

Finally, the use of azathioprine and 6-mercaptopurine has been shown to have steroid-sparing effects in three adult patients with steroid-dependant EoE [56]. However, similar to other treatments, cessation of the immunomodulator therapy resulted in recurrence of eosinophilia. Additional trials with these and other biologic agents are ongoing in adult and pediatric populations, and results are eagerly awaited.

Dietary Therapy

Since the pivotal studies by Kelly et al. [25] advocating food elimination as EoE therapy, three strategies of dietary therapy have evolved. The first is total elimination of all food allergens with elemental or amino acid–based formula. The second is a targeted elimination diet guided by allergy testing, typically skin prick testing or patch testing. The third is an empiric elimination diet removing the six most common known food groups that are triggers of EoE: soy, egg, milk, wheat, nuts, and seafood. All three approaches demonstrate symptomatic and histologic resolution in 70% to 97% of pediatric patients in uncontrolled studies [17, 26, 27]. The duration of the treatment is usually 4 to 6 weeks, followed by a reintroduction period once remission has been achieved.

Food elimination has not been widely studied in adults. Gonsalves et al. [28] conducted a prospective trial of the six-food elimination diet in 33 adult patients for a duration of 6 weeks. Patients eliminated six food groups commonly found to be triggers of EoE: milk, soy, egg, wheat, nuts, and seafood. Esophageal eosinophilia decreased after the six-food elimination diet from a mean of 36 per high power field to 2 per high power field in the proximal esophagus and from 50 per high power field to 5 per high power field in distal biopsies ($P<0.001$)[28]. Overall, 76% of patients had greater than 50% reduction in peak eosinophil count after the six-food elimination diet: 48% were reduced to less than 5 eosinophils per high power field, 61% to less than 10 per high power field, and 64% to less than 15 per high power field. Symptoms improved in 94% of patients. Endoscopic features of rings, furrows, and exudates also showed improvement. Systematic reintroduction of food groups was completed in 11 responders. In every case, the specific food trigger was identified, most commonly milk and wheat. Of note, skin testing correctly identified only 22% of culprit foods and 7 of 11 patients with identified food triggers had negative skin prick testing to all six food groups. These findings suggest that allergy testing with skin prick testing is poorly predictive of food allergy in adults with EoE.

Although an elemental formula diet has remained the "gold standard" of the available dietary options, elimination diets guided by allergy testing and empiric elimination diets have practical benefits of decreased cost, palatability, and the avoidance of nasogastric or gastrostomy tubes. However, the effectiveness of the elimination diet strategies appears to be lower than that of an elemental diet. To maximize effectiveness, elimination diet protocols require careful education of patients by a dietitian trained in

eosinophilic disorders and strict avoidance of specified foods and ingredients.

Esophageal Dilation

Esophageal dilation has been used in adult EoE patients with strictures or small caliber esophagus; however, concern exists regarding the risks. Long mucosal tears, hospitalizations for chest pain, and four cases of esophageal perforation have been reported following esophageal dilation for EoE [57, 58]. The perforations were managed conservatively without surgical repair. However, other series have shown that esophageal dilation may be performed safely. In a large series of 207 adult EoE patients treated with esophageal dilation, results led to a significant increase in esophageal diameter and to an improvement in dysphagia ($P<0.001$). After dilation, dysphagia recurred after 20 to 23 months. No esophageal perforation or major bleeding occurred. Among the patients surveyed, 74% reported retrosternal pain after dilation; however, all were agreeable to repeated dilation if required. Eosinophil peak infiltration, eosinophil load, and EoE-associated histologic signs were not significantly affected by esophageal dilation. Therefore, although esophageal dilation is highly effective in providing long-lasting symptom relief and can be performed safely, it did not influence the underlying inflammatory process [59]. Because of the possible risks described previously, esophageal dilation is generally reserved for patients with persistent dysphagia despite treatment with medical or dietary therapy [11••].

Conclusions

EoE remains an emerging clinical entity with increasing incidence in children and adults. Although clearly related to food and aeroallergens, the natural history of the disorder is unknown. Severe complications including fibrosis, narrow caliber esophagus, and stricture are well known, but predictors for which patients will develop these complications are not yet known.

