

Eosinophilic Esophagitis—A Primer for Otolaryngologists

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IMPORTANCE Eosinophilic esophagitis (EoE) is a chronic, inflammatory condition of the esophagus. Prevalence of EoE is on the rise and, owing to its associated extragastrointestinal manifestations and comorbidities, otolaryngologists are increasingly encountering this condition in their practice.

OBSERVATIONS Symptoms of EoE are vague and vary greatly based on patient's age. The gastrointestinal symptoms include dysphagia, food impaction, feeding difficulties, symptoms mimicking gastroesophageal reflux, abdominal pain, vomiting, and failure to thrive. Several otolaryngologic symptoms are associated with EoE including rhinosinusitis, chronic cough, recurrent croup, hoarseness, and other aerodigestive symptoms refractory to gastroesophageal reflux therapy. Eosinophilic esophagitis is also frequently associated with other atopic conditions, such as asthma, eczema, and food allergies. The diagnosis is made on endoscopy with biopsies that reveal eosinophil-predominant esophageal inflammation. There are 3 major treatment approaches to EoE, commonly referred to as the 3 Ds: diet, drugs, and dilation. Untreated inflammation of esophagus from EoE can result in irreversible structural damage to the esophagus, leading to fibrosis, strictures, and impaired esophageal function.

CONCLUSIONS AND RELEVANCE Eosinophilic esophagitis is now a fairly prevalent condition with considerable morbidity. Otolaryngologists should be familiar with the various clinical presentations of this condition in different age groups. Early diagnosis and treatment of this condition is a key for avoiding or postponing its complications.

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Eosinophils are physiologically present in most parts of the gastrointestinal (GI) tract; the esophageal epithelium, however, is devoid of eosinophils in the healthy state. Presence of eosinophils in the squamous epithelium of the esophagus is abnormal and denotes a broad differential (Box), one of which is eosinophilic esophagitis (EoE). Eosinophilic esophagitis is a chronic inflammatory condition of the esophagus characterized by symptoms of esophageal dysfunction and eosinophilic inflammation (>15 eosinophils per high-power field) of the esophageal mucosa diagnosed after exclusion of other causes of esophageal eosinophilia.^{1,2}

Eosinophilic esophagitis is being increasingly recognized in Western countries, resulting in a considerable surge in published literature over the past 2 decades. Despite heightened awareness, EoE remains an underdiagnosed condition, partly because the symptoms can be nonspecific. Patients with EoE usually present with gastrointestinal symptoms but recent studies have brought to attention that EoE can present with extraesophageal manifestations including otolaryngologic symptoms that may be refractory to conventional treatment.³ Extraesophageal manifestations of EoE are especially common in younger children and may be the main presenting symptom(s). In addition, patients with EoE have increased rates of comorbid otolaryngologic conditions and are more likely to undergo otolaryngologic surgeries, such as tonsillectomy, adenoidectomy, and myringotomy with tubes.⁴ Although otolaryngologists are familiar with airway manifestations of gas-

trointestinal conditions such as gastroesophageal reflux,⁵ it is important that they be as familiar with the extraesophageal manifestations of EoE; a recent review suggested that up to 10% to 15% of pediatric patients with EoE present first to an otolaryngologist prior to seeing a gastroenterologist.⁶

This review discusses common presenting symptoms, associated otorhinolaryngology symptoms, diagnostic workup, endoscopic features, and treatment of EoE for the general otolaryngologist.

