Current Diagnostic and Treatment Strategies for Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus diagnosed by the presence of esophageal symptoms accompanied by an esophageal eosinophilic infiltrate. EoE has an increasing worldwide prevalence and can be a cause of dysphagia and food impactions. There is an important role for the use of proton pump inhibitors in the diagnostic pathway of EoE. Treatment paradigms for EoE aim to minimize esophageal inflammation and improve symptom control. Dietary therapy targets dietary allergens and encompasses the elemental diet, the allergy testing–directed elimination diet, and the empiric elimination diet. Pharmacologic options include topical corticosteroids as the standard first-line treatment. Multiple other pharmacologic interventions are currently under investigation and are not recommended in the most recent guidelines. Endoscopic dilation is usually reserved for patients who relapse on pharmacologic or dietary regimens or who have symptomatic stricturing disease. This article provides a comprehensive discussion of existing diagnostic and management strategies for EoE.

Keywords
Eosinophilic esophagitis, dysphagia, dietary therapy, corticosteroids, proton pump inhibitors

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus with increasing worldwide prevalence. The disease is characterized by an eosinophilic infiltrate in the esophageal epithelium with associated esophageal symptoms. Both genetic and environmental factors are thought to play a role in the disease pathogenesis. Malignancy has not been found to be associated with EoE.[1]

Treatment paradigms have been evolving with an increasing understanding of the disease process. The goals of therapy focus on minimizing esophageal inflammation and improving symptom control. Management options range from dietary and pharmacologic interventions to endoscopic treatment. This article provides a comprehensive discussion of existing diagnostic and management strategies for EoE.

Epidemiology

Since EoE was first reported in the literature in 1978, the disorder has been increasingly recognized in both pediatric and adult populations.[2] Population-based studies of EoE epidemiology show large heterogeneity based on study methodology and geographic location.[3] A 2016 meta-analysis estimated a worldwide pooled incidence of 3.7 per 100,000 persons per year and a pooled prevalence of 22.7 cases per 100,000 persons.[4] Both incidence and prevalence were noted to be higher in adults than in children. In adults, the disorder is most commonly diagnosed during the third decade of life.[5,6] Other studies have found prevalence to be as high as 56.7 per 100,000 persons in the United States, equivalent to 152,152 cases.[7] Men are more commonly affected, with an estimated 3-fold higher prevalence compared to women.[4,6] The disease is also present predominantly in white patients, who comprise 84% of affected individuals.[8,9] Furthermore, studies have noted an association with cold and arid climates as well as urban areas.[10,11]

In addition to environmental factors, the disease pathogenesis is influenced by genetic susceptibility. Genome-wide association studies have identified specific genetic EoE-risk loci, several of which are associated with a variety of allergic conditions.[12] Family studies have estimated the overall risk of developing EoE to be 41% in monozygotic twins, 22% in dizygotic twins, and 2.4% in siblings, all higher than in the general population.[13] Future directions in genetic analysis aim to describe molecular mechanisms and build genetic risk models on the individual level.[14]

Diagnosis

Clinical Symptoms

The diagnosis of EoE relies on the combination of esophageal symptoms, endoscopic features, and an eosinophilic infiltrate on histology. Symptoms of EoE vary significantly by age, particularly within the pediatric population. The symptoms themselves, however, rarely change from the time of symptom onset to the time of diagnostic endoscopy.[15] Infants and toddlers most commonly present with maladaptive feeding behaviors, whereas vomiting, abdominal pain, and gastroesophageal reflux dominate later in childhood.[16] In contrast, dysphagia and food impactions are the most common presenting symptoms during the teenage years.[15,17] For adults, the most common presenting symptom is dysphagia.[18] Among patients presenting for an evaluation of dysphagia, EoE has been identified as the etiology in 12% to 15% of cases.[18] The underlying mechanism of this phenomenon is the suspected progression from esophageal inflammation to fibrostenotic changes.[19] Esophageal remodeling and deposition of subepithelial fibrous tissue lead to alterations in esophageal motility and stricture formation. Food impaction, the most extreme manifestation of dysphagia, is caused by EoE in half of reported cases, more than any other condition.[20,21]

