

Eosinophilic Esophagitis: Diagnosis and Management

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KEYWORDS

- Eosinophilic esophagitis • Diagnosis • Diet • Treatment
- Fluticasone • Budesonide • Food allergy

Eosinophilic esophagitis (EoE) represents a diagnostic and therapeutic challenge to many allergists and gastroenterologists alike. This challenge is evidenced by a recent survey, which demonstrated that practicing physicians currently use a wide array of diagnostic criteria and therapeutic strategies when caring for patients with suspected EoE, many of which are admittedly not based on the published consensus guidelines at the time.¹ Because EoE is a disease characterized by tissue eosinophilia, and because most patients with EoE demonstrate sensitization to environmental or food allergens, many patients will end up in the care of an allergist. It is, therefore, important that practicing allergists be familiar with the presentation, diagnosis, and available treatment options for EoE so that they can effectively work in conjunction with gastroenterologists to optimize patient care. In this article, the authors review the clinical characteristics and endoscopic and histologic findings that define EoE and discuss various available therapies for EoE.

DIAGNOSIS

EoE is not simply a histologic diagnosis based on set number of eosinophils populating the esophageal mucosa. Rather, EoE is a chronic, immune-mediated disease that is defined by multiple criteria: (1) symptoms suggestive of esophageal dysmotility; (2) histologic evidence of eosinophilia is limited to the esophagus (and not in other

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parts of the gastrointestinal tract), where finding 15 esophageal intraepithelial eosinophils per high power field (HPF) is accepted as the minimum threshold for diagnosis; (3) the esophageal eosinophilia should remit with certain exclusion diets or topical corticosteroid therapy; and (4) the esophageal eosinophilia should not be responsive to proton pump inhibitor (PPI) therapy alone.² With these criteria established, one can now examine the typical presentation, endoscopic appearance, and histologic findings that are typically associated with EoE.

Clinical Presentation

The classic, on-paper case presentation for EoE is that of a Caucasian man in his second or third decade of life who presents with dysphagia or food impaction. The reality is that EoE has a diverse clinical presentation. Although there is a male predominance of 2:1 to 3:1, EoE can present in all age groups.^{3,4} Racial disparity is also described, with most patients being white, non-Hispanic. It is not yet clear, however, if this finding is simply the result of referral patterns to various reporting centers or caused by a genetic predisposition to the disease. In fact, a relatively recent study conducted at a US-based military medical center revealed a larger percentage of African American patients with EoE than previously reported.⁵ However, there is current evidence that EoE has a strong familial association.^{3,6} Based on a population prevalence for EoE of 5 per 10,000 people, the sibling recurrence ratio for EoE is estimated at around 80. By comparison, the ratio is around 2 for other atopic diseases, such as asthma.⁷

Symptoms

Age-related differences in presenting symptoms are noticed with EoE. In the pediatric population, patients with EoE typically present with abdominal pain; gastroesophageal reflux symptoms, including nausea and vomiting; and, at times, failure to thrive.^{4,8} Discerning EoE from acid-induced gastroesophageal reflux disease (GERD) by symptoms alone can be difficult, although dysphagia and early satiety/anorexia in children seem to be more commonly seen in EoE than in GERD.^{9,10} In infants and younger children, symptoms can be hard to delineate, and the disease may simply manifest as feeding difficulties, such as food refusal and gagging with foods.¹¹

In the adult population, symptoms are slightly better defined, with dysphagia and heartburn/chest pain being the most common presenting symptoms.^{4,12} In fact, when examining a cohort of patients with refractory reflux-type symptoms, dysphagia was the lone symptom that predicted EoE rather than GERD.¹³ When one looks at cohorts of patients referred for endoscopy for the complaint of dysphagia, 12% to 15% of those patients were eventually diagnosed with EoE.^{14,15} Thus, in adult patients presenting with dysphagia, EoE should be strongly considered in the differential diagnosis.