Epidemiology

Several population-based studies have shown that the incidence and prevalence of EoE is on the rise, especially in western countries.^{7,8} The prevalence of EoE is estimated at 0.5 to 1 in 1000 in western countries, making EoE as common as inflammatory bowel disease.⁹⁻¹² It is unclear if the increase in diagnosis of EoE truly represents an increasing incidence or rather an increased recognition of this condition by primary care physicians, gastroenterologists, otolaryngologists, pulmonologists, and pathologists, or both. Approximately 2% to 7% of adult patients undergoing esophagogastroduodenoscopy (EGD) with biopsies are found to have EoE,^{13,14} and this number increases to 22% if dysphagia is the indication for endoscopy.¹⁵ Furthermore, over a third of adults presenting with

esophageal food impaction are found to have EoE as the underlying diagnosis.^{16,17}

Eosinophilic esophagitis affects patients of all age groups, with a bimodal peak incidence between the ages of 5 to 10 years and in the fourth decade of life. Males are 3 to 4 times more commonly affected than females.¹⁸ Eosinophilic esophagitis is more common in white patients and has a strong association with concomitant atopic conditions such as asthma, eczema, rhinitis, and food allergies.⁷

Pathogenesis

A complex interplay of genetics, environmental factors, allergens, and host factors are implicated in the pathogenesis of EoE. Although the pathogenesis is incompletely understood and the field is rapidly changing, there is enough evidence to suggest that EoE is a T helper cell-2 (Th2)-mediated immune response, as seen in other allergic conditions.¹⁹ It is postulated that exposure of the esophageal mucosa to the putative antigen (thought to be food and/or aero-allergen) triggers a Th2 response that results in secretion of several cytokines, including interleukin (IL)-4, IL-5, IL-13, and transforming growth factor (TGF) β .²⁰ These cytokines induce an immune response and lead to disruption of barrier function in the esophageal mucosa. These changes further modify an extensive set of esophageal transcriptomes including eotaxin-3 gene, which is important for recruitment of eosinophils to the esophagus.²¹ Periostin, induced by IL-13, plays a role in recruitment and adhesion of eosinophils to the esophagus.²² Activated eosinophils release granule proteins, with further cellular activation including eosinophils, basophils, neutrophils, and mast cells, with resulting inflammatory reaction and tissue damage.

Persistent inflammation leads to remodeling changes in the esophagus including epithelial basal cell hyperplasia, fibrosis of lamina propria, expansion of the muscularis propria, and increased vascularity, resulting in esophageal fibrosis. Interleukin-5, fibroblast growth factor (FGF)-9, and TGF- β have been implicated in fibrogenic response in EoE.^{23,24} There is increasing evidence to suggest a role of genetics in the pathogenesis of EoE.^{21,25} There are several reports of familial clustering²⁶⁻²⁸ and multiple genome-wide association studies have identified genetic risk loci implicated in EoE pathogenesis.^{29,30}

Clinical Presentation

Symptoms of EoE vary greatly based on patient age, adding to diagnostic challenges, especially when confounded by extraesophageal symptoms.

Younger patients usually present with nonspecific symptoms mimicking gastroesophageal reflux, feeding difficulties, vomiting, failure to develop normal eating patterns (eg, not advancing past liquids/soft solids), choking with meals and, less commonly, failure to thrive. Dysphagia to liquids is a common presenting symptom in children younger than 1 year of age who are eventually diagnosed with EoE.³¹ The likely reason for this unusual symptom in infants is that they are predominantly eating a liquid diet. School-age children are more likely to present with symptoms of vomiting, regurgitation, and abdominal pain, whereas adolescents and adults present with dysphagia and food impactions.⁷

Box. Differential Diagnoses of Esophageal Eosinophilia

- Gastroesophageal reflux disease
- Eosinophilic esophagitis
- Proton pump inhibitor-responsive esophageal eosinophilia
- Celiac disease
- Crohn disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue disease
- Infections (viral, fungal)
- Graft-vs-host disease
- Drug injury

Because EoE is a chronic condition, most patients with EoE develop coping mechanisms to compensate for their symptoms. A detailed history often reveals these mechanisms which include eating slowly, chewing excessively, taking small bites, cutting foods into smaller pieces, lubricating food with different sauces, drinking fluid after most bites, and avoiding textured food such as meat and bread.³²

