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Eosinophilic esophagitis

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Synopsis

Eosinophilic esophagitis is a chronic disorder characterized by symptoms of esophageal dysfunction and esophageal inflammation with intraepithelial eosinophils. EoE represents an important cause of upper gastrointestinal morbidity. Primary care providers are pivotal for timely and accurate recognition of symptoms of eosinophilic esophagitis, for facilitating diagnoses through specialist referrals, and for understanding management strategies. This process begins with a thorough understanding of the clinical features of EoE, its associated atopic conditions, and its evolving epidemiology.

Keywords

eosinophilic esophagitis; dysphagia; food bolus impaction; heartburn

Introduction

Eosinophilic esophagitis (EoE) is a chronic disorder characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophilic infiltration of the esophageal epithelium.[1–3] The disease belongs to the spectrum of eosinophilic gastrointestinal disorders whereby eosinophilic inflammation of the gastrointestinal tract occurs in the absence of secondary causes. Prior to the 1990s when esophageal eosinophilia was thought to be solely due to reflux esophagitis,[4] EoE was rarely recognized. However, by the mid-1990s, seminal papers described the condition,[5] and the number of publications on EoE increased dramatically.[6] EoE represents an important contributor to upper gastrointestinal morbidity throughout the world, a growing health problem, and a significant burden for healthcare systems.[7,8]

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Important roles exist across medical specialties for the co-management of EoE. This includes primary care providers, allergists, gastroenterologists, pathologists, and nutritionists treating both adult and pediatric patients. For the primary care provider, the identification and referral of patients with suspected EoE is indispensible. Despite the increase in EoE-pertinent literature, patients endorse a protracted diagnostic delay following symptom initiation. Furthermore, this delay has yet to decrease and correlates with prognosis.[1,9] Primary care providers are thus pivotal not only for timely and accurate diagnosis, but also to recognize the existence of co-morbid conditions and to initiate specialist referrals.[2]

This article aims to provide the critical information necessary to facilitate the incorporation of primary care providers into the co-management of EoE. To achieve this, we provide an overview of EoE clinical, endoscopic, and histologic features as well as treatment options and future directions in management.

Clinical presentation

Symptoms reported by eosinophilic esophagitis patients

The diagnosis of EoE starts with a thorough investigation of presenting symptoms. These vary by patient age (Table 1).

Practitioners should consider EoE in adolescents and adults when the predominant complaint is esophageal dysphagia,[10] which is reported by 60–100% of patients,[6,11,12] and food impaction can be seen in more than 25%.[13,14] Heartburn (30–60%) and non-cardiac chest pain (8–44%) are commonly reported, [11,15] and EoE may be present in 1–8% of patients with proton pump inhibitor (PPI) refractory reflux symptoms.[16,17] Abdominal pain, nausea, vomiting, diarrhea, GI bleeding, and weight loss are uncharacteristic in adults with EoE, and a different process or more diffuse eosinophilic gastrointestinal disorder (e.g. eosinophilic gastroenteritis, eosinophilic colitis) should be considered when these features predominate.

Children with EoE report non-specific complaints (Table 1).[18] Difficulty feeding, choking, refusal of food, and vomiting are also found in infants and toddlers.[19,20] When constitutional symptoms, such as fever and weight loss predominate, an alternative disease should be sought.

Elucidating symptoms of dysphagia can be a subtle task, as many patients have subconsciously developed compensatory eating behaviors over years to minimize symptoms. Specific behaviors to assess include:

- Eating slowly
- Excessive food chewing
- Lubrication of food boluses or drinking a copious amount of liquid after each bite
- Repeated swallows to facilitate food bolus passage
- Avoidance of troublesome foods

- Crushing or avoiding pills

Co-morbid conditions associated with eosinophilic esophagitis

Atopy is commonly encountered in EoE cohorts, and for adult EoE patients, the prevalence of any atopic condition is 20–80%.[12] Children with EoE have a prevalence of 30–50% and 50–75% for asthma and allergic rhinitis, which compares to 10–30% for either condition in the general pediatric population. Furthermore, children with EoE are more likely to develop environmental allergies and IgE-mediated food allergy (e.g. urticaria, anaphylaxis).[21,22] Moreover, a family history of an atopic disorder is found in more than 50% of EoE patients.[23]

EoE also develops in association with some genetic syndromes, including inherited connective tissue disorders that exhibit hypermobility.[24,25] However, this is rare and only 1% of EoE patients present with this phenotype.