Perhaps the most concerning, and clearly the most urgent, symptom of EoE is food impaction, which can be the presenting symptom for some adults. In studies examining cohorts of patients with solid food impaction requiring endoscopic removal, approximately 50% of these patients were later identified as having EoE.^{16,17} Whether food impaction is a common long-term complication for all patients with EoE, however, is difficult to assess. A recent survey-based follow-up study of a large population of patients with histologic evidence consistent with EoE demonstrated that at least self-reported food impaction is common in these patients, with an incidence as high as 40% at a median follow-up of 15 years.¹⁸

Endoscopic Findings

Various esophageal endoscopic abnormalities exist in patients with EoE. These abnormalities include esophageal rings (resulting in an appearance referred to as esophageal trachealization), whitish exudates or plaques, linear furrows, edema, and esophageal narrowing or strictures (**Fig. 1**). When present, these findings can be predictive of EoE^{10,12,19} but are not pathognomonic for the disease. In fact, in 2 studies examining endoscopy and biopsy results for all patients referred for dysphagia, only 34% to 38% of the patients with the previously mentioned endoscopic findings were found to have histologic evidence of EoE; and in one of the studies, 10% of those patients with histologic evidence of EoE had a normal-appearing esophagus on endoscopy.^{14,15} Thus, although EoE will typically demonstrate characteristic findings of esophageal disease on endoscopy, these are not diagnostic alone.

Histologic Findings

Number of eosinophils

Given the range of symptoms and endoscopic findings in EoE, histologic examination of esophageal tissue must be performed before a diagnosis of EoE can be established (**Fig. 2**). A simple quantitative assessment of the number of eosinophils per HPF in hematoxylin-eosin-stained esophageal tissue sections is helpful in establishing the

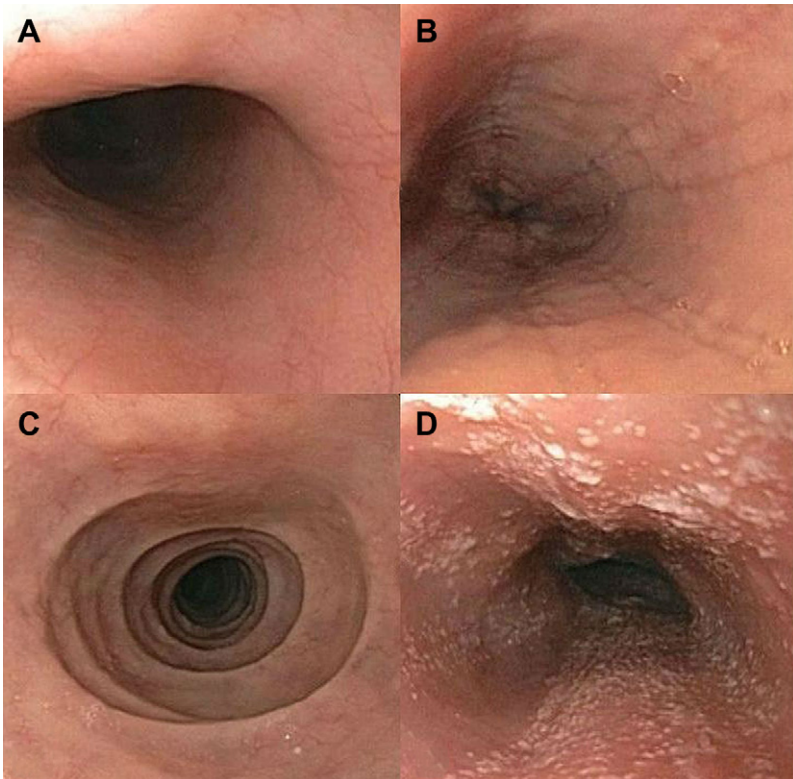


Fig. 1. Endoscopic findings in EoE. (A) Normal esophagus, (B) linear furrows, (C) esophageal rings, (D) white plaques.

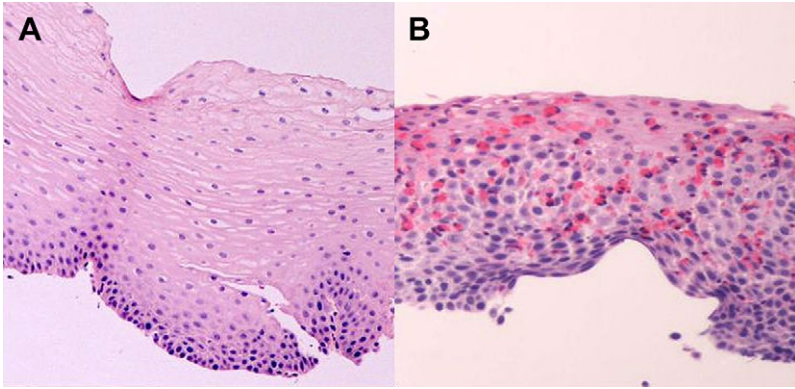


Fig. 2. Sections from endoscopically obtained esophageal biopsies (hematoxylin-eosin, original magnification $\times 200$). (A) Esophageal epithelium in a healthy individual. (B) Esophageal epithelium in a patient with EoE.