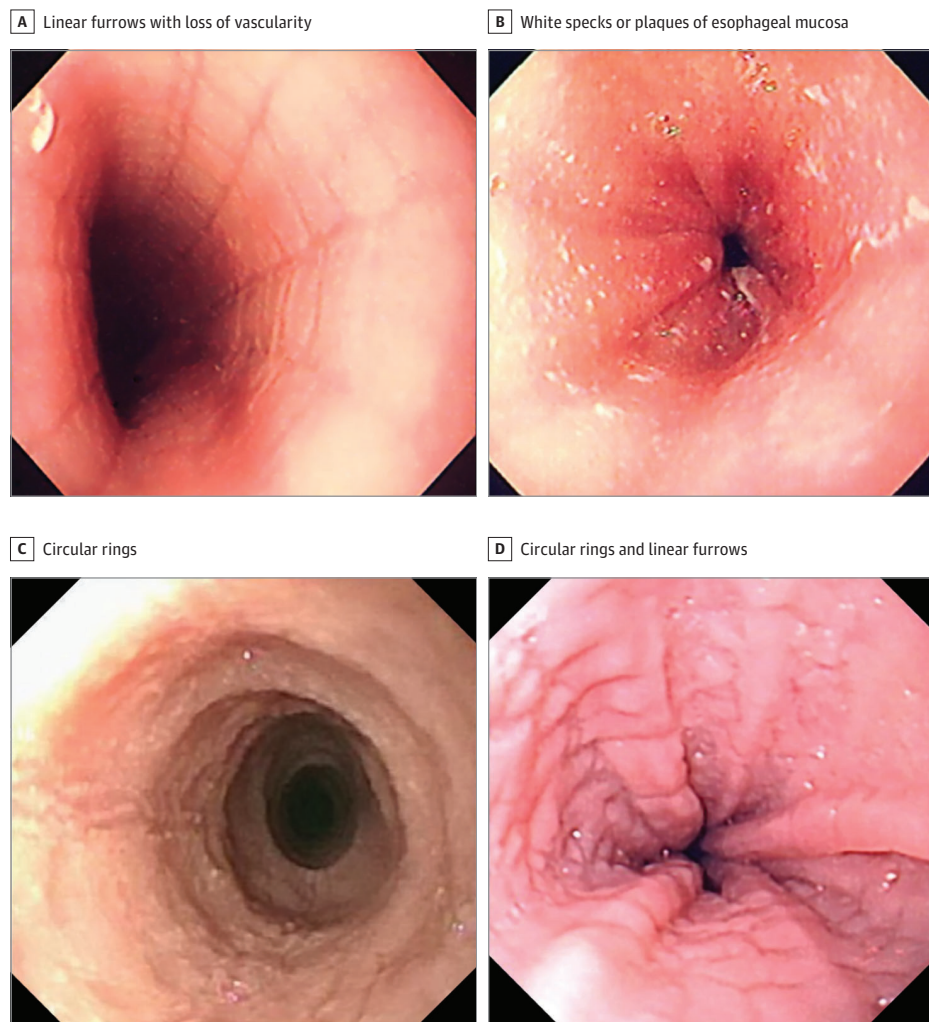
There is a strong association between EoE and allergic conditions such as food allergies, environmental allergies, atopic dermatitis, and asthma. Concomitant atopy is reported by more than 50% of patients with EoE; more than 70% of children with EoE have a family medical history of atopy and 6% have a family medical history of EoE.⁷

Several studies have reported an association between EoE and otolaryngologic symptoms. In some patients these otolaryngologic features could be the presenting symptom. Otolaryngologic manifestations associated with EoE include rhinosinusitis, which has been reported in up to 25% of pediatric patients with EoE.^{33,34} Laryngeal symptoms attributed to EoE include chronic cough, recurrent croup, hoarseness, and dysphonia.^{35,36} Improvement of laryngeal symptoms that are refractory to gastroesophageal reflux therapy with EoE treatment have been reported.^{33,37,38} Flexible endoscopic examination of patients with croup found EoE in 7% of patients.³⁹ A retrospective review reported that 3.7% of children presenting with refractory aerodigestive symptoms were eventually diagnosed with EoE.³ Eosinophilic esophagitis has also been implicated in cases of subglottic stenosis where laryngotracheal reconstructive surgeries failed despite treatment of gastroesophageal reflux.⁴⁰ In some medical centers it has become a standard of care to rule out EoE before attempting laryngotracheal reconstruction.³⁷