The first step in the management of EoE is to properly identify the disease. Common symptoms in adults that implicate EoE are dysphagia, food impactions, heartburn, and atypical chest pain. It is important to ask patients about their allergic history including dietary allergies, dietary intolerance, asthma, or seasonal allergy in addition to any family history of these disorders or dysphagia. An endoscopy should be performed for all young patients with complaints of dysphagia. It is not necessary to perform a barium esophagram prior to endoscopy. The one caveat would be in patients with suspected small caliber esophagus. In these cases, a barium swallow may be helpful to help determine the diameter of the esophagus and help guide therapy if endoscopic dilation becomes necessary. During endoscopy for suspected EoE, multiple biopsies

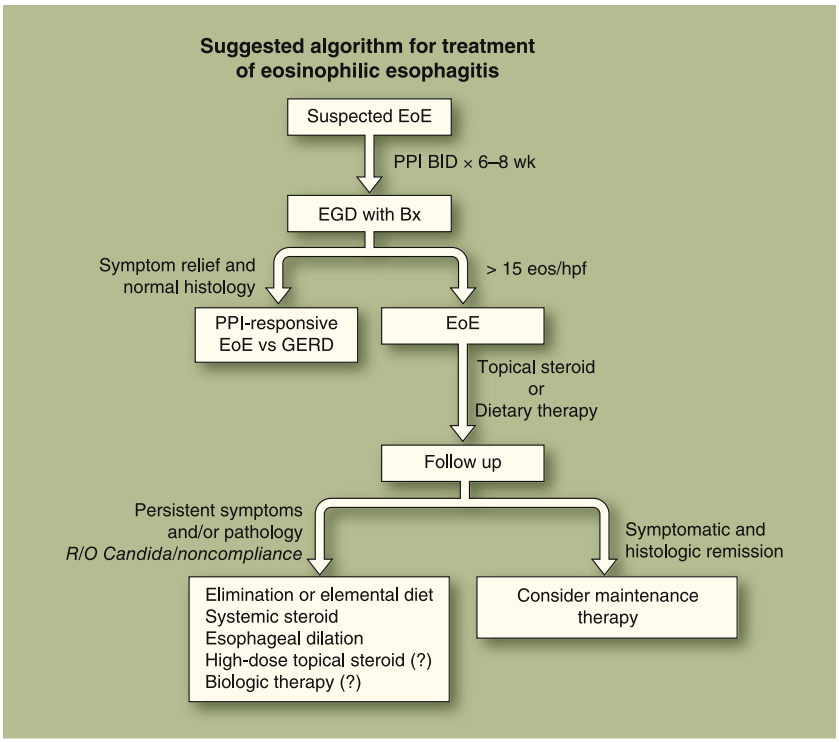


Fig. 1 Suggested treatment algorithm of patients with eosinophilic esophagitis. (*Adapted from* Hirano, et al. [60].) BID—twice daily; Bx—biopsy; EGD—esophagogastroduodenoscopy; EoE—eosinophilic esophagitis; eos/hpf—eosinophils per high-power field; GERD—gastroesophageal reflux disease; PPI—proton pump inhibitor; R/O—rule out

should be obtained at multiple levels in the esophagus, regardless of endoscopic features, due to the patchy nature of the disease. It is also helpful to alert the pathologist of your suspicion and request eosinophil counts on esophageal biopsies.