diagnosis. The presence of at least 15 eosinophils per HPF in the maximally affected esophageal tissue samples is considered diagnostic.² This number, however, is not 100% specific for EoE because many other conditions can result in significant esophageal eosinophilia, especially severe GERD. Recent studies have shown that 39% to 75% of patients with esophageal eosinophilia (>15 per HPF) have resolution of their pathologic condition with PPI therapy alone.^{20–22} Therefore, one needs to rule out PPI-responsive esophageal eosinophilia before diagnosing patients with EoE. This practice is typically done by an empiric therapy with a PPI at a high dose for 8 to 12 weeks before obtaining biopsies. An alternative to PPI therapy to rule out GERD is acid pH monitoring, but this procedure can be cumbersome and has limitations.²³

When using the number of eosinophils as the histologic diagnostic criterion for EoE, one notices that a variety of methods have been used when establishing this value across studies and, therefore, not all data is comparable.^{24,25} For example, using the average rather than the peak number of eosinophils per HPF may lead to a lower reported number of eosinophils per HPF. Variation in the number of endoscopic biopsies evaluated can also result in a different eosinophil count because EoE is a patchy disease, therefore, a lower number of biopsies may result in a lower sensitivity for diagnosis.²⁶ Finally, wide variations in the size of the high power field among microscopes have been reported, also affecting eosinophil counts.²⁴

It should be noted that symptom severity does not seem to correlate with the extent of esophageal eosinophilia (ie, higher esophageal eosinophil counts do not translate to worse symptoms). Dysphagia is the only symptom that has been shown to have a positive correlation with the absolute number of esophageal eosinophils, although no validated symptom scores for EoE yet exist to evaluate this issue in depth.^{9,27}

Other histologic markers

Given that quantitative assessment of eosinophils is not absolute in defining EoE, several studies have looked into additional histologic markers to better identify EoE. Pathologic changes, such as eosinophilic microabscesses and severe basal zone hyperplasia, are seen more often in tissue specimens from patients with EoE as compared with controls (including patients with GERD) and, therefore, can help distinguish EoE from other causes of esophageal eosinophilia.^{28,29} Many studies have shown increases in extracellular staining of eosinophilic granules, such as major basic

protein, eosinophil-derived neurotoxin, and eosinophil peroxidase, in patients with EoE as compared with healthy and GERD controls, suggesting that eosinophils may not merely be innocent bystanders in the disease process.^{30–32} This eosinophilic degranulation likely plays a role in the development of subepithelial esophageal fibrosis, a long-term complication of EoE, and itself acting as a marker that, if present, also suggests a diagnosis of EoE over GERD.^{33–35}

The examination of other cell types has shown that esophageal biopsies from patients with EoE have increased numbers of mast cells and increased tryptase staining in the esophageal epithelium^{34,36–38} as well as increased lymphocytes.³⁹

ALLERGY EVALUATION

It is thought that EoE is caused by multiple food allergens, based on several short-term studies resulting in disease remission in response to dietary eliminations.^{40–42} The immunologic reaction underlying the role played by food antigens is thought to be a mix of immunoglobulin E (IgE)-mediated and non-IgE (cell mediated) hypersensitivity responses.⁴⁰ Results from skin prick testing (SPT) and atopy patch testing (APT) may help to identify foods that contribute to the disease process, and removal of identified foods can be an effective treatment,^{43,44} although the sensitivity of these tests seems to be lower for foods not known to be common allergens (Table 1), rendering skin testing as a tool for guiding therapy no more effective than empiric elimination of common food allergens.^{42,43}

In addition, prolonged avoidance of a food to which patients were sensitized but were previously ingesting without clinical reactions can result in the occurrence of systemic reactions on reintroduction of that food into the diet.^{45,46} Therefore, if treating patients with an elimination or elemental diet, SPT or serum IgE testing may be advisable before reintroduction of foods to which sensitization was present, to better predict if patients are at risk for IgE-mediated clinical allergic reactions with the reintroduction of these foods.