Patients with EoE are more likely to undergo otolaryngological surgeries, such as bilateral myringotomy with tubes, tonsillectomy, adenoidectomy, bronchoscopy, and sinus irrigation.⁴ A recent study by Kubik et al³⁵ reported that patients with EoE presenting with airway symptoms to otolaryngologists tend to be younger and demonstrate fewer gastrointestinal symptoms.

Physical examination of patients with EoE is often unrevealing; however, a thorough physical examination in children can identify comorbid atopic and otolaryngologic conditions and may suggest alternate pathology.

Figure 1. Common Endoscopic Abnormalities Seen in Eosinophilic Esophagitis



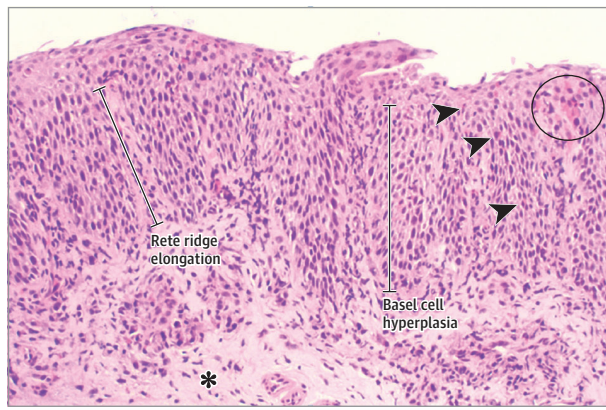
Evaluation

Esophagogastroduodenoscopy with visual examination of the mucosa and biopsies of the upper gastrointestinal tract for histologic examination is considered diagnostic test of choice for EoE. Several endoscopic features are seen with EoE (Figure 1): the esophageal mucosa may appear edematous with loss of vascularity; linear furrows, initially referred to as vertical lines; white specks of the esophageal mucosa (WSEM), which are highly specific for this condition and are representative of eosinophilic exudates on histology; concentric rings that give the esophagus an appearance of trachea (trachealization) and represent chronic remodeling change.^{18,41} Normal esophageal appearance, however, does not rule out EoE and it is imperative that multiple-level esophageal mucosal biopsies be obtained because diagnosis may be missed otherwise. In some centers, food impactions are treated by otolaryngologists using a rigid endoscope. Williams et al,⁴² reported that despite the fact that esophageal biopsies play an important role in diagnosis of EoE, otolaryngologists and surgeons do not perform routine mucosal biopsies in patients presenting with food impaction and other esopha-

geal foreign bodies. One otolaryngology series reported that biopsies were obtained in only 27 of their 271 pediatric patients presenting with esophageal foreign bodies.⁴³ Importantly, 18 of those 27 (67%) were eventually diagnosed with EoE.⁴³ In addition, it is recommended to perform biopsies of stomach and duodenum to exclude associated conditions such as eosinophilic gastroenteritis and celiac disease.¹

Biopsies from patients with EoE show an increased number of eosinophils with more than 15 intraepithelial eosinophils per high-power field being considered diagnostic of EoE. Other histologic findings noted in EoE include mucosal edema, basal cell hyperplasia, vascular papillae elongation, eosinophil microabscesses, and lamina propria fibrosis (Figure 2).⁴⁴ Owing to the patchy nature of the disease, there is a possibility of biopsy findings yielding a false-negative result. To minimize this risk, it is recommended to obtain multiple biopsies from both the proximal and distal levels of the esophagus.¹ It is important to point out that there are various causes of esophageal eosinophilia (Box) and presence of eosinophils in esophagus alone is not diagnostic of EoE. Rather, this histologic finding should be interpreted in the clinical context in which the biopsy was obtained.