Familial susceptibility to eosinophilic esophagitis

While EoE does not demonstrate classic Mendelian inheritance, there is a genetic component[26] and a familial history of EoE increases individual risk for the condition above the approximately 1/2000 seen in the general population (see epidemiology, below). The risk varies by the particular relationship:[19]

- Any first degree relative: 1.8% individual risk (recurrence risk ratio: 33)
- Father: 2.4% individual risk (recurrence risk ratio: 43)
- Mother: 0.6% individual risk (recurrence risk ratio: 10)
- Brother: 3.5% individual risk (recurrence risk ratio: 64)
- Sister: 1.3% individual risk (recurrence risk ratio: 24)[27]

There is also significant concordance for EoE in both monozygotic (40%) and dizygotic twins (30%). The latter findings implicates the role of early-life exposures in EoE susceptibility.[27]

Endoscopic findings common to eosinophilic esophagitis

Multiple, though non-specific,[28] structural changes of the esophagus are seen with EoE,[2] and these can vary by patient age.[11] Fibrostenotic findings such as esophageal rings, strictures, or narrowing are more common in adults, while inflammatory findings such as white plaques/exudates, linear furrows and edema/decreased vascularity are more common in children (Figure 1). While all findings can be seen across the age spectrum, the difference in findings by age is thought to reflect a fibrotic esophageal response to chronic eosinophilic inflammation.[29–31] Other findings include a diffusely narrowed or small-caliber esophagus,[32,33] and crepe-paper mucosa (e.g. tearing of the esophageal mucosa from passage of an endoscope). Endoscopic findings of EoE are frequently described using the EoE endoscopic reference score (EREFS), which stands for the five key findings of Edema, Rings, Exudates, Furrows, and Strictures.[34] This system provides greater uniformity in the description of

findings, identifies and discriminates between non-EoE and EoE patients, and correlates with treatment.[35,36]

Histologic features of eosinophilic esophagitis

All patients exhibit increased intraepithelial eosinophils that may be found in all regions of the esophagus (Figure 2). Eosinophil surface layering and eosinophilic microabscesses, dilated intercellular spaces, a thickened mucosa with basal layer hyperplasia and papillary elongation, and extracellular deposition of eosinophil granule proteins such as eosinophil peroxidase are also found.[37,38] Patients with fibrostenotic complications of EoE (e.g. rings, strictures) exhibit increased collagen deposition within the lamina propria.[39]

Diagnostic criteria

Diagnostic criteria and consensus guidelines definition

EoE is a chronic immune and antigen-mediated *clinicopathologic* disease,[1–3] and diagnostic criteria require both the appropriate clinical and histologic features:

- Symptoms of esophageal dysfunction (Table 1)
- Presence of esophageal eosinophilia with a peak of at least 15 eosinophils in a high-power microscopy field (eos/hpf)
- Exclusion of alternative etiologies of esophageal eosinophilia[1]

Though initially selected by expert opinion, the threshold of 15 eos/hpf achieves a sensitivity of 100% and a specificity of 96% for establishing the diagnosis.[40] It is worth noting that patients with lower levels of eosinophilia and phenotypic features have been reported, and they may have EoE in appropriate settings.[41]

In regards to the third criterion stipulated above, previous guidelines[1] required non-response to a PPI trial to establish the diagnosis. Patients responding to PPI were labeled with PPI-responsive esophageal eosinophilia (PPI-REE), which became an area of substantial controversy.[42] However, this distinction is no longer required, and PPIs have evolved from a diagnostic tool to a treatment option.[3]

Alternative etiologies of esophageal eosinophilia

Esophageal eosinophilia is not pathognomonic for EoE. Alternative etiologies should be sought and ruled out following a thorough history, physical examination, and select laboratory tests. The most prevalent competing or overlapping diagnosis is GERD. Less common competing diagnoses include:[1–3]

- Achalasia
- Infection
- Connective tissue diseases
- Crohn’s disease
- Pill esophagitis

- Hypereosinophilic syndrome
- Drug hypersensitivity[1–3]

When more generalized eosinophilic infiltration of the gastrointestinal tract is noted, the findings may be consistent with eosinophilic gastroenteritis and/or colitis with esophageal involvement.