Current available treatments are effective at reducing symptoms and esophageal eosinophilia. Once esophageal eosinophilia is demonstrated, patients should undergo a 4– to 6-week trial of proton pump inhibitor therapy to see if this results in clinical or histologic improvement (Fig. 1) [60]. Alternatively, pH monitoring may be performed, but the utility of this test for predicting proton pump inhibitor–responsive EoE is unknown. If symptoms and eosinophilia persist despite proton pump inhibitor therapy, other treatment options should be pursued. Swallowed topical corticosteroids are the most commonly used treatment in adults, but dietary therapy is being investigated with promising results. Notably, the sensitivity and specificity of allergy testing to identify culprit foods have not been as promising in adults as in children. Systemic corticosteroids are reserved for severe disease refractory to other therapies. Esophageal dilation may be performed cautiously in patients with stricturing, who have not responded to dietary or medical therapy. The optimal duration of therapy is unknown and should be individualized based on disease severity and responsiveness. Expert opinion suggests that a maintenance regimen may be needed because of the recurrence rate of symptoms and eosinophilia when therapy is discontinued; however, this has not been formally studied. Although past research has provided substantial insight into the diagnosis of this unique illness, there is much to learn about the natural history, pathophysiology, and treatment outcomes. Results from ongoing investigations into these areas are eagerly anticipated.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Rothenberg ME: *Pathogenesis and clinical features of eosinophilic esophagitis.* J Allergy Clin Immunol 2001, **108**:891–894.
2. Croese J, Fairley SK, Masson JW, et al.: *Clinical and endoscopic features of eosinophilic esophagitis in adults.* Gastrointest Endosc 2003, **58**:516–522.
3. Straumann A, Spichtin HP, Grize L, et al.: *Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years.* Gastroenterology 2003, **125**:1660–1669.
4. Fox VL, Nurko S, Furuta GT: *Eosinophilic esophagitis: it's not just kid's stuff.* Gastrointest Endosc 2002, **56**:260–270.
5. Cheung KM, Oliver MR, Cameron DJ, et al.: *Esophageal eosinophilia in children with dysphagia.* J Pediatr Gastroenterol Nutr 2003, **37**:498–503.
6. Noel RJ, Putnam PE, Rothenberg ME: *Eosinophilic esophagitis.* N Engl J Med 2004, **351**:940–941.
7. Straumann A, Simon HU: *Eosinophilic esophagitis: escalating epidemiology?* J Allergy Clin Immunol 2005, **115**:418–419.
8. Prasad GA, Alexander JA, Schleck CD, et al.: *Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota.* Clin Gastroenterol Hepatol 2009, **7**:1055–1061.
9. Veerappan GR, Perry JL, Duncan TJ, et al.: *Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study.* Clin Gastroenterol Hepatol 2009, **7**:420–426, 426 e1–2.
10. Kugathasan S, Judd RH, Hoffmann RG, et al.: *Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study.* J Pediatr 2003, **143**:525–531.
11. •• Furuta GT, Liacouras CA, Collins MH, et al.: *Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment.* Gastroenterology 2007, **133**:1342–1363. *This systematic review provides a comprehensive evaluation of the current literature and evidence-based recommendations for the diagnosis and management of adults and children with eosinophilic esophagitis*.
12. Sgouros SN, Bergele C, Mantides A: *Eosinophilic esophagitis in adults: a systematic review.* Eur J Gastroenterol Hepatol 2006, **18**:211–217.
13. Assa'ad A, Putnam PE, Collins MH, et al.: *Eosinophilic esophagitis: association with allergic disorders.* Gastrointest Endosc Clin N Am 2008, **18**:119–132; x.
14. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al.: *Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis.* Gastrointest Endosc 2006, **64**:313–319.
15. Morrow JB, Vargo JJ, Goldblum JR, et al.: *The ringed esophagus: histological features of GERD.* Am J Gastroenterol 2001, **96**:984–989.
16. Zimmerman SL, Levine MS, Rubesin SE, et al.: *Idiopathic eosinophilic esophagitis in adults: the ringed esophagus.* Radiology 2005, **236**:159–165.
17. Liacouras CA, Spergel JM, Ruchelli E, et al.: *Eosinophilic esophagitis: a 10-year experience in 381 children.* Clin Gastroenterol Hepatol 2005, **3**:1198–1206.
18. Parfitt, JR, Gregor JC, Suskin NG, et al.: *Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients.* Mod Pathol 2006, **19**:90–96.
19. Aceves SS, Newbury RO, Dohil R, et al.: *Esophageal remodeling in pediatric eosinophilic esophagitis.* J Allergy Clin Immunol 2007, **119**:206–212.
20. Chehade M, Sampson HA, Morotti RA, et al.: *Esophageal subepithelial fibrosis in children with eosinophilic esophagitis.* J Pediatr Gastroenterol Nutr 2007, **45**:319–328.
21. Shah A, Kagalwalla A, Gonsalves N, et al.: *Histopathologic variability in children with eosinophilic esophagitis.* Am J Gastroenterol 2009, **104**:716–721.
22. Mishra A, Hogan SP, Brandt EB, et al.: *An etiological role for aeroallergens and eosinophils in experimental esophagitis.* J Clin Invest 2001, **107**:83–90.
23. Fogg MI, Ruchelli E, Spergel JM: *Pollen and eosinophilic esophagitis.* J Allergy Clin Immunol 2003, **112**:796–797.
24. Wang FY, Gupta SK, Fitzgerald JF: *Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children?* J Clin Gastroenterol 2007, **41**:451–453.