Figure 2. Histopathologic Findings of Eosinophilic Esophagitis (EoE)



Histopathologic image of EoE demonstrating mucosal eosinophilia (arrowheads), eosinophilic microabscess formation (circle), basal cell hyperplasia, rete ridge elongation, and lamina propria fibrosis (asterisk).

Laboratory studies tend to be of limited utility in evaluation of patients with EoE; although up to 40% of patients with EoE have peripheral eosinophilia, it is generally mild elevation and not diagnostic. Elevated immunoglobulin (Ig) E levels can be seen in up to 50% of patients with EoE.⁴⁵ Absence of elevated IgE and/or peripheral eosinophilia does not, however, rule out the diagnosis nor does their presence secure the diagnosis. Several serum biomarkers are being studied to assist with noninvasive diagnosis and monitoring of EoE, but none are ready for routine clinical use as of yet.⁴⁶

Similar to laboratory tests, radiologic studies carry limited value in establishing a diagnosis of EoE. Contrast studies of the upper GI tract are not sensitive enough to pick up the subtle changes of EoE but can help identify alternate pathology or complications of EoE such as esophageal stricture (Figure 3), which may be long and escape detection during endoscopy. Esophageal narrowing in patients with EoE can be subtle, and better detected by esophagogram rather than esophagogastroduodenoscopy.^{47,48}

Newer Tests

Newer tests being developed for diagnosis and long-term monitoring of EoE include esophageal string test⁴⁹ and swallowed cytosponge test,⁵⁰ which are minimally invasive tools to assess disease activity; initial data show good correlation with esophageal tissue eosinophilia. Unsedated transnasal endoscopy (TNE) is also being studied for diagnosis and monitoring of EoE and may provide a less invasive method for EoE disease monitoring in the future.⁵¹ Introduction of TNE in the otolaryngology office has led to increased exposure of otolaryngologists to different esophageal pathologies including EoE. Transnasal endoscopy has obvious advantages, including that it does not require anesthesia or sedation and can be performed in the outpatient setting. Transnasal endoscopy may have limited utility in young children because it is performed without sedation and can not examine gastrointestinal tract beyond esophagus.⁵¹

Treatment

Until recently, for patients with histologic findings of esophageal eosinophilia, an 8-week trial of high-dose proton-pump inhibitor (PPI)

Figure 3. Barium Esophagogram Showing a Small-Caliber Esophagus in a Patient With Eosinophilic Esophagitis



(1 mg/kg per dose, twice per day in children to a maximum recommended adult dose of 20-40 mg twice daily in adults) was recommended with follow-up endoscopy to exclude PPI-responsive esophageal eosinophilia.¹ Persistence of esophageal eosinophilia despite high dose PPI confirmed the diagnosis of EoE; resolution of the eosinophilia, on the other hand, was termed PPI-responsive esophageal eosinophilia. Recently the diagnostic criteria was updated, suggesting that PPI usage is better classified as a therapeutic option for EoE rather than a diagnostic test.² The therapeutic mechanisms associated with PPIs on esophageal eosinophilia are unclear but may include acid suppression and anti-inflammatory properties.⁵²

Treatment goals in patients with EoE not only include symptom improvement but also resolution of esophageal histological changes. EoE is a unique in that symptoms and histology do not always correlate, and symptoms resolution alone cannot be used as reliable indicator of disease activity or response to treatment.⁵³ This discordance often necessitates repeated EGD in these patients. There are 3 major treatment approaches to EoE, often referred to as the 3 Ds: diet, drugs, and dilation. Each of these approaches will be discussed separately.

Dietary Therapy

Dietary therapy offers an effective nonpharmacologic treatment option but can be challenging to implement in older children and adolescents. It may lead to nutritional deprivation, poor compliance, psychological problems in older children, and food aversion in young children. In addition, dietary modifications may be long term.

