

Eosinophilic Esophagitis

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Abstract Eosinophilic esophagitis is a chronic inflammatory disorder characterized by dense eosinophilic infiltration of the esophageal mucosa. The pathogenesis is incompletely understood and food allergies and aeroallergens have been implicated. The most common clinical presentation in adults is dysphagia to solids. Its associated endoscopic findings are distinct and include concentric rings and longitudinal furrows, although endoscopy may be unremarkable in a minority of patients. A number of management strategies exist; however, data are limited in adults, and only a few are based on randomized controlled trials. Management options include dietary modifications, pharmacological therapy, and endoscopic dilation.

Keywords Eosinophilic esophagitis ·
Esophageal eosinophilia · Dysphagia · Food impactions

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder characterized by eosinophilic infiltration of the esophageal mucosa. Over the last decade, and especially during the last 5 years, EoE has gained increasing recognition in both the medical and research community. Its pathogenesis remains unclear; however, there is a growing body of literature that supports a role for allergen involvement. Controversies remain surrounding the diagnosis and treatment of this condition. Although several management

strategies exist, few appear to provide long-term benefit. This article provides an up-to-date summary of the most current understanding of EoE.

Epidemiology

In the adult population, EoE predominantly presents in Caucasian middle-aged (30s–40s) men, although this disease has been described in women, in all age groups, and in different ethnic backgrounds [1–4]. Reports are mainly from industrialized countries (North America, Europe, East Asia, and Australia) with very isolated reports in South America [5–7]. EoE has not yet been reported in Africa [5].

The incidence and prevalence of EoE appear to be increasing. Whether this increase is a real phenomenon or partially explained by the increase in awareness of this disease is unclear. In a pediatric population from Hamilton County, Ohio, the incidence of EoE increased from approximately 1:10,000 patients to over 4:10,000 patients over a 4-year period [2]. In Olten County, Switzerland, where one gastroenterologist and one pathologist have followed the same population over several years, the number of new cases increased from 2:100,000 to 43:100,000 over a 19-year period [8].

In a Swedish population, upper endoscopy was performed on 1,000 random asymptomatic patients. Using 15 eosinophils per high power field (hpf) as a diagnostic threshold, the prevalence of EoE was 1.1% [9]. At our institution, we performed upper endoscopy with random biopsies on 400 consecutive patients presenting to our gastroenterology clinic for a variety of indications, which revealed a prevalence of EE of 6.5% using 20 eosinophils/hpf as a cutoff [10]. The prevalence of EoE in patients with dysphagia was 10%. In another study, upper endoscopy was performed on

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376 patients presenting with dysphagia, of which 33 of 222 (15%) patients had EoE [11].

Some data suggest that EoE has a genetic predisposition. Zink et al. [12] reported 17 cases of EoE in seven different families spanning two generations in some families and involving siblings in one family. Furthermore, 6.8% of patients with EoE had a first degree relative with EoE [13]. Liacouras et al. [14] reported a history of atopic disease in 43% of first degree relatives of patients with EoE.

Natural History

Straumann et al. [2] described the natural history of EoE in a cohort of 30 patients (22 men and 8 women, mean age 40.6 years) followed over an average of 7.2 years (1.4–11.5 year period). Esophageal dilations were performed in 11 patients with severe or frequent dysphagia. The remaining 19 did not have symptoms severe enough to require dilation. Of the treated patients, six were free of dysphagia, and symptom improvement was noted in four patients. One patient had no response to dilation. After a mean of 8.6 months, dysphagia eventually persisted or recurred in 29 of 30 patients (96.7%). However, only a minority of the patients had symptoms that impacted their quality of life.

In one retrospective longitudinal study in a pediatric population, Liacouras et al. [14] followed 381 children with EoE (66% male, mean age 9 years) treated with systemic and topical corticosteroids. Among 39 patients treated with oral methylprednisolone (1.5 mg/kg/day, maximum dose 40 mg/day), 34 of 39 (87%) had recurrence of symptoms within 6 months. Seventeen patients were treated with swallowed aerosolized fluticasone propionate (110 mcg twice daily for children <8 years of age and 220 mcg twice daily for children >8 years of age). Symptoms recurred in 16 of 17 (94%) patients within 6 months of discontinuation of medical therapy.

These studies suggest that EoE is a chronic disorder that may not respond to short-term therapies. There have been no known malignancies or deaths associated with EoE; however, recent reports describe patients with EoE and Barrett's esophagus with dysplasia [15, 16]. It is unclear whether this association is secondary to the possible relationship between EoE and gastroesophageal reflux disease (GERD) or a coincidental and unrelated occurrence [17].

