Eosinophilic esophagitis: A newly established cause of dysphagia

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Abstract
Eosinophilic esophagitis has rapidly become a recognized entity causing dysphagia in young adults. This review summarizes the current knowledge of eosinophilic esophagitis including the epidemiology, clinical presentation, diagnostic criteria, pathophysiology, treatment, and prognosis. An extensive search of PubMed/Medline (1966-December 2005) for available English literature in humans for eosinophilic esophagitis was completed. Appropriate articles listed in the bibliographies were also attained. The estimated incidence is 43/10⁵ in children and 2.5/10⁵ in adults. Clinically, patients have a long history of intermittent solid food dysphagia or food impaction. Some have a history of atopy. Subtle endoscopic features may be easily overlooked, including a "feline" or corrugated esophagus with fine rings, a diffusely narrow esophagus that may have proximal strictures, the presence of linear furrows, adherent white plaques, or a friable (crepe paper) mucosa, prone to tearing with minimal contact. Although no pathologic consensus has been established, a histologic diagnosis is critical. The accepted criteria are a dense eosinophilic infiltrate (>20/high power field) within the superficial esophageal mucosa. In contrast, the esophagus associated with acid reflux disease can also possess eosinophils but they are fewer in number. Once the diagnosis is established, treatment options may include specific food avoidance, topical corticosteroids, systemic corticosteroids, leukotriene inhibitors, or biologic treatment. The long-term prognosis of EE is uncertain; however available data suggests a benign, albeit inconvenient, course. With increasing recognition, this entity is taking its place as an established cause of solid food dysphagia.

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INTRODUCTION
The esophagus normally is rather devoid of eosinophils. Not merely a simple conduit for swallowing food and liquids, the esophagus is being recognized as an immunologically active organ that can respond to a variety of stimuli like gastric acid and allergens by recruiting eosinophils and eliciting an inflammatory response. Eosinophils, for example, commonly infiltrate the lower esophagus in conjunction with gastroesophageal reflux disease (GERD). A relatively new entity, eosinophilic esophagitis, with more extensive eosinophilic infiltration, particularly in the proximal esophagus, possesses clinical features that differ from GERD. This entity is becoming increasingly recognized as a cause of dysphagia, often with a history of food impaction. Since its original description in 1978, EE has exploded onto the clinical scene, becoming a recognized cause of solid food dysphagia, first identified in the pediatric and now the adult population. Eosinophilic esophagitis is a disorder in which eosinophils infiltrate the superficial mucosa of the esophagus. Previously thought to be a rarity, case reports of eosinophilic esophagitis are rapidly accumulating in the literature. Clinical presentation and the endoscopic and histological features have become more firmly established, although a consensus is still lacking for an absolutely clear-cut diagnosis. Eosinophilic esophagitis has been associated with food allergies and atopic conditions such as asthma and atopic dermatitis.

Eosinophilic esophagitis is better known in the pediatric population through several published studies and reviews. Infiltration of eosinophils into the esophagus may result from conditions such as food allergy, infection, gastroesophageal reflux disease (GERD), or systemic eosinophilic conditions. The mechanism of dysphagia from eosinophilic esophagitis has yet to be defined.

This review summarizes the epidemiology, clinical presentation, possible pathophysiological mechanism, diagnosis, treatment, and prognosis for eosinophilic esophagitis, primarily focusing on adults with this condition.
Table 1 Clinical features of eosinophilic esophagitis

| Conditions          | Adult                                                                 | Pediatric                                                                 |
|---------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------|
| **Common**          | Dysphagia                                                           | Abdominal pain                                                           |
|                     | Food impaction/foreign body                                        | Failure to thrive                                                         |
|                     | Esophageal stricture                                                | Nausea/vomitting                                                          |
|                     | Nausea/vomiting/regurgitation                                       | Dysphagia                                                                 |
|                     | Heartburn                                                           | Food allergy                                                              |
|                     | Food allergy                                                        | Heartburn                                                                 |
| **Uncommon**        | Hematemesis                                                        | Food impaction                                                           |
|                     | Globus                                                              |                                                                           |
|                     | Weight loss                                                         |                                                                           |
|                     | Chest pain                                                         |                                                                           |
|                     | Abdominal pain                                                      |                                                                           |
| **Associated**      | History of atopy                                                    | Asthma                                                                    |
| Conditions          | Asthma                                                              | Allergic rhinitis                                                         |
|                     | Allergic rhinitis                                                   | Eczema                                                                    |
|                     | atopy                                                               | Atopic dermatitis                                                         |
|                     |                                                                     | Strong family                                                             |