Three types of diets have been shown to be effective in patients with EoE:

- (1) Elemental diet: in this regimen all solid foods are replaced with an elemental, amino acid based formula.
- (2) Targeted elimination diet: this involves the elimination of foods based on allergy testing. Diagnostic accuracy can be a problem owing to false-positive and false-negative test results.
- (3) Empirical elimination diet: this does not require allergy testing and an option is 6-food elimination method in which milk/dairy, soy, wheat, egg, tree nuts/peanuts, and fish/seafood are eliminated from the diet.

Any 1 dietary therapy approach may not be feasible for every patient and family, and practitioners may have to individualize dietary approach. Once clinical and histologic remission is achieved, foods are gradually reintroduced with repeated histologic examination to ensure ongoing remission and to identify culprit food antigen(s). Compliance can be a challenge and perseverance and a close relationship with an experienced dietician are of paramount importance.

Pharmacologic Treatment

A variety of corticosteroid preparations have been studied for treatment of EoE and found to be effective at inducing remission in patients with EoE.⁵⁴ The potential adverse effects of long-term systemic corticosteroids have led to the off-label use of topical corticosteroid preparation such as swallowed fluticasone propionate and budesonide. Both these medications are effective at improving symptoms and histology in patients with EoE, and are considered as a first-line pharmacologic therapy. Adverse effects of topical corticosteroid preparations include esophageal candidal overgrowth, the risks of which can be mitigated with close attention to drug administration. Recent literature has raised concern about possible risk of adrenal suppression in patients on chronic topical corticosteroid treatment.⁵⁵ Systemic corticosteroids have a limited role in treatment of EoE and are generally reserved for patients with severe disease in whom other approaches are not feasible or have failed.

Fluticasone Propionate

Fluticasone is administered using a metered dose inhaler without a spacer for treatment of EoE. Patients swallow the medication that is delivered into the posterior oral cavity and not inhale it; they should not eat, drink, or rinse their mouth for 30 minutes following which a small amount of liquid is ingested to “wash off” the medication and mitigate risk of candida overgrowth. Treatment is generally well tolerated and patients often require long-term therapy because there is a 45% to 91% relapse rate on treatment discontinuation.^{56,57}

Budesonide

Budesonide has been evaluated in randomized trials and appears to be as effective as fluticasone in treating EoE. Budesonide is administered in an oral viscous slurry form to promote drug-to-esophageal mucosal contact. Oral viscous slurry can be compounded by mixing budesonide with a variety of nonallergenic carrier substances like sucralose (Splenda), Neocate Nutra, and other pudding-consistency foods.^{58,59} We recommend the slurry/paste be made using a small amount of carrier substance and be eaten slowly over 10 minutes. As with fluticasone, patients should not eat or drink for 30 minutes after taking budesonide and then drink some liquid to “wash off” the medicine.

Several other medications have been studied in the treatment of EoE including leukotriene receptor antagonists, sodium cromoglycate,

and immunosuppressive drugs, but most of these medications have not been found to be consistently effective in the treatment of EoE.⁶⁰⁻⁶³ It should, however, be noted that a limited number of studies have been conducted to assess the efficacy of different noncorticosteroid drugs.

Endoscopic Treatment

While endoscopic treatment does not address the underlying pathologic process, it is useful for management of long-term complications of EoE such as esophageal strictures.^{64,65} Our preference, if clinically indicated, is to document failure to medical therapy before performing dilation. Relapse is common after dilation although prolonged symptom remission can occur in some patients.⁶⁴ Though the data are conflicting, there is concern about slightly higher risk of esophageal mucosal shearing and perforation associated with dilation in patients with EoE.^{66,67}

Newer Treatment Options

A number of newer treatment options, including monoclonal antibodies against IL-5, IL-13, IL-4, and eotaxin-3, are under various stages of clinical trials. Multiple topical corticosteroid preparations, including a viscous budesonide suspension and a dissolving fluticasone tablets, are also being tested for use in EoE. An oral dissolving tablet of budesonide has been recently approved for use in adults by the European Medicines Agency.⁶⁸