Table 1 Predictive values of SPT and APT in causing esophageal eosinophilia						
Food	SPT		APT		SPT + APT	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Milk	96	58	83	59	92	41
Egg	85	75	78	83	85	88
Soy	70	69	67	87	74	93
Wheat	78	65	74	84	77	90
Corn	57	71	66	94	63	93
Beef	82	75	94	87	85	93
Chicken	50	83	67	96	63	99
Rice	50	86	59	97	61	100
Potato	60	90	54	95	61	97
Peanut	78	98	75	98	71	100
Oat	33	90	47	99	50	100
Barley	43	91	90	99	73	100

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
Data from Spergel JM, Brown-Whitehorn T, Beausoleil JL, et al. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. J Allergy Clin Immunol 2007;119(2):509–11.

As for other allergic diatheses, most pediatric and adult patients with EoE have allergic rhinitis, asthma, atopic dermatitis, or food allergies and evidence of sensitization to multiple environmental or food allergens.^{47,48} Although it is unclear if there is any causal effect of sensitization leading to EoE or vice versa, there at least seems to be a seasonality associated with EoE diagnosis, possibly suggesting some role for aeroallergens in the disease.^{49–51} Because of the high incidence of concomitant allergic diatheses seen in patients with EoE, allergy evaluation to help manage these conditions is warranted in all patients with EoE.² Testing for respiratory allergies is not likely to alter the management or natural history of EoE, however, because treatment of allergic respiratory diseases has not been shown to effect EoE outcomes, although this has never been formally studied. This conclusion is in contrast to information obtained from food allergy testing, which may have an impact on EoE treatment and outcome.

TREATMENT

Current therapy goals in EoE include symptom improvement, improved quality of life, and resolution of esophageal eosinophilia. Although not all of these outcomes have been rigorously examined in well-designed trials, there are several reports on the outcomes of various therapies. When extrapolating the results of these studies into clinical practice, one should note that most data are generated from short-term studies, and there are very little data from long-term trials.

Dietary Therapy

Elemental diet

The first case series of patients displaying a clinical picture of non-GERD esophageal eosinophilia was so defined by the clinical and histologic response to an elemental diet (despite failure to respond to acid suppression therapy or Nissen fundoplication).⁴⁰ Applying the current definition of EoE, it is clear that the group of patients in that case series would be diagnosed with EoE. Subsequent, larger, retrospective studies in children confirmed that an elemental diet was effective in treating EoE in up to 97% of patients. The elemental diet consisted of complete elimination of dietary antigens and using an amino acid–based formula instead. Children were also allowed water and a single fruit, either grape or apple, and its juice.^{3,41} This dietary regimen, although effective, can be difficult to adhere to given its obvious dietary restrictions and the requirement for ingestion of large volumes of formula to meet caloric needs. In fact, in some patients, nasogastric or gastrostomy tubes must be placed to allow for adequate caloric intake.

Elimination diet

Dietary elimination of certain food allergens is an alternative to an elemental diet that allows patients to consume a larger variety of foods and, thus, is more lenient in its restrictions and may be more attractive for older children and adults. In designing the elimination diet, one can either restrict proteins based on allergy testing or simply restrict the most common food allergens. No randomized, prospective trials yet exist comparing the two elimination methods. However, retrospective studies have generated data regarding both methods. With elimination of foods that test positive by SPT and APT, one could see improvement in esophageal eosinophilia in up to 77% of patients, whereas the elimination of the most common food allergens (cow's milk, soy, wheat, egg, peanut, tree nuts, and seafood) led to improvement in eosinophilia in 74% of patients in one report.^{42,43} Although these elimination diets may offer a better lifestyle over an elemental diet, the elemental diet seems to have a greater success

rate in improving symptoms and esophageal eosinophil numbers in retrospective studies comparing both methods.^{3,42}

When disease remission is achieved with a dietary restriction, it is advisable to gradually reintroduce foods into the diet of patients with EoE, keeping those that do not result in disease relapse in the patients' diet. This practice may contribute in improving the quality of life of patients with EoE and in preventing the rare possibility of loss of tolerance to those foods from an immediate reactivity standpoint, as previously explained. A report by Spergel and colleagues⁴⁴ provides some insight on the utility of testing in deciding which foods are likely to result in relapse of esophageal eosinophilia based on SPT and APT results (see [Table 1](#)). In sum, when food reintroduction is attempted, the likelihood of a food leading to an IgE-mediated reaction or relapse of esophageal eosinophilia, the nutritional value of the food, and the desirability of the food to patients need to be taken into account. Avoidance of some antigens may need to be continued indefinitely.