**EPIDEMIOLOGY**

Epidemiological studies on eosinophilic esophagitis are lacking, likely from inadequate recognition and a paucity of established diagnostic criteria. Most publications are case reports or case series. Information is more widely available for the pediatric population compared to adults. This may be due to increased aggressiveness in investigating children with GI symptoms, or practice habits of pediatric gastroenterologists performing random biopsies in all cases. Fox et al. estimated that 6.8% of children with esophagitis had eosinophilic esophagitis, while Liacouras et al. indicated 3.4% of such children experienced reflux symptoms. A previous estimate of frequency was 1 per 100,000. A recent population-based study by Noel et al. in Ohio based on 103 children suggested a much higher figure: an annual incidence of 1 per 10,000 and a prevalence of 4.296 per 10,000 children, which rose over the period of the study - from 2000 to 2003. Whether this represented a true increase in the entity or bias from improved detection is unknown. A strong familial pattern was evident. In Italy the prevalence was reported to be 3.5%. A worldwide pediatric registry has been established.

Population-based data is lacking in the adults. Croese et al. identified eosinophilic esophagitis in 19 adult patients from a population of 198,000 over a 21 months period. The study, however, used 30 eosinophils per high power field as its criteria for diagnosis, a value higher than in most studies (usually >20/high power field). Therefore the incidence may be underestimated. The study also included both pediatric and adult populations with an age range of 14-77. Nevertheless, eosinophilic esophagitis appears to be an increasingly recognized entity with an accelerating frequency.

**DIAGNOSIS**

The diagnosis of eosinophilic esophagitis is based on clinical presentation, endoscopic or radiographic features, and histopathological criteria.

**Clinical features**

Clinical features (Table 1) of eosinophilic esophagitis have been previously well defined. There is a male predilection and a wide range of ages from pediatric to adult populations. Mean age in children ranges from 7-10 years, and 30-40 years in adults. Dysphagia is the most common symptom in adults and is usually longstanding. Food impaction, reflux symptoms, vomiting or regurgitation, and food allergy are also common. Abdominal pain (30%), vomiting (30%) and failure to thrive (20%) are more common in the pediatric population compared to only 3% adults with abdominal pain, however there may be a selection bias based on more aggressive evaluation of these symptoms in children compared to adults. The majority of the pediatric population will have a history of atopic conditions, such as asthma, allergic rhinitis, eczema, or atopic dermatitis. Noel et al. found 57.4% of children with eosinophilic esophagitis had a history of rhinoconjunctivitis, 36.8% wheezing, 46% possible food allergy, and 73.5% a family history of atopy. Adults also may have a history of atopy, but this is not as prevalent as in children. Croese et al. found that 46% of adults with eosinophilic esophagitis had a history of atopy, and only 25% food allergy. No relation has been found to connective tissue diseases such as scleroderma, rheumatoid arthritis, or lupus. Uncommon symptoms include hematemesis, globus, and waterbrash.

Laboratory features have not been extensively reported in eosinophilic esophagitis, therefore sensitivity and specificity of laboratory tests are unknown. Peripheral blood eosinophilia range from 5%-50% in the adult population with eosinophilic esophagitis. Increased serum IgE, positive skin prick or radioallergosorbent test (RAST) may be found in 40%-73% of patients. In a study of 26 children, 19 tested positive for skin prick testing, and 21/26 had positive patch testing. Skin testing may therefore help to identify causative food agents. These cases of rather overt immediate hypersensitivity are often not apparent in the adult patient. Indeed, food allergies in childhood may not persist to adulthood. Limited studies are available on the use of these laboratory values for the diagnosis of eosinophilic esophagitis.

**Radiological features**

The most common diagnostic imaging test that to date has detected eosinophilic esophagitis is a barium study. Zimmerman et al. retrospectively assessed 14 patients with confirmed eosinophilic esophagitis and found 10 with strictures (mean length 5.1 cm), of whom 7 had multiple fixed ring-like indentations. Four patients had esophagitis, 10 hiatus hernia, and 9 with evidence of reflux.