Since GERD can induce esophageal eosinophilia and produces similar symptoms to EoE, the differentiation of the two conditions proves challenging.[43] Complicating this matter, the relationship between GERD and EoE remains controversial. For instance, GERD and EoE may simply overlap, EoE may induce GERD through impaired esophageal clearance of refluxate, or GERD may conceivably cause EoE by damaging the epithelial border and thus allowing for the presentation of antigens and a subsequent allergic response.[44] Altogether, symptoms of reflux should be sought and treated, and pH monitoring has not successfully discriminated GERD from EoE.[45]

Epidemiology

EoE is found globally. Many cases have been reported in North America, South America, Europe, and Australia. Cases also exist from Asia and the Middle East. India and Sub-Saharan Africa are exceptional with no cases documented from these areas.[46] EoE is more common in cold and arid climates, and in rural areas, [47] and most frequently affects those younger than 50,[48] men, and caucasians.[7]

According to data derived largely from North American and European cohorts, the pooled incidence rate of EoE is 3.7/100,000 patient years (95% confidence interval: 1.7 – 6.5).[49] Additionally, all studies examining EoE incidence have found an increasing incidence over time[50] not explained by disease awareness or utilization of endoscopy.[11] Similarly, prevalence data estimated an overall pooled prevalence of 22.7/100,000 (95% confidence interval: 12.4 – 36.0), [49] and this value has also increased over time.[7]

The aforementioned changes in EoE incidence and prevalence suggest that environmental factors, as opposed to genetic factors, drive the changing epidemiology,[46] but the exact etiology is not known. Early life exposures including antibiotic use in infancy, cesarean delivery, preterm birth, and lack of breastfeeding have been implicated as disease risk factors.[27,51] It has been hypothesized that these factors may affect the microbiome and the developing immune system. In addition, decreased Helicobacter pylori prevalence, increased proton pump inhibitor use, changes in food sources, and food packaging have also been implicated in the changing epidemiology of EoE.[7]

Pathogenesis

Animal models, genetic studies, co-morbid allergic disorders, and the efficacy of elimination diets suggest that EoE is an atopic condition.[26] Most patients are sensitive to one or more foods[52] and have aeroallergen hypersensitivity[2] or respiratory allergy.[53] Similarly, the role of antigen sensitization is supported by clinical and histologic improvements with elimination

diets devoid of precipitating allergens.[54] Mounting data show that EoE is not IgE-mediated[55] and IgG4 may have a role in disease pathogenesis.[55]

EoE is also Th2 mediated. Th2 cells produce inflammatory cytokines including IL4, IL5, and IL13 that in turn increase eotaxin-3. The latter molecule is a potent chemokine inducing eosinophilic infiltration into and activation within the esophagus.[56] Once activated, eosinophils produce additional factors such as TGF-beta. TGF-beta promotes tissue remodeling of the esophagus that contributes to the fibrostenotic complications of EoE.[57,58]

Treatments

Drugs, *diet*, and *dilation* encapsulate the treatment paradigms for EoE.[59] Drugs and diet reduce EoE-associated inflammation while dilation targets esophageal strictures and narrowing. Treatment choice is predicated on patient preference, clinical features, and cost. Goals of therapy include clinical and histologic improvement and reduction in long-term complications. No Food and Drug Administration approved medication exists for EoE, and as such, all medications are used off label in the U.S. Many patients with EoE will continue to be followed by their primary care provider, so it is important to be familiar with EoE treatment options, even if these are initially directed by specialists.

PPIs are an initial pharmacologic choice for EoE. If PPI non-response occurs (Figure 3), corticosteroids or elimination diet are utilized. Treatment should be optimized and factors associated with response (e.g. adherence, drug dose, inadvertent antigen exposure, esophageal infection, stricture) assessed at each follow-up visit.[60]

Corticosteroids, whether delivered topically or systemically, improve the clinical symptoms and histologic features of EoE. Systemic corticosteroids are now reserved for patients requiring a prompt therapeutic response, such as severe symptoms or growth failure, owing to their long-term adverse effects as well as the results of an RCT illustrating similar efficacy of topical and systemic corticosteroids.[61] Methods for delivering topical corticosteroids include swallowing fluticasone (puffed into the mouth from an asthma multi-dose inhaler (MDI) and then swallowed) or budesonide (mixed in a viscous slurry from the aqueous asthma nebulizer formulation).