Given the complexity of dietary elimination diets and the possibility of caloric restriction and elimination of key nutrients, it is strongly recommended to consult with a dietitian with expertise in food allergies to supervise the process. The dietitian can provide patients with EoE with education on proper avoidance of food allergens, aid in dietary adherence, and prevent potential nutritional deficiencies.

Pharmacologic Therapy

Oral corticosteroids

As with most eosinophilic diseases, oral steroids improve esophageal eosinophilia and symptoms in patients with EoE.^{3,52} Unfortunately, because disease relapse is common within less than 6 months following the cessation of the oral steroids and because of the established adverse effects of long-term treatment with systemic steroids, oral steroids are typically used only in severe cases. When required, the recommended dose is 1 to 2 mg/kg of prednisone equivalent.²

Topical corticosteroids

Topical corticosteroids were first reported as a treatment of EoE in a case series of 4 patients in 1998, and have since become a mainstay of treatment of EoE.⁵³ The first randomized, double-blind, placebo-controlled trial of topical steroids for EoE showed the superiority of swallowed fluticasone propionate over placebo in inducing histologic remission.⁵⁴ The treatment induced full remission in 50% of the patients in the active arm. The treatment effect of fluticasone was even more impressive in the only comparative trial to date of a topical steroid versus oral prednisone.⁵⁵ In that trial, 80 pediatric and adolescent subjects were randomized to either swallowed fluticasone ($n = 40$) or oral prednisone ($n = 40$) for 4 weeks. Histologic improvement was seen in 94% of the subjects in both groups, although to a greater degree in the prednisone group; symptom resolution was seen in all subjects in the prednisone group and in 97% of the subjects in the fluticasone group at week 4 of therapy.⁵⁵ In addition, one prospective trial examined both topical fluticasone and dietary therapy. In that study, fluticasone seemed to be more effective in resolving esophageal eosinophilia than dietary therapy.⁵⁶

Swallowed budesonide, another form of topical corticosteroids, has also been shown to be effective in pediatric and adult patients with EoE using randomized, double-blind, placebo-controlled trials.^{57,58} In the pediatric study,⁵⁷ budesonide suspension was mixed with sucralose to make a slurry termed oral viscous budesonide, which was swallowed. With this preparation, 87% of the subjects in the active arm achieved histologic resolution (defined as <7 eosinophils per HPF on follow-up

esophageal biopsies), whereas none of the subjects in the placebo arm achieved resolution. Mean symptom scores and endoscopy scores also improved to a greater degree in those receiving viscous budesonide as compared with placebo. In the adolescent and adult study,⁵⁸ the budesonide suspension was nebulized and swallowed. Results from this trial showed at least some histologic response in 89% of the subjects and complete resolution in 72% in the active arm versus 11.1% disease resolution in the placebo arm. In addition to the resolution of eosinophilia and symptom improvement, topical steroid therapy has also been shown to reverse sub-epithelial fibrosis.⁵⁹

Unfortunately, as seen with oral steroids, the therapeutic effect of topical steroids on the disease is abolished following cessation of treatment. In a 3-year follow-up study, 91% of patients reported recurrence of symptoms at an average of 9 months after receiving a 6-week treatment of swallowed fluticasone.⁶⁰ Even with a low-dosage (0.25 mg twice daily) maintenance regimen of budesonide, esophageal eosinophilia and associated symptoms can return.⁶¹ Therefore, patients may have to continue on therapeutic dosages for an indefinite amount of time. Currently, ongoing trials continue to study fluticasone, budesonide, and beclomethasone. Published dosing for both topical steroids is outlined in **Table 2**.

Although not studied in depth, the observed adverse effects of topical steroids tend to be mild in general. In the one trial comparing topical fluticasone with prednisone,⁵⁵

Table 2 Reported doses for topical corticosteroids for EoE from prospective studies		
Study	Study Design and Number of Patients	Medication and Dosage^a
Teitelbaum et al, ⁵⁶ 2002	Open label, prospective N = 13	Fluticasone propionate 2 puffs twice daily: Age 2–4 y: 44 mcg/puff Age 5–10 y: 110 mcg/puff Age >10 y: 220 mcg/puff
Konikoff et al, ⁵⁴ 2006	RDBPC N = 36	Fluticasone propionate 2 puffs twice daily: All subjects received 220 mcg/puff Ages ranged from 3–16 y
Schaefer et al, ⁵⁵ 2008	Open label, randomized N = 80	Fluticasone propionate 2 puffs 4 times daily: Age 1–10 y: 110 mcg/puff Age >10 y: 220 mcg/puff
Dohil et al, ⁵⁷ 2010	RDBPC N = 24	Oral viscous budesonide ^b Subjects <5 ft tall: 1 mg daily Subjects >5 ft tall: 2 mg daily Age range was 1–17 y
Straumann et al, ⁵⁸ 2010	RDBPC N = 36	Swallowed nebulized budesonide All subjects received 1 mg twice daily All subjects were aged >16 y