Physicians should take a comprehensive history of upper gastrointestinal symptoms and inquire about eating habits. A detailed record of prior food impactions and therapeutic endoscopic interventions should also be obtained. Of note, many patients develop adaptive feeding mechanisms such as prolonged chewing and extended meal time to cope with their underlying EoE symptoms. Given the close association with allergic disease, patients should be evaluated for concomitant atopic dermatitis, asthma, and food allergies.[22]

Multiple groups have developed potential instruments to clinically assess EoE symptoms, including the Dysphagia Symptom Questionnaire, Eosinophilic Esophagitis Activity Index Patient-Reported Outcome Score, and the Pediatric Eosinophilic Esophagitis Symptom Score.[23-25]

Endoscopic Evaluation

The goals of endoscopy are to rule out alternative diagnoses, evaluate for distinctive endoscopic features, and obtain biopsies for histologic analysis. Characteristic endoscopic findings include linear furrows, concentric rings, strictures, white exudates, and a decreased vascular pattern (Figure). Linear furrows run longitudinally along the esophageal wall, whereas rings are located horizontally and are commonly referred to as trachealization.[26] The white exudate is composed of eosinophilic microabscesses, which can be confirmed on histology.[27] Studies have shown that exudates, furrows, and edema correlate with inflammation, and rings and stricturing reflect fibrotic remodeling.[28,29]

Other esophageal abnormalities have been described, including feline esophagus (transient concentric rings that disappear with insufflation), narrow caliber esophagus, and crepe paper esophagus defined by mucosal fragility.[1,30] Differences have been noted in endoscopic features between adults and children, with the latter more often having a normal-appearing esophagus.[31]

The Eosinophilic Esophagitis Endoscopic Reference Score was developed to standardize endoscopic assessment.[32] The score utilizes the 5 major endoscopic EoE features and has been applied both at the time of diagnosis as well as to monitor symptoms.[33] Follow-up studies have noted variable results of the score's ability to predict histologic activity and remission, and have concluded that endoscopic findings alone cannot be used to define an EoE diagnosis.[34,35]