Pathogenesis

The underlying pathogenic mechanism of EoE is poorly understood, and both food allergies and aeroallergens have been implicated [18, 19]. Data supporting the association

between food allergies and EoE predominantly comes from the pediatric population. Assa'ad et al. [20] studied 39 children with EoE (mean age 6.6 years old). All patients underwent skin prick testing (SPT), and 26 of 39 (67%) had a positive reaction to food. Furthermore, most pediatric patients have improvement of symptoms when treated with an allergy-free diet [21]. Mishra et al. [22] demonstrated that intranasal introduction of an aeroallergen (*Aspergillus fumigatus*) in a mouse can induce esophageal eosinophilia, which also supports aeroallergen involvement in the pathogenesis. A case report describes a woman with EoE presenting with exacerbation of symptoms during pollen season with subsequent resolution of symptoms and near resolution of esophageal eosinophilia seen in the winter time [23]. A seasonal variation in the diagnosis of EoE has been noted in the pediatric and adult population suggesting aeroallergen involvement in the pathogenesis [24, 25]. At our institution, we noted a correlation between grass and tree pollen and the number of EoE patients seen in the spring time, and a correlation between weed pollen and EoE patients seen in the summer time [26]. These findings may be explained by allergen sensitization inducing esophageal eosinophilia. Aeroallergens may be deposited in the nares and pharynx and introduced in the esophagus with swallowing of secretions [23]. Another explanation may be related to the systemic immune response of allergens. Once a susceptible patient is exposed to an allergen, the bone marrow increases eosinophil production with subsequent migration of eosinophils to the esophagus in patients with EoE, similar to the migration of eosinophils to the airways in asthmatics [27, 28].

The "allergic response" theory is outlined as follows: (1) antigen presenting cells (APC) bind allergens, process them, and display them on their cell surface to T cells; (2) this stimulates T cells to become TH-2 (T Helper-2) cells, which produce interleukin-5 (IL-5) and other cytokines [29]; (3) IL-5 activates the bone marrow to produce eosinophils, which are released into the blood stream [30]; (4) in response to allergens, mast cells release interleukins (IL-4 and IL-13), which upregulate the production of eotaxin-3 [31]; (5) this chemotactic cytokine plays a central role in the activation and recruitment of eosinophils by binding to chemoattractant chemokine receptor-3 (CCR-3), which is highly expressed on the surface of the eosinophil [32]. One recent study analyzed esophageal tissue by a genome-wide microarray expression analysis in 13 children with EoE. The gene which encodes eotaxin-3 was over-expressed and induced more than 50-fold when compared with controls [33]. (6) TH-2 cytokines induce the expression of very late antigen-4 (VLA-4) and vascular cell adhesion molecule (VCAM), which mediate adhesion on the surface of eosinophils [34]; and (7) through diapedesis, eosinophils migrate into the esophageal mucosa, which

should not harbor any eosinophils under normal conditions (Fig. 1) [35]. Injury then occurs secondary to degranulation with release of inflammatory mediators, including major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidases [35–37].

Recently, Spechler et al. [17] suggested a complex relationship may exist between GERD and EoE. It has been established that GERD can cause a low level of esophageal eosinophilia (<7 eos/hpf). However, a recent study discovered that a small percentage of adult patients with severe GERD had greater than 20 eosinophils per hpf [38]. Although the presence of EoE and GERD may be a chance association without a pathogenic link, there are multiple theories describing how EoE and GERD are related. In some patients with EoE, gastric acid may damage the tight junctions of epithelial cells resulting in increased permeability which allows penetration of allergens (food or aeroallergens) between these cells (Fig. 2) [17, 39]. Further confusing the distinction are the histologic findings of basal cell hyperplasia and dense epithelial eosinophilia in the esophagus which may be characteristic of both disorders.

Clinical Manifestation

Dysphagia is the most common presenting symptom ($>90\%$) in patients with EoE. Patients typically describe the dysphagia as intermittent and mostly with solid foods. Food impactions may also be the presenting sign of EoE in many patients. Desai et al. [41] studied 31 patients presenting with food impactions over a 3-year period; 17 of 31 (55%) had histologic evidence of EoE. Lastly, heartburn may be a presenting symptom in one quarter of patients [40].

Diagnosis

The diagnosis of EoE may be suggested based on clinical presentation, barium upper gastrointestinal series, or endoscopic findings; however, esophageal tissue demonstrating eosinophilic infiltration of the mucosa is required to establish the diagnosis. Variability in the literature exists regarding the number of eosinophils required to make the diagnosis. Most studies have used 15–20 eosinophils in the