The decision to utilize an elimination diet depends upon multiple factors:

- Acceptability of the diet by patient and family
- Provider expertise
- Availability of dieticians

Types of elimination diets include elemental liquid amino acid-based formulations,[62] empiric elimination diets,[54,63] and allergy test-directed diets. [64–66]

Efficacy of pharmacologic and dietary treatment strategies

Studies analyzing adults and children illustrated that between 33–74% of patients with EoE respond to PPIs.[45,67] Moreover, a meta-analysis documented a pooled PPI response rate of approximately 50%.[68] The long-term efficacy of PPIs is less clear. A recent prospective

study documented that most pediatric patients (78%) remain in clinical and histologic remission following one year of maintenance therapy,[69] and similar data are available for adults.[70] Additionally, temporary discontinuation of PPI therapy results in recurrence of symptoms and/or histologic relapse. However, PPI reintroduction recaptures response in most patients.

Topical corticosteroid efficacy has been well studied in multiple randomized controlled trials, and several meta-analyses summarize their data.[71,72] They have consistently produced reductions in esophageal eosinophil counts versus comparator and are capable of maintaining remission in a proportion of patients. The typical doses utilized for oral viscous budesonide as well as fluticasone in clinical trials are summarized below (Table 2).

Correct techniques must be stressed to optimize esophageal deposition of topical corticosteroids. Topical corticosteroids should be taken following meals and patients should avoid eating or drinking for 30 to 60 minutes after swallowing the medication. Additionally, MDIs are ideally administered at end expiration following a breath hold.

A common complication of topical corticosteroid use is esophageal candidiasis, which is seen on follow-up endoscopy in 10–20% of EoE patients.[73] A rare complication is herpes esophagitis.[74] Additionally, a recent systematic review noted that adrenal suppression following topical corticosteroids is uncommon.[75]

The efficacy of food elimination diets varies according to the diet utilized. A meta-analysis of adult EoE patients reported that elemental diets were effective in 91%, empiric elimination diets in 72%, and allergy test-directed diets in 46%.[64] Elemental diets produce histologic remission in most patients. However, practical limitations limit their use (e.g. cost, palatability, gastrostomy tube placement, quality of life).[1] Conversely, allergy test-directed diets produce lower rates of remission as a consequence of their low predictive value for the identification of culprit foods.[54,76] Empiric diets have thus become the elimination strategy of choice. The most common and best described is the ‘six-food elimination diet’ that removes dairy, wheat, egg, soy, peanut/tree nut, and fish/shellfish. For patients undergoing dietary elimination, working with a nutritionist or dietician is recommended to help increase compliance, decrease inadvertent contamination, and prevent nutritional deficiencies.[77]

The role of esophageal dilation in eosinophilic esophagitis

Esophageal stricture or narrowing is treated best by dilation, which is safe and effective when done cautiously. This is an important treatment to improve symptoms of dysphagia, but it does not impact the underlying eosinophilic inflammation.[78] A meta-analysis determined a 0.3% risk for perforation, though at expert centers, and this value is comparable to the risk of perforation following dilation of non-EoE patients.[79]

Future directions

Future directions in the management of EoE pertain to diagnosis and follow up, topical corticosteroids formulations, and novel treatments. Researchers are actively seeking less invasive and more efficient diagnostic tools (e.g. tethered capsule endoscopy, un-sedated

trans-nasal endoscopy, cytosponge-obtained esophageal tissue collection, or string-based analysis of esophageal inflammatory factors).[80–83] Genetic features may also assist in the diagnosis of EoE: the EoE transcriptome may accurately identify the disease[84] and assist in predicting clinical outcomes.[85] Serum biomarkers are of intense interest, but to date none have been found to be ready for clinical use. [86,87]

New formulations for topical corticosteroid delivery are under study. An effervescent budesonide tablet was highly effective as a means of delivery in an RCT,[88] and has been recommended for approval for EoE in Europe. Another RCT found pre-prepared viscous budesonide to be both safe and effective and capable of inducing clinical, endoscopic, and histologic remission.[89]

Small molecules including angiotensin receptor blockers (e.g. losartan)(NCT1808196), JAK kinase inhibitors,[90] and OCT000459[91], an oral drug that blocks the effects of prostaglandin D2, are emerging as potential treatment options and have been studied to varying degrees. Biologic agents, including anti-IL-5 monoclonal antibodies (which are approved for eosinophilic asthma),[92–94] anti-IL13 antibodies[95,96], and the anti-IL-4r blocker dupilumab (which has recently been approved eczema)[97], are also under study. The place of these biologics in the treatment algorithm for EoE has yet to be determined.