Abbreviation: RDBPC, randomized, double blind, placebo controlled.

^a All subjects were instructed to swallow medications and not to eat/drink for 30 minutes after treatment.

^b Oral viscous budesonide = 10 g sucralose added per 1 mg budesonide suspension.

40% of the subjects in the prednisone arm developed systemic adverse effects of steroid therapy compared with none in the fluticasone arm. Topical fluticasone led, however, to candidal overgrowth in the esophagus in 15% of the fluticasone-treated subjects. A similar degree of candidal overgrowth was also seen in trials with budesonide (16.7%).⁵⁸ However, this may be a dose-related phenomenon, as in a long-term treatment study whereby patients treated with 0.5 mg of swallowed budesonide daily for 50 weeks did not show any evidence of fungal or viral esophageal infection.⁶¹

Other pharmacologic therapies

Because interleukin (IL)-5 is a known inducer of eosinophil proliferation and activation, and with the success of anti-IL-5 in lowering blood eosinophilia in other hypereosinophilic syndromes, it stands to reason that anti-IL-5 could be a useful therapy for patients with EoE. The first anecdotal evidence for this was published in 2004 in a case series of patients with various forms of eosinophilia, one of whom was an 18-year-old patient with EoE nonresponsive to steroid therapy.⁶² In that case, mepolizumab led to a 10-fold decrease in the mean number of esophageal eosinophils with improvement in symptoms. This finding led to an open-label study 2 years later in 4 adult patients that once again showed a decrease in mean and maximum esophageal eosinophil numbers and an improvement in symptoms after 3 monthly infusions.⁶³ This study was followed by the first double-blind, placebo-controlled trial of mepolizumab, published in 2010.⁶⁴ In this study, 11 adult patients were randomized to mepolizumab ($n = 5$) or placebo ($n = 6$). Although the active treatment led to a greater decrease (54%) in mean esophageal eosinophil counts when compared with placebo (5%), the complete resolution of esophageal eosinophilia was not seen in any subject. In addition, no significant difference in symptom improvement was seen between the 2 groups. Larger multicenter trials using anti-IL-5 (mepolizumab and reslizumab) are currently ongoing, the final results of which are not yet published.

Other biologic agents that are currently under investigation for the treatment of EoE include anti-tumor necrosis factor (TNF) agents and anti-IgE therapy (omalizumab). There is currently one case series reporting the use of an anti-TNF agent (infliximab) in EoE in 3 adult patients refractory to steroids.⁶⁵ In this limited study, one patient had partial histologic response, another had no change, and the third had an increase in esophageal eosinophilia. There are currently no published studies to date using omalizumab; however, there is a single case report of 2 atopic patients with EoE who had symptom improvement with omalizumab but no improvement in endoscopic or histologic findings.⁶⁶

Given that cysteinyl leukotrienes are known eosinophil chemoattractants, leukotriene antagonists seemed to be an attractive therapeutic option for EoE. One early study reported that montelukast at a dosage of 20 to 40 mg daily resolved symptoms in 6 out of 8 adult patients with EoE, but tissue eosinophilia remained.⁶⁷ Since that pilot study, studies examining cysteinyl leukotriene levels in esophageal biopsies have found them not to be increased in patients with EoE, and montelukast has recently been shown to be ineffective in maintaining histologic and clinical remission induced by fluticasone.^{68,69}

Esophageal Dilation

Esophageal dilation can be an effective treatment of dysphagia, especially when this is caused by strictures. Although an in-depth review of the techniques, outcomes, and complications is beyond the scope and goal of this review, it is clear that the procedure can provide clinically significant symptomatic relief in up to 83% of patients, which can last for an average of 20 months.^{70,71} Complications include chest pain

(~4%), deep mucosal tears (3%–9%), and rarely perforation (0%–1%).^{70,72} The disadvantage of this therapy option is that it does not address the underlying esophageal inflammation, therefore, resulting in stricture recurrence.