**Endoscopic features**

The “feline esophagus”, also known as the “corrugated esophagus”, “ringed esophagus”, or “concentric mucosal rings”, is the classic endoscopic description of eosinophilic esophagitis. A small caliber esophagus with a narrow fixed internal diameter, with or without a proximal esophageal stenosis, may also be the major feature. Adherent white exudates, vesicles, or papules along with loss of vascular pattern may indicate focal areas.
of eosinophilic infiltration\(^{30,31}\). Vertical esophageal lines also may indicate eosinophilic esophagitis\(^{32}\). Finally, the esophageal mucosa may be fragile, or the so called “crépe paper mucosa”\(^{33}\). This would explain the frequency of esophageal tears following dilation when treating the dysphagia associated with an apparently narrowed esophagus or its ringed structure (appearing like stricture). Thus the fragile esophagus is also characteristic. Endoscopic ultrasound, when performed, will show circumferential but asymmetric thickening of the muscularis propria\(^{34}\). The most common endoscopic findings in one relatively large series\(^{15}\) were, in order of frequency: mucosal rings (81%), furrows (74%), strictures (31%), exudates (15%), small caliber (10%) and edema (8%). The endoscopic appearance is helpful but not diagnostic without a confirmatory biopsy. All patients with endoscopic features of eosinophilic esophagitis should have distal and proximal esophageal biopsies to confirm eosinophilic esophagitis. Furthermore, this should be assessed prior to medical dilation of strictures, as medical treatment for eosinophilic esophagitis should be the initial treatment. There have been no studies assessing the histopathological diagnosis of eosinophilic esophagitis in those with dysphagia and normal endoscopy. Therefore, it is unclear whether all these patients should have the proximal esophagus biopsied.

### Histopathology

The diagnosis of eosinophilic esophagitis is dependent on eosinophilic infiltration of the squamous epithelium (Table 3). Although there is no consensus statement, most studies agree that >20 eosinophils per high power field (HPF) are diagnostic of eosinophilic esophagitis\(^{6,36,37}\). GERD can increase eosinophilic infiltration in the distal esophagus and therefore, mid or upper esophageal biopsies with increased eosinophils is more specific for eosinophilic esophagitis. Nevertheless, increased tissue eosinophils associated with GERD occur at a lower density <10/HPF\(^{36,37}\) (Table 4). Other features that are helpful but not essential for the diagnosis include basal zone hyperplasia, increased papillary size, and superficial layering of eosinophilic aggregates or microabscesses (aggregate of 4 or more contiguous eosinophils).

### PATHOPHYSIOLOGY

Eosinophils originate in the bone marrow. When mature, only a small number circulate in the peripheral blood; rather they are predominantly tissue-dwelling cells. In health, other than hematopoietic sites, eosinophils only reside in the lamina propria of the gastrointestinal tract, the exception being the esophagus. Resident in the
Avoidance of allergen depending on results of skin testing. Mice devoid of IL-5 or lacking the receptor for IL-5 have a significant reduction in GI eosinophils. Overexpression of IL-5 can promote eosinophilic accumulation\[38\]. Eotaxin is constitutively expressed in the GI tract and has a critical role in eosinophilic recruitment\[38\]. Transgenic IL-5 mice deficient in eotaxin fail to recruit eosinophils to the GI tract. It seems to be more important for chemotaxis to the stomach and intestine\[40,42\]. Fujiwara, however, showed significant staining of eosinophils with anti-eotaxin-antibodies in patients with EE\[43\].

IL-13 is a profibrotic cytokine and its production has been demonstrated in eosinophils. Likely Th2 mediated, IL-13 contributes to an inflammatory response and bronchial hyperreactivity\[10,44\]. Intratracheal IL-13 was shown to induce eosinophilic esophagitis, linking pulmonary to esophageal eosinophilic inflammation\[45\]. It appears that IL-13 is a key mediator of eosinophilic inflammatory pathways and in the recruitment of eosinophils to the esophagus\[10,45\]. IL-13 may be a serologic indicator of systemic inflammation\[46\]. IL-13 induction of eosinophilic esophagitis seems to be dependent on IL-5, eotaxin, and STAT-6\[45\]. Interestingly, mepolizumab, an anti-IL-5 antibody, was shown to be beneficial for symptomatic and histologic improvement in eosinophilic esophagitis\[37\]. It is possible that the interaction of IL-13, IL-5 and eotaxin may be a component to the development of eosinophilic esophagitis. IL-4 and IL-13 share a signal transduction pathway involving IL-4 receptor α chain and STAT-6\[45\]. IL-4 has been implicated in eosinophilic accumulation, regulating trafficking, and promoting adhesion to endothelial surfaces. Increased IL-4 secreting T cells in esophageal lesions were evident in one trial of patients with secondary eosinophilic esophagitis\[48\], but do not induce eosinophilic infiltration into the murine esophagus\[49\].