In addition to the aforementioned future directions, health care transition from pediatric-to adult-focused systems represents an important and under-studied topic.[98] In one study, most patients and parents of children with EoE were found to be unfamiliar with health care transition. Readiness for transition was also low compared with other chronic diseases.[99] As such, exploration of barriers limiting transition readiness should be a priority especially in light of the large cohort of EoE patients transitioning to adult care, and coordination of this care transition is another role for primary care providers.

Conclusion

Eosinophilic esophagitis is a chronic disorder characterized by symptoms of esophageal dysfunction and esophageal inflammation with intraepithelial eosinophils. EoE represents an important global contributor to gastrointestinal morbidity. Primary care providers are pivotal for timely and accurate detection of symptoms potentially related to EoE, referral to proper specialists for diagnosis, coordination of care between multiple providers as well as transition of care from pediatric to adult providers, all with the goal of improving patient quality of life and to reduce long-term EoE complications.

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Key points

- Eosinophilic esophagitis has emerged as an important contributor to upper gastrointestinal morbidity.
- Primary care providers are indispensible for the timely and accurate diagnosis of eosinophilic esophagitis.
- A delay in diagnosis of eosinophilic esophagitis contributes to the risk of long-term complications.

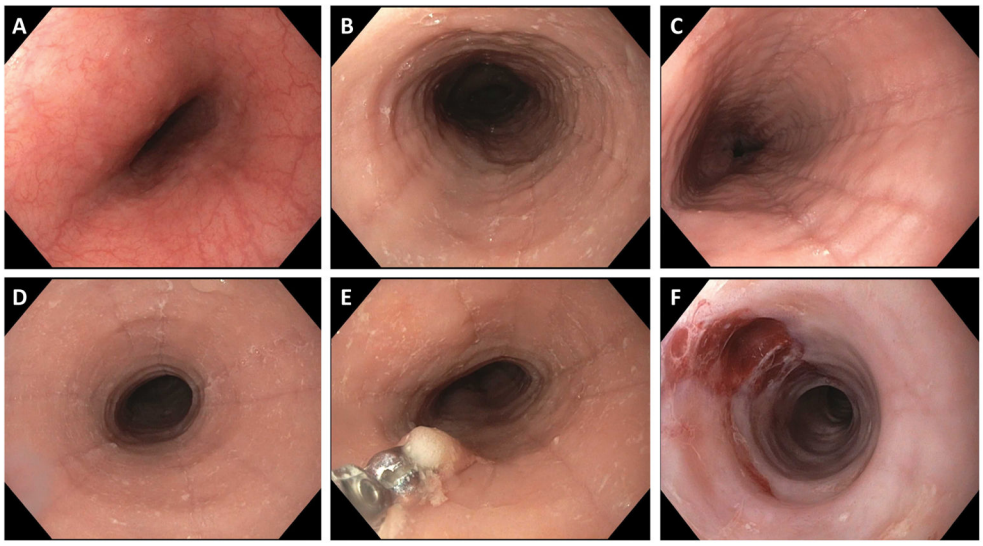

Figure 1.

Endoscopic images of EoE. **(A)** The endoscopic appearance of the normal esophagus. Note the uniform and smooth appearance of the esophageal mucosa, with the fine vascular pattern clearly visible. **(B)** An EoE patient with evidence of esophageal rings, furrows, edema, and exudates. **(C)** An EoE patient with esophageal edema, deep furrows, and mild exudates. **(D)** An EoE patient with a focal stricture, in addition to mild rings, furrows, edema, and exudates. **(E)** Esophageal biopsy underway. **(F)** An EoE patient with a very narrow caliber esophagus and tight rings, as well as edema, after esophageal dilation. Good dilation effect (mucosal rent) is seen in the 11 o'clock position.