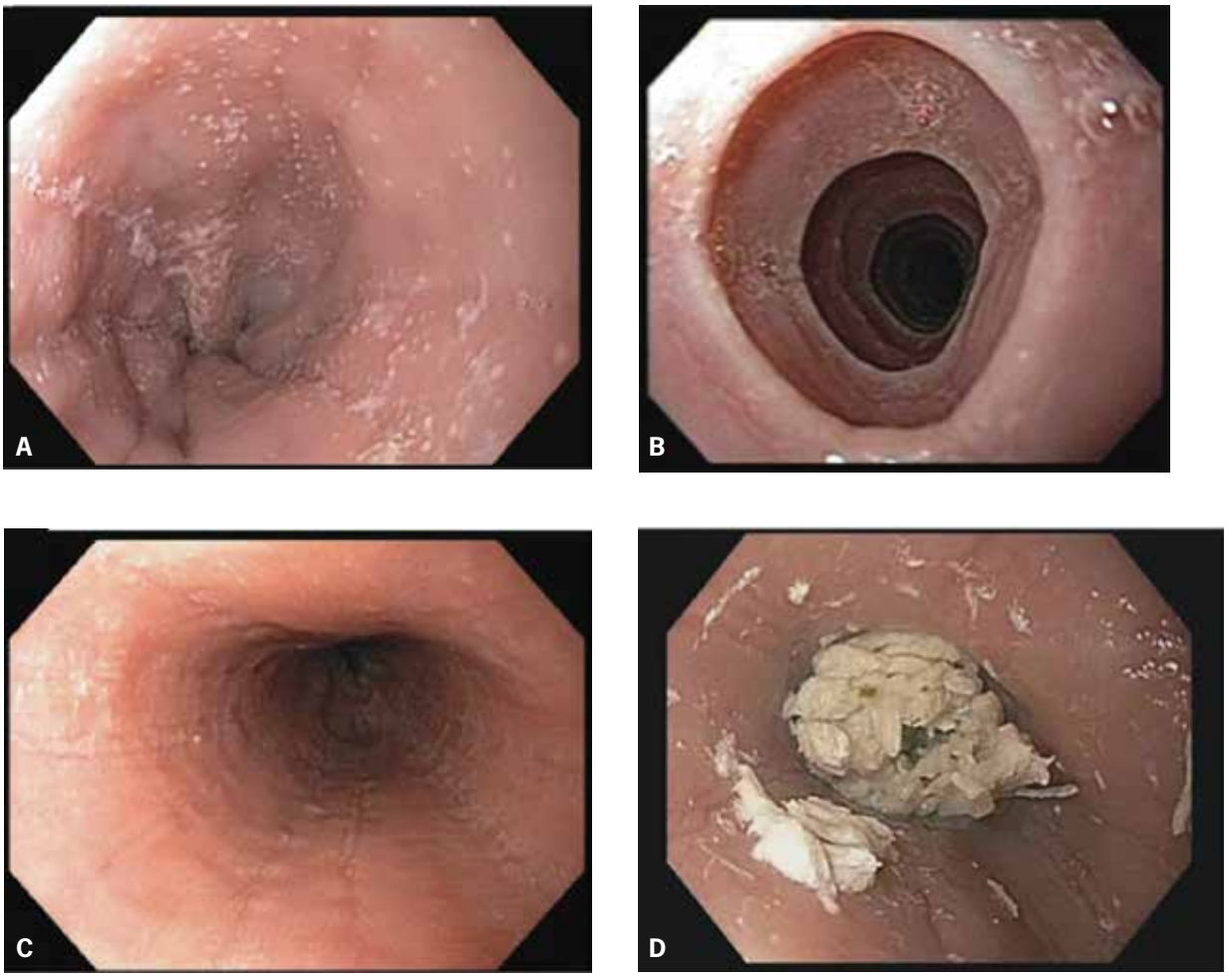

Figure. Endoscopic images of patients with eosinophilic esophagitis showing white specks of esophageal mucosa consistent with eosinophilic microabscesses (**A**), ringed appearance of the esophagus (**B**), linear furrowing of esophageal mucosa (**C**), and esophageal food impaction (**D**).

Histologic Evaluation

Patients with EoE have an increased eosinophil burden on histologic examination of biopsied tissue. Eosinophils are typically absent in the esophagus; thus, eosinophilic infiltration of the esophagus signifies pathology.[36] However, the presence of esophageal eosinophils alone is not diagnostic of EoE, as several other conditions lead to eosinophil-mediated esophageal inflammation. Secondary esophageal eosinophilia has a wide differential diagnosis, including gastroesophageal reflux disease (GERD), eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, celiac disease, Crohn's disease, achalasia, graft vs host disease, infection, and drug hypersensitivity.[26]

The discovery of 15 or more eosinophils in at least 1 microscopic high-power field of both the proximal and distal esophageal epithelium is suggestive of an EoE diagnosis, but similar to clinical and endoscopic features, this alone cannot confirm EoE.[29] This threshold is applied to both adult and pediatric patients. To obtain adequate tissue sampling, guideline recommendations advise acquiring 2 to 4 biopsies of both the distal and the proximal esophagus.[37] Gastric and duodenal biopsies in asymptomatic patients are not routinely recommended.[29]

All patients found to have 15 eosinophils per high-power field on biopsy who have not undergone a trial of proton pump inhibitor (PPI) therapy are recommended to initiate this treatment.[38] Given that GERD is the most common etiology of secondary esophageal eosinophilia, PPI treatment of GERD will likely result in improved GERD symptoms and a decreased number of eosinophils.[39] Patients with a classic EoE presentation in whom GERD is excluded but who have a positive histologic response to PPI therapy are termed to have PPI-responsive esophageal eosinophilia (PPI-REE).[40] There is ongoing

debate on whether PPI-REE is a subtype of EoE or its own disease, and its natural history is unclear; therefore, further research is needed to define this disease entity.

Other Diagnostic Studies

To date, no serologic markers have been identified in EoE to aid in either diagnosis or treatment monitoring. Both serum immunoglobulin (Ig) E levels and peripheral eosinophilia are frequently elevated in EoE patients, but neither has adequate sensitivity and specificity to utilize in clinical practice.[41,42] It is unclear whether these markers correlate with EoE-associated allergic diatheses or with EoE itself.