Prognosis

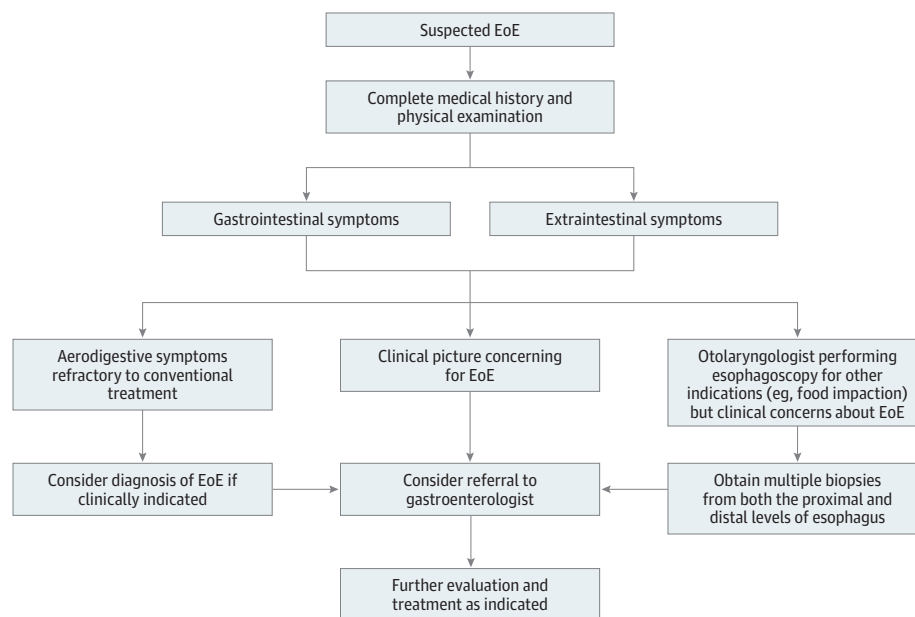
Knowledge on the natural history of EoE is limited and many aspects including complications incompletely defined. Data thus far does not suggest that EoE limits life expectancy or is associated with malignant diseases, but there is concern that the chronic, unchecked inflammation will result in irreversible structural damage to esophagus, leading to fibrosis, strictures, and impaired function of the esophagus. Recent studies have shown that increased duration of untreated EoE is strongly associated with increased development of strictures over time.⁶⁹ These findings not only provide important prognostic information but also underscore the importance of early diagnosis and treatment of inflammation associated with EoE.

Referral to Gastroenterologist

Eosinophilic esophagitis should be considered in patients presenting with gastroesophageal symptoms, such as unexplained vomiting, feeding difficulties, dysphagia, failure to thrive, and food impactions, especially in those with personal or family medical history of food allergies and atopic diseases. Eosinophilic esophagitis should also be considered in patients with refractory aerodigestive symptoms such as chronic cough, chronic rhinosinusitis, hoarseness, dysphonia, recurrent croup, and chronic laryngeal edema after other common causes of these conditions have been ruled out and symptoms are unresponsive to conventional treatment.

Early recognition and treatment of EoE is important because delays in diagnosis and/or uncontrolled inflammation can lead to fibrosis and esophageal luminal narrowing. Otolaryngologists are very well positioned in fostering early recognition and treatment of this condition. If the diagnosis of EoE is entertained or made by an otolaryngologist

Figure 4. Algorithm for Management of Eosinophilic Esophagitis (EoE)



gist, consideration should be made to refer the patient to a gastroenterologist for further, dedicated evaluation and treatment (Figure 4).

Future Direction

Eosinophilic esophagitis is an emerging condition with numerous opportunities for future research. Our understanding of pathophysiology of EoE and how it affects the esophagus and the airway is incomplete and future research opportunities include role of mast cells, and mechanisms of fibrosis seen in EoE. Recent advances in the field, with discovery of EoE transcriptome, have opened new avenues for personalized medicine both in terms of identifying subtypes of EoE and predict response to different therapies. Furthering engagement of patients and families, and awareness among clinicians, is paramount in treatment of this chronic condition.

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