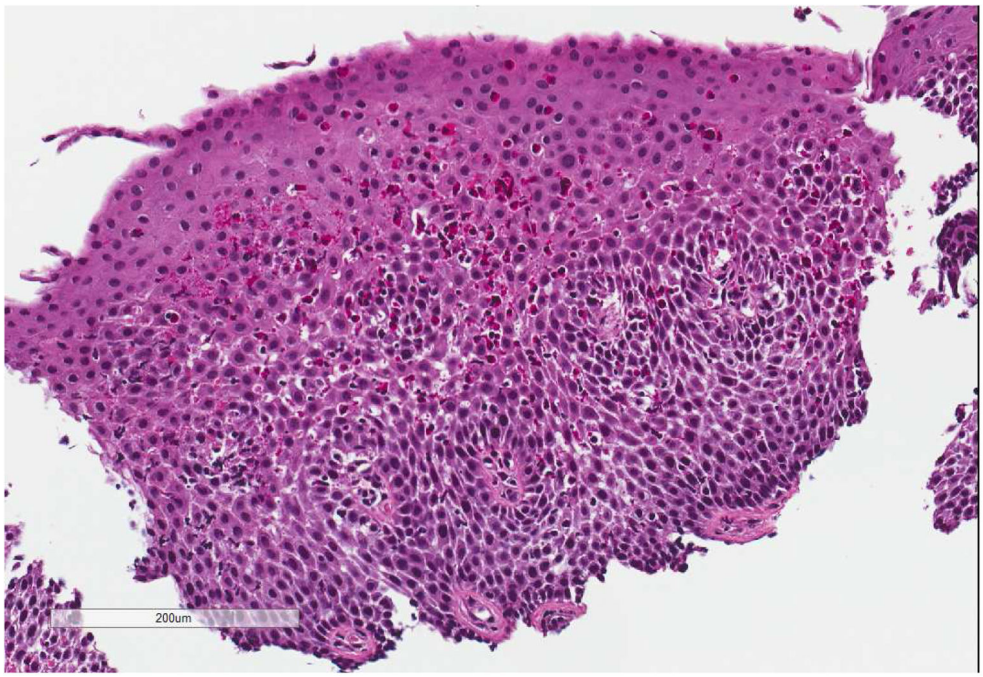

Figure 2.

Histologic image of an esophageal biopsy in EoE. In addition to the prominent eosinophilic infiltration (>15 eos/hpf), there is eosinophil degranulation, basal zone hyperplasia, and spongiosis.

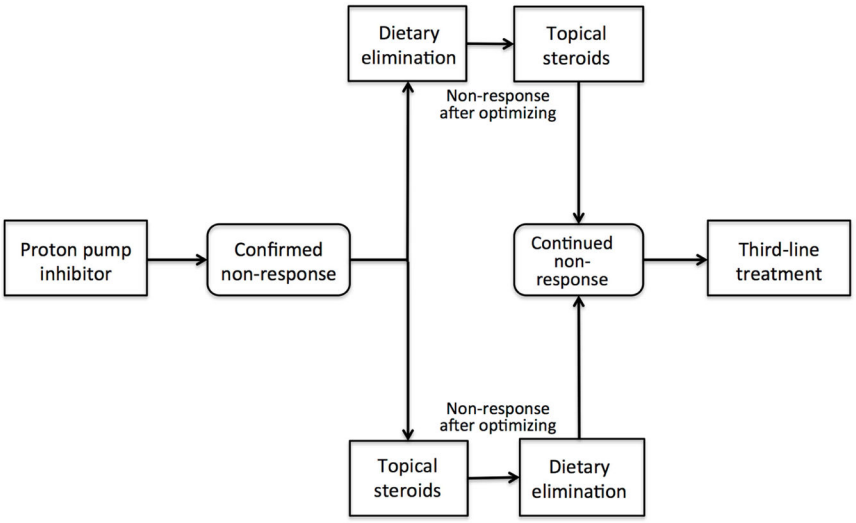

Figure 3.
Treatment algorithm for the primary and secondary treatment of eosinophilic esophagitis.

Table 1

Common symptoms associated with eosinophilic esophagitis

Adolescents and adults	Children
Solid food dysphagia	Nausea and vomiting
Food bolus impaction	Regurgitation
Heartburn	Heartburn
Chest pain	Abdominal pain
	Chest pain
	Anorexia/feeding refusal/failure to thrive

Table 2

Typical doses of topical corticosteroids for eosinophilic esophagitis

Topical corticosteroid	Age	Dose
Fluticasone via MDI	Children	440 – 880 mcg/day
	Adults and adolescents	880 – 1760 mcg/day
Oral viscous budesonide	Children	1 mg/day
	Adults and adolescents	2–4 mg/day