EoE-related inflammation and fibrosis impact esophageal function; however, there is no existing role for esophageal manometry in the diagnostic algorithm. Studies have not revealed distinct motility patterns, and manometric findings have not been observed to correlate with endoscopic features or with symptoms.[43] A recent study of high-resolution manometry in EoE patients undergoing corticosteroid therapy also did not identify clear manometric parameters for treatment monitoring.[44]

Other measurements of esophageal inflammation are being investigated, as endoscopy with esophageal biopsies is the current diagnostic standard of care. Furuta and colleagues reported that esophageal mucosal biopsies contain a high number of eosinophil granule proteins and developed a mechanism by which to obtain and measure these proteins using the Esophageal String Test (EnteroTrack).[45] This study in children with EoE found that the quantity of the eosinophil-derived proteins correlated with mucosal inflammation.[45] Other researchers have examined the role of the Cytosponge (University of Cambridge) as a minimally invasive way to collect esophageal tissue in EoE patients.[46] This study found the sponge to be a well-tolerated method, and that the number of collected eosinophils correlated with endoscopic biopsy findings.[46] Further research is needed to expand our knowledge of the efficacy of these methods before they can become a routine part of clinical practice.

The Endoluminal Functional Lumen Imaging Probe (EndoFLIP, Crospon Medical Devices) has been utilized in EoE to evaluate esophageal mechanical properties.[47] However, given the limited data, diagnostic and treatment decisions are not recommended to be based on EndoFLIP findings.[48] Radiographic studies are also not recommended to aid in diagnosing EoE, although barium radiography does have a limited utility in EoE patients for closer examination of esophageal strictures.[49]

The Role of Proton Pump Inhibitors in Diagnosis

Acid suppression achieved through a PPI regimen plays an important role in the EoE diagnostic pathway. PPIs are recommended to be administered twice daily and continued for a minimum 2-month course after esophageal eosinophilia is discovered.[50] Afterwards, a repeat endoscopy with biopsies is performed to evaluate for persistent eosinophilic infiltration.[37] Patients with a positive histologic response to a PPI course are determined to have either PPI-REE or GERD. Separate from acid suppression, benefits of PPI therapy are also thought to originate from anti-inflammatory properties related to cytokine inhibition, eotaxin-3 level reduction, and anti-oxidant effects.[51,52]

A large meta-analysis demonstrated symptomatic improvement after PPI use in 60% of patients with EoE and a histologic response in 50%.[53] No difference has been noted in PPI responsiveness between adult and pediatric patients. Given the reported loss of therapeutic response in a subset of treated patients, the role of chronic PPI therapy in PPI-REE patients is unclear.[54] A 2015 study reported that an estimated 27% of PPI-REE patients relapsed on histology over a 1-year follow-up period, requiring PPI dose escalation.[54]

Treatment

The treatment approach to EoE is categorized into diet, drugs, and dilation (Table). Selection of treatment depends on prior therapy and the severity of presentation, with the ultimate goals of improving symptoms and minimizing the risk of complications such as food impactions. Dietary therapy encompasses 3 possible approaches: the elemental diet, the allergy testing–directed elimination diet, and the empiric elimination diet, which has subtypes of the 6- and 4-food elimination diets. Pharmacologic therapy ranges from topical corticosteroids to experimental systemic therapies such as biologic agents and monoclonal antibodies. Patients with symptomatic fibrostenotic disease or refractory symptoms may benefit from endoscopic dilation therapy.

Dietary Therapy

Dietary allergens have been found to be associated with EoE in both pediatric and adult populations.[50] Targeting these allergens through carefully designed dietary modifications provides a nonpharmacologic treatment alternative. The dietary strategy is often chosen using a team approach involving an allergist and a certified dietitian, and is influenced by patient preference.

Elemental Diet The elemental diet is the strictest dietary plan and also the most effective, inducing histologic remission in 90.8% of patients.[55] The diet is free of allergens and based on a formula of amino acids, basic carbohydrates, and medium-chain triglycerides.[56] The

Table. Eosinophilic Esophagitis Treatment Summary

Therapy	Description/Findings
Dietary Therapy	
Elemental Diet	• Amino acid–based, allergen-free formula followed by slow reintroduction of foods • Most effective but also most strict, causing difficulty with adherence
Allergy Testing–Directed Elimination Diet	• Elimination of food groups based on allergy testing • Overall poor efficacy and the least favored of the 3 dietary regimens
Empiric Elimination Diet	• Six most commonly allergenic food groups (milk, wheat, egg, soy, peanut/tree nuts, shellfish/fish) are removed from the diet and slowly, individually reintroduced after a symptomatic and histologic response
Pharmacologic Therapy	
Topical Corticosteroids[a]	• Used for initial and maintenance therapy in eosinophilic esophagitis unresponsive to proton pump inhibitor therapy • Budesonide viscous suspension 1 mg/day for children or 2 mg/day for adults, typically in a divided dose, or fluticasone via metered-dose inhaler 88-440 mcg/day in a divided dose for children or 880-1760 mcg/day in a divided dose for adults
Endoscopic Therapy	
Endoscopic Dilation	• Usually reserved for patients who relapse on dietary or pharmacologic therapy • First-line therapy if high-grade strictures are present