The net result of such chronic inflammation is irreversible structural change with loss of mucosal elasticity and the development of fibrosis in the subepithelial layers\[21\].

**TREATMENT**

The majority of reports on eosinophilic esophagitis are case reports or series. Therefore, randomized controlled trials (RCTs) for eosinophilic esophagitis treatment are not available. Indeed, a recent Cochrane review did not yield any RCTs, nor were the authors able to make any conclusions on benefits and harms of treatment regimens\[49\]. Treatment falls into two categories: (1) avoidance/removal of stimulation and (2) immune modulation. The majority of studies have been published in pediatric literature (Table 5). Avoidance of stimulation involves dietary changes with the elimination of foods or an elemental diet. Given that skin testing may help identify causative foods\[23,24\], this may help in avoidance of the specific culprit in some cases. Skin prick and skin patch testing may be more effective than skin prick testing alone. As shown by Spigel et al\[25\] in 26 children with documented eosinophilic esophagitis, 68 foods were identified in 19/26 by skin prick testing, and 67 foods in 21/26 by skin patch testing, for an average

| Table 4 Differential diagnosis \[40\] |
|-----------------|-----------------|
| **Primary**     | Idiopathic eosinophilic esophagitis |
|                 | Familial eosinophilic esophagitis |
|                 | Atopic esophagitis |
| **Secondary: Eosinophilic related** | Esophagitis |
|                 | Familial gastroenteritis |
|                 | Hypereosinophilic syndromes |
| **Secondary: Non – eosinophilic related** | GERD |
|                 | Recurrent vomiting |
|                 | Infection (helminth, parasitic, fungal) |
|                 | Esophageal GI stromal tumor |
|                 | Myeloproliferative disorders |
|                 | Carcinomatosis |
|                 | Allergic vasculitis |
|                 | Sclerodermia |
|                 | Drugs/iatrogenic |

| Table 5 Treatment regimens for eosinophilic esophagitis |
|-----------------|-----------------|
| **Treatment option** | **Protocol** |
| Elimination Diet | Avoidance of allergen depending on results of food allergy testing |
|                 | Oligoantigenic diet: Eliminate large number of suspected foods and allow limited nutritionally balanced diet |
|                 | Elemental diet: Various formulas such as Neocate (free amino acids, corn syrup solids, medium chain triglycerides) |
| Topical corticosteroids: | Fluticasone 220 μg puffer 4 puffs BID x 6 wk, swallowed, no spacer |
|                   | Rinse mouth with water and spit out |
|                   | No food or drink for 3 h after dose |
| Systemic (oral) corticosteroids | Methylprednisolone 1.5 mg/kg per day (or equivalent dose prednison) |
| Montelukast | Initial dose: 10 mg po daily |
|               | Titrating: Dose up to 100 mg/d depending on symptoms and tolerance |
|               | Maintenance: Once symptoms relieved taper down to minimal dose to maintain remission (usually 20 - 40 mg/d) |
| Mepolizumab | 10 mg/kg iv infusion q 4 wk x 3 doses |

BID: twice daily; PO: oral; IV: intravenous.
of 2.7 foods per patient. With specific food avoidance, 18 had complete resolution and 6 partial improvement. Kelly et al.[58] used an elemental diet in 10 children with eosinophilic esophagitis, and showed partial or complete resolution of symptoms in all 10. Markowitz et al.[51] conducted a study in 346 children with chronic GERD symptoms of which 51 were eventually diagnosed with eosinophilic esophagitis. They were then given an elemental formula (Neocate 1+, SHS Northa America, Gaithersburg, MD) consisting of free amino acids, corn syrup solids, and medium chain triglyceride oil. Forty-eight patients were fed via a nasogastric tube, 49/51 patients improved symptomatically and there was a significant decrease in the number of eosinophils in the distal esophagus. Average time to improvement was 8.5 d. Unknown is if any of these measures of food avoidance or elemental diets are effective in adults.