25. Kelly KJ, Kazenby AJ, Rowe PC, et al.: *Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula.* Gastroenterology 1995, **109**:1503–1512.
26. Kagalwalla AF, Sentengo TA, Ritz S, et al.: *Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis.* Clin Gastroenterol Hepatol 2006, **4**:1097–1102.
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**:363–368.
28. Gonsalves N, Yang G, Doerfler B, et al.: *A prospective clinical trial of six food elimination diet and reintroduction of causative agents in adults with eosinophilic esophagitis.* Gastroenterology 2008, **134**:A104.
29. Mishra A, Hogan SP, Brandt EB, et al.: *IL-5 promotes eosinophil trafficking to the esophagus.* J Immunol 2002, **168**:2464–2469.
30. Mishra A, Rothenberg ME: *Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism.* Gastroenterology 2003, **125**:1419–1427.
31. Mishra A, Wang M, Pemmaraju VR, et al.: *Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia.* Gastroenterology 2008, **134**:204–214.
32. Gupta SK, Fitzgerald JF, Kondratyuk T, et al.: *Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis.* J Pediatr Gastroenterol Nutr 2006, **42**:22–26.
33. Simon D, Marti H, Heer P, et al.: *Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases.* J Allergy Clin Immunol 2005, **115**:1090–1092.
34. Patel SM, Falchuk KR: *Three brothers with dysphagia caused by eosinophilic esophagitis.* Gastrointest Endosc 2005, **61**:165–167.
35. Meyer GW: *Eosinophilic esophagitis in a father and a daughter.* Gastrointest Endosc 2005, **61**:932.
36. Zink DA, Amin M, Gebara S, et al.: *Familial dysphagia and eosinophilia.* Gastrointest Endosc 2007, **65**:330–4.
37. • Blanchard C, Wang N, Stringer KF, et al.: *Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis.* J Clin Invest 2006, **116**:536–547. *This article describes pivotal research investigating the genetic factors behind EoE and demonstrating a signature gene-expression profile that differentiates patients with EoE from those with GERD.*
38. Lucendo AJ, Navarro M, Comas C, et al.: *Treatment with topical steroids downregulates IL-5, eotaxin-1/CCL11, and eotaxin-3/CCL26 gene expression in eosinophilic esophagitis..* Am J Gastroenterol 2008, **103**:2184–2193.
39. Bhattacharya B, Carlsten J, Sabo E., et al.: *Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease.* Hum Pathol 2007, **38**:1744–1753.
40. Wolfsen HC, Hemminger LL, Achem SR: *Eosinophilic esophagitis and Barrett's esophagus with dysplasia.* Clin Gastroenterol Hepatol 2007, **5**:A18.
41. Dranove JE, Horn DS, Davis MA, et al.: *Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia.* J Pediatr 2009,154:96–100.
42. Garrean CP, Zhang Q, Gonsalves N, et al.: *Acid reflux detection and symptom-reflux association using 4-day wireless pH recording combining 48-hour periods off and on PPI therapy.* Am J Gastroenterol 2008, **103**:1631–1637.
43. Ngo P, Furuta GT, Antonioli DA, et al.: *Eosinophils in the esophagus–peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia.* Am J Gastroenterol 2006, **101**:1666–1670.
44. Liacouras CA, Wenner WJ, Brown K, et al.: *Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids.* J Pediatr Gastroenterol Nutr 1998, **26**:380–385.
45. Arora AS, Perrault J, Smyrk TC, et al.: *Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults.* Mayo Clin Proc 2003, **78**:830–835.
46. Remedios M, Campbell C, Jones DM, et al.: *Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate.* Gastrointest Endosc 2006, **63**:3–12.
47. Lucendo AJ, Pascual-Turrion JM, Navarro M, et al.: *Endoscopic, bioptic, and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series.* Endoscopy 2007, **39**:765–771.
48. Konikoff MR, Noel RJ, Blanchard C, et al.: *A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis.* Gastroenterology 2006, **131**:1381–1391.
49. Aceves SS, Bastian JF, Newbury RO, et al.: *Topical viscous budesonide suspension for treatment of eosinophilic esophagitis.* J Allergy Clin Immunol 2005, **116**:705–706.
50. Straumann A, Felder S, Bussman C, et al.: *Budesonide as induction treatment for active eosinophilic esophagitis in adolescents and adults: A randomized, double blind, placebo controlled study (BEE-I Trial).* Gastroenterology 2008, **134**:A726.
51. Attwood SE, Smyrk TC, Demeester TR, et al.: *Eosinophilic oesophagitis: a novel treatment using Montelukast.* Gut 2003, **52**:181–185.
52. Stein ML, Collins MH, Villanueva JM, et al.: *Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis.* J Allergy Clin Immunol 2006, **118**:1312–1319.
53. Straumann A, Conus S, Grzonka P, et al.: *Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial.* Gut 2010, **59**:21–30.
54. Foroughi S, Foster B, Kim N, et al.: *Anti-IgE treatment of eosinophil-associated gastrointestinal disorders.* J Allergy Clin Immunol 2007, **120**:594–601.
55. Straumann A, Bussman C, Conus S, et al.: *Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis.* J Allergy Clin Immunol 2008, **122**:425–427.
56. Netzer P, Gschossmann JM, Straumann A, et al.: *Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission.* Eur J Gastroenterol Hepatol 2007, **19**:865–869.
57. Cohen MS, Kaufman AB, Palazzo JP, et al.: *An audit of endoscopic complications in adult eosinophilic esophagitis.* Clin Gastroenterol Hepatol 2007, **5**:1149–1153.
58. Eisenbach C, Merle U, Schirmacher P, et al.: *Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis.* Endoscopy 2006, 38(Suppl 2):E43– E44.
59. Schoepfer AM, Gonsalves N, Bussman C, et al.: *Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation.* Am J Gastroenterol 2009 (Epub ahead of print).
60. Hirano I, Gonsalves N, Ditto A: *Eosinophilic esophagitis*. In *Patterson's Allergic Diseases*. Edited by Grammer L, Greenberger P. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:633–646.

Copyright of Current Gastroenterology Reports is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.