SUMMARY AND KEY POINTS

EoE represents a clinicopathologic disease that is best managed by a team of health care providers, including gastroenterologists and allergists. With updated consensus recommendations available,² providers now have a resource to guide them in accurately diagnosing and effectively treating this disease. The following are some key points regarding this:

- The diagnosis of EoE should be made when there are symptoms suggestive of esophageal dysmotility in conjunction with evidence of esophageal eosinophilia despite adequate acid suppression (either with adequate PPI therapeutic trial or with evidence of a normal esophageal pH).
- A peak count of 15 intraepithelial eosinophils per HPF in an esophageal biopsy section is accepted as the minimum value to diagnose EoE.

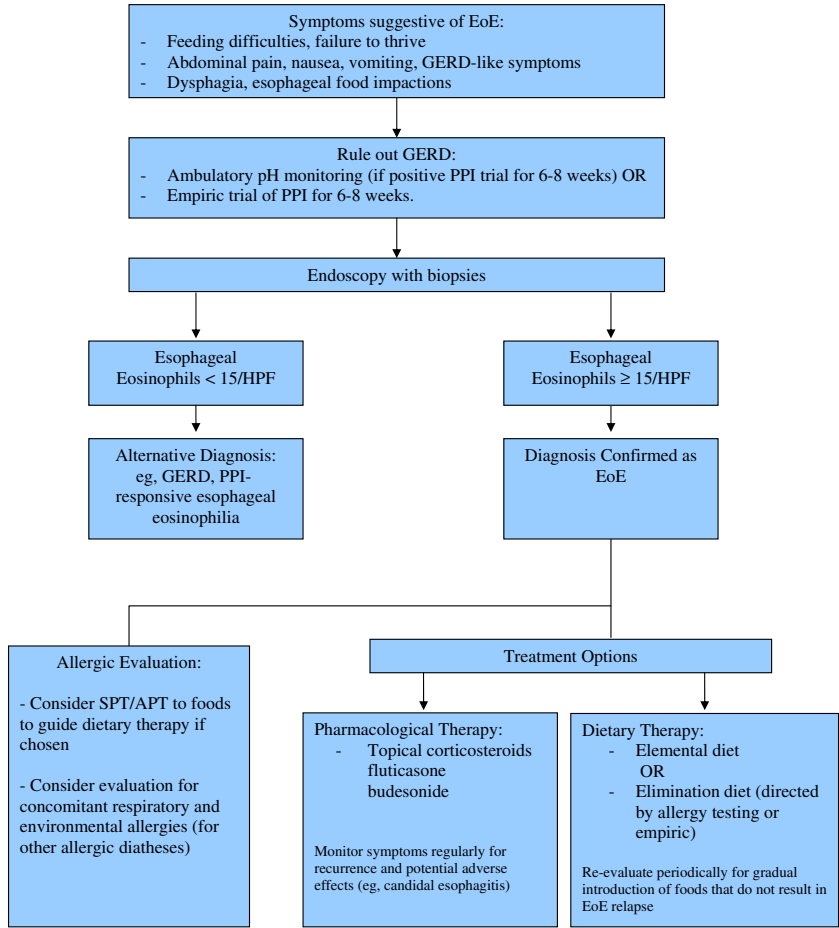


Fig. 3. Proposed approach for diagnosis and management of patients suspected to have EoE.

- Characteristic findings on endoscopy include esophageal rings, whitish exudates or plaques, linear furrows, edema, and esophageal narrowing. These findings, however, are not specific for EoE, and up to 10% of cases of EoE can have a normal-appearing endoscopy.
- Allergic evaluation is appropriate for all patients with EoE given the high prevalence of concomitant atopic disease. Although testing for food allergy may alter management decisions, there are no data to suggest that aeroallergen testing or treatment of respiratory allergy can alter disease.
- There are no Food and Drug Administration–approved treatments for EoE. However, various dietary therapies (amino acid–based formula, dietary restriction based on positive allergy testing, and empiric restriction of common food allergens) and topical corticosteroids have all been shown to be effective and are accepted therapies for the disease. Other therapies (eg, oral steroids and anti-IL-5) have been shown to be effective but should now be limited to refractory disease or investigational studies.
- A proposed algorithm for diagnosis and treatment of patients with EoE can be seen in **Fig. 3**.

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