[a]No therapies for eosinophilic esophagitis have been approved by the US Food and Drug Administration to date. The dosing listed in the Table is based on the 2013 American College of Gastroenterology guidelines.

majority of studies evaluating the elemental diet have been conducted in the pediatric population, demonstrating its effectiveness in improving both symptoms and histologic inflammation.[31,57,58] However, studies have demonstrated remission in adults on the elemental diet as well.[55,59] The main limitation of the elemental diet is its very narrow profile, causing difficulty with long-term compliance. After achieving clinical and histologic remissions, reintroduction of foods is begun under close monitoring. The diet is frequently reserved for those who lack response to other therapies, and practitioners may need to use enteral feeding modalities to reach nutritional needs.[60]

Allergy Testing–Directed Elimination Diet Food allergy testing guides therapy in the allergy testing–directed elimination diet. Patients undergo skin-prick testing or radioallergosorbent testing to identify specific allergens.[28] Large variability has been reported in the effectiveness of this dietary approach. A study in the pediatric population demonstrated histologic remission in 77% of patients, whereas a study in adults showed a poorer response of 34%.[61,62] A meta-analysis of both children and adults concluded that only 45.5% of patients achieved histologic remission.[55] Overall, this dietary approach is limited by a poor demonstrated association between allergens identified by the standard testing protocols and EoE exacerbation.[63,64] Currently, more data are needed for this strategy to become a mainstay of treatment in the adult population.

Empiric Elimination Diet The empiric elimination diet is the least restrictive of the 3 methods and the most extensively studied. In the 6-food elimination diet, the nutrition plan is altered by removing 6 potential allergens: milk, wheat, egg, soy, nuts, and seafood.[65] After confirmed symptomatic and histologic improvements, the food groups are slowly and individually reintroduced. Most patients isolate 1 to 2 allergens and are able to reestablish the other foods back into their diet. Following reintroduction, the most commonly identified food trigger has been found to be wheat (60%), followed by dairy (50%).[66] Histologic remission has occurred in 72% to 73% of patients using this therapy.[55,67]

The alternative 4-food elimination diet, in which milk, wheat, egg, and nuts are withheld, has been less studied but provides an alternative for patients wishing to decrease the amount of dietary restrictions.[60] One study shows less success with this therapy, with 54% of patients achieving clinicopathologic response.[68]

Dietitian guidance is important for all EoE dietary therapies to increase adherence and minimize the risk of inadequate nutritional intake.

Pharmacologic Therapy

Pharmacologic therapy encompasses topical corticosteroids, which are the mainstay of treatment, systemic corticosteroids, and multiple experimental systemic therapies. Several newer agents are currently under investigation and are described in this article; however, their clinical application is limited until additional data emerge. It is important to note that to date, there are no medical therapies for EoE that are approved by the US Food and Drug Administration.

Topical Corticosteroids Topical corticosteroids constitute the mainstay of EoE treatment and are frequently used as first-line agents once an EoE diagnosis is confirmed.[29,69] Corticosteroids decrease eosinophil mucosal migration by inhibiting cytokines, leading to reduced remodeling and tissue fibrosis.[70,71] Limited side effects and a good safety profile are further benefits of this regimen. The most commonly cited side effect is candidiasis, and compared with systemic corticosteroids, adrenal axis suppression is rare.[72]

Both fluticasone administered via a metered-dose inhaler and budesonide swallowed in liquid form have been shown to have good treatment efficacy.[73] Studies comparing fluticasone to placebo in both adults and children reported a 50% to 65% remission rate.[74,75] Randomized, controlled trials of budesonide vs placebo also highlighted significant improvement in symptoms and eosinophil burden on histology.[76,77]

Systemic Corticosteroids Limited data exist regarding the use of systemic corticosteroids in EoE. A randomized, controlled trial comparing oral prednisone to topical fluticasone demonstrated no significant difference in reaching clinical and histologic improvements.[78] However, 40% of patients who received prednisone experienced systemic adverse effects compared to no systemic effects in the fluticasone group.[78] In practice, systemic corticosteroids are reserved for severe refractory cases or instances in which a rapid response is needed.