Topical steroid therapy has been shown to be helpful in a number of uncontrolled case series reports for both the pediatric[35,52,53] and adult populations[54]. Arora et al treated 21 adult patients with eosinophilic esophagitis (diagnosed via solid food dysphagia, ringed esophagus, and eosinophils >20/hpf in mid to distal esophagus) with a 6 wk regimen of fluticasone 220 μg 4 puffs swallowed twice daily. All patients had complete symptomatic relief for at least 4 mo. The only side effect was dry mouth, with no oral candidiasis reported. Three out of 21 patients had relapse at 4 months and 50%-60% of patients had recurrence of symptoms at 1 year[54]. Systemic steroid therapy was first reported by Liacouras et al in the pediatric population[58]. Of 1809 patients with reflux, 20 had documented eosinophilic esophagitis and were treated with 1.5 mg/kg oral methylprednisolone divided twice daily for 4 wk. Steroids and anti-reflux medications, such as proton pump inhibitors, were then tapered and withdrawn after 6 wk. Thirteen out of 20 patients had a complete response and 6/20 marked clinical improvement (total 19/20 responders). Average time to improvement was 8 d. All had histologic evidence of improvement and a significant decrease in peripheral eosinophil counts and quantitative IgE levels. At 1-year follow-up, 10/20 were asymptomatic and 9/20 relapsed. Relapers were treated with dietary changes, of which two required a second course of oral steroids. A randomized controlled trial comparing oral to inhaled corticosteroids is ongoing.

Leukotrienes promote eosinophilic trafficking, smooth muscle constriction, and mucous hypersecretion. Eosinophils generate large quantities of leukotriene C4, which is then metabolized to leukotriene D4 and E4 (LTD4 and LTE4 respectively). Montelukast is a selective inhibitor of the LTD4 receptor. Attwood et al[50] reported 12 adult patients with dysphagia secondary to eosinophilic esophagitis and investigated the use of montelukast in 8/12[59]. Patients were given an initial dose of montelukast 10 mg orally once daily and titrated up to a total of 100 mg daily. Once symptoms were relieved, dose was reduced to a “maintenance level” (20-40 mg/d). All patients were previously treated with proton pump inhibitors and 2 previously responded to corticosteroid treatment. All patients had symptomatic improvement, with only 2 having residual discomfort. Patients have been treated for a median of 14 months with no relapse. Six out of 8 experienced recurrence of symptoms within 3 wk of dose reduction or cessation. Important side effects were nausea and myalgias. Treatment did not change the density of eosinophils on repeat biopsy.

The central role of IL-5 in eosinophilic regulation and activation makes it a viable target for therapy. Mepolizumab is a humanized anti-IL-5 monoclonal antibody shown to be safe and effective in reducing sputum eosinophils in asthma but ineffective in outcome measures[56]. Garrett et al[19] performed an open label pilot study on 4 patients with hypereosinophilic syndromes, of which 3 had idiopathic hypereosinophilic syndrome and only 1 patient had eosinophilic esophagitis. This patient had dysphagia, esophageal narrowing on endoscopy with marked eosinophilia on biopsy, and was unresponsive to dietary elimination, topical, and oral corticosteroid treatment. Three doses of mepolizumab (10 mg/kg intravenous) infused at 4 wk intervals were given and patients followed for 18 wk after first infusion. Remarkable symptomatic improvement was achieved. Endoscopic and histologic improvement was seen at 4 wk after the last infusion. Peripheral eosinophils were reduced immediately after the first infusion and continued to the end of follow up. No serious adverse events were noted. No larger trials have been published. Other medications successfully used in eosinophilic gastroenteritis such as cromolyn and ketotifen (mast cell stabilizing medications), and suplatast tosilate (selective Th2 IL-4 and IL-5 inhibitor) have not been studied in eosinophilic esophagitis[24].