Experimental Pharmacologic Agents A number of other pharmacologic agents have been studied in EoE, although data are currently limited and the most recent treatment guidelines do not recommend their use. A leukotriene D4 receptor antagonist, montelukast, was investigated in a small study involving 8 patients that demonstrated symptomatic but not histologic improvement with use of this drug, and relapse was common when montelukast was withdrawn.[79] A more recent prospective study of 38 adult patients showed that this drug did not maintain symptom remission after topical corticosteroid therapy.[80]

Humanized antibodies to interleukin (IL)-5 have also been tested in EoE. Mepolizumab (Nucala, GlaxoSmithKline) was studied in the adult and pediatric populations, and although a significant histologic effect was discovered, the symptomatic response was inadequate.[81,82] A randomized, controlled trial comparing reslizumab (Cinqair, Teva Respiratory, LLC) to placebo also revealed a decline in eosinophil count, but no significant improvement in symptoms.[83] In another study, 3 refractory EoE patients were treated with the anti–tumor necrosis factor-α agent infliximab (Remicade, Janssen), with neither histologic nor clinical change.[84] A recent study examined the role of a novel recombinant, humanized, anti–IL-13 monoclonal antibody (RPC4046) in EoE treatment.[85] This randomized, controlled trial of 90 patients showed improvement in both histologic and endoscopic features in treated subjects compared to placebo.[85]

Other investigated agents include immunomodulators such as 6-mercaptopurine and azathioprine. These were shown in a small case series to induce remission, but due to their extensive side-effect profile, they are not recommended in practice.[86] Omalizumab (Xolair, Genentech), an anti-IgE antibody, binds to the IgE receptor and has been used to treat atopic asthma and allergic rhinitis. A pilot study of 15 patients found full clinical and histologic remissions in 33% of the treatment subjects, particularly among those with low peripheral blood absolute eosinophil counts.[87]

Finally, an antagonist to the chemoattractant receptor homologous molecule on Th2 cells (CRTH2) may be a novel therapeutic target. A study comparing CRTH2 to placebo revealed a reduction in the eosinophil count and beneficial clinical effects.[88] Overall, significantly more investigation, including large randomized trials, is needed to determine the potential role of these agents in the management of EoE.

Endoscopic Dilation Therapy

Endoscopic treatment is recommended for patients with a high-grade stricture or those who clinically relapse despite dietary or pharmacologic therapy. Dilation does not have an effect on eosinophilic infiltration or underlying inflammation.[89] The technique can be performed using either a bougie dilator or a through-the-scope balloon. No data exist demonstrating the superiority of one technique over another.[37] A conservative gradual approach to dilation is recommended to avoid complications, with the objective to dilate the esophagus between 15 to 18 mm in diameter.[90] Success of endoscopic dilation, defined by symptom improvement, has been found in 75% to 83% of patients.[91,92] However, dilation may not clinically benefit patients without severe strictures.[93] Serial dilations are often performed to attain symptom response. A study of

164 EoE patients who underwent dilation concluded that 75% required repeat dilation within 1 year.[94]

Esophageal perforation is rarely seen in EoE and can result from a multitude of causes, including food impaction, prolonged retching, or mechanical dilation.[95,96] A retrospective examination of 511 patients estimated the risk of perforation in EoE at 2%, with 80% of cases resulting from a prolonged food impaction.[94] Studies investigating the risk of perforation after dilation therapy found the perforation rate to be below 1%.[91,96,97]

Summary

EoE is one of the leading causes of dysphagia and food impactions. Diagnosis requires the presence of esophageal symptoms accompanied by persistent esophageal eosinophilia. There is an important role for the use of PPIs in the diagnostic pathway of EoE. Existing treatment strategies target the underlying inflammation and aim to provide symptomatic relief. Patients with confirmed EoE are initiated on topical corticosteroids or dietary therapy, most commonly the empiric elimination diet. In the presence of unrelenting symptoms on therapy or severe stricturing disease, repeat endoscopy with potential dilation can be performed. Multiple other treatments are currently undergoing investigation.

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