PROGNOSIS

Esposito et al[18] followed 7 children with eosinophilic esophagitis for 4 years, ages ranging from 6 months to 14 years old. All were treated with inhaled fluticasone. Two children experienced relapse at 1 year and 4 years post treatment, respectively, which improved with a second course of inhaled corticosteroid. Compliance was low in 2 patients and both had poor clinical and histologic response. Repeat treatment with appropriate dosing cured their symptoms. All children had normal growth after treatment. Interestingly, density of eosinophil infiltrate was inversely proportional to age, and progressively reduced with time. This may explain the higher incidence in children compared to adults. Liacouras et al[16] found a 50% one year relapse rate after a course of oral steroids. Finally, Orenstein et al[14] found that 1/3 of patients were asymptomatic without any therapy.

Straumann et al[11] documented the natural history of eosinophilic esophagitis in 30 adult patients. Mean age was 40.6 and mean follow up time was 7.2 years. None were treated with dietary changes or medical therapy. Only those with severe and frequent attacks were treated with dilatation. No patients died and all were in “good health” with maintenance of body weight. Twenty-nine of 30 (96.7%) patients had dysphagia throughout follow up: 7 experienced increasing dysphagia, 11 persistent but stable dysphagia, 11 decreasing dysphagia, and 1 complete resolution. Eleven out of 30 required dilatation, of which 10 had reduction or cure of dysphagia. In terms of the impact of
dysphagia on quality of life, 1/30 reported a significant negative impact on socioprofessional activities, 15/30 minor, and 14/30 reported no significant impact. No increased risk of malignancy was found and no eosinophilic gastroenteritis was documented. It appears that in the adult population disease tends to be stable with no significant effect on morbidity or mortality, at least for up to 11 years' follow up. Whether a persistent inflammatory state will affect motility, mechanical obstruction, inflammatory bowel disease, malignancy, or mortality in the long term has yet to be seen.

SHORTFALLS

A lack of consensus for diagnosis hinders research progress in eosinophilic esophagitis. Case descriptions to date have used variable cutoffs for eosinophil infiltration ranging from >15/HPF to >30/HPF. This not only affects the epidemiological data for incidence and prevalence, but also affects the inclusion/exclusion into trials and historical response to therapy. Furthermore, no distinction is made between proximal and distal esophageal biopsies, which might influence the pathologist into the diagnosis of esophagitis secondary to reflux rather than idiopathic eosinophilic esophagitis. Biopsies are essential for the accurate diagnosis of eosinophilic esophagitis and are best taken from the proximal esophagus to better distinguish this entity from reflux esophagitis, even though the latter has a less dense eosinophilic infiltrate.

No objective criteria have been developed to assess the response to treatment. All studies to date have employed subjective improvement in symptoms, which is prone to bias. No randomized controlled trials to date have validated the efficacy of any treatment regimen. Elimination diets are inconvenient and result in low compliance. Topical steroid treatment seems safe and may be the most convenient and effective therapy in adults, though technique may be an issue. Oral corticosteroid has its myriad of side effects and complications. Montelukast may be effective but would be long-term treatment given its relapse rates off treatment. Given its benign natural history in which the majority of patients have minor or no impact on quality of life, these therapies should be validated with vigorous clinical trials that include an analysis of cost effectiveness.

Finally, what should be done with the non-responsive patient? Compliance should definitely be confirmed. Repeat treatments may be beneficial. Combination therapy has yet to be explored. New biologic agents may be beneficial, but efficacy needs to be confirmed, and cost will be a limiting factor.

CONCLUSION

Since its original description, most publications have emphasized the clinical and histopathological presentation of eosinophilic esophagitis. The epidemiology is being better understood as clinicians are recognizing this unique disease entity. Diagnostic criteria are evolving which will improve the quality of future research. A consensus on the diagnosis of eosinophilic esophagitis is urgently needed. Despite a plethora of case reports, case series, case cohorts and reviews, randomized placebo-controlled trials are needed to confirm the efficacy of treatment regimens. In adult patients, topical corticosteroid appears to be the most convenient and efficacious treatment. As the pathophysiology of eosinophilic recruitment and activation in the esophagus is further elucidated, future treatment targets are possible. The long term natural history and response to treatment is awaited. Eosinophilic esophagitis may be a relatively new entity, undoubtedly overlooked in the past but this disease is here to stay. With better recognition, it has moved into the forefront of esophageal diseases.

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