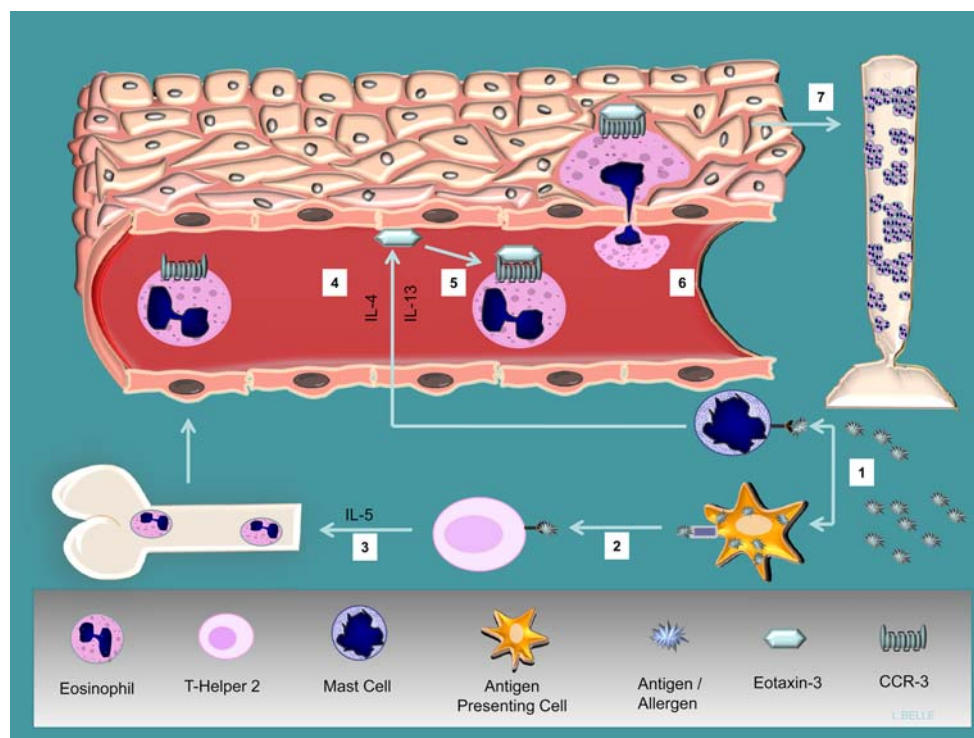


Fig. 1 1 Allergens bind to mast cells and antigen presenting cells (APC), which process them and display them on their cell surface to T cells. 2 This stimulates T cells to become TH-2 cells which produce interleukin-5 (IL-5). 3 IL-5 activates the bone marrow to produce eosinophils. 4 In response to allergens, mast cells release interleukins (IL-4 and IL-13), which upregulate the production of eotaxin-3. 5 This cytokine plays a central role in the activation and recruitment of eosinophils by binding to chemoattractant chemokine receptor-3

(CCR-3), which is highly expressed on the surface of the eosinophil. 6 Through diapedesis, eosinophils migrate into the esophageal mucosa. 7 This causes eosinophilic infiltration in the esophagus. Injury then occurs secondary to degranulation with release of inflammatory mediators, including major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidases. Illustration by Laverne Belle

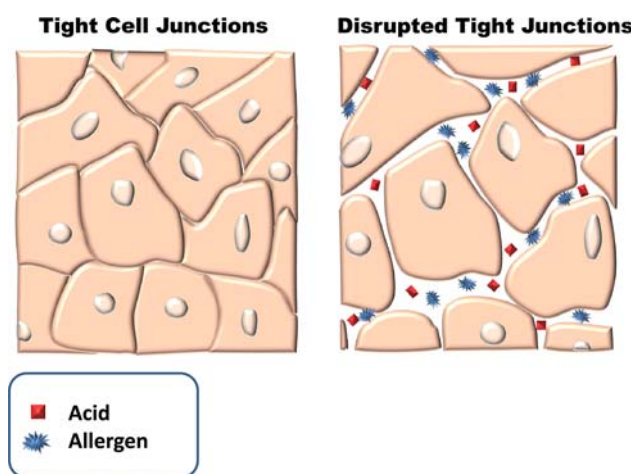


Fig. 2 Peptic acid causing damage to tight cell junctions allowing increased permeability and easier penetration of allergens. Illustration by Laverne Belle

peak high power field (400 $\times$) [42]. The American Gastrointestinal Association (AGA) released a consensus statement recommending greater than 15 eosinophils in any high power field as criteria to make a diagnosis of EoE. The number of eosinophils chosen was arbitrary. The biopsies should be taken from several locations to maximize diagnostic yield [21]. Gonzalves et al. [43] demonstrated that five biopsies increased the sensitivity of diagnosis of EoE to 100% using greater than 15 eosinophils/hpf as a diagnostic threshold. It is our practice to take 4 biopsies (2 passes with double-bite biopsy forceps) from the distal esophagus (3–5 cm above the squamocolumnar junction) and 4 biopsies proximal to this location at 25–30 cm from the incisors due to the patchy nature of the disease.

Pathology

The presence of increased number of eosinophils in the esophageal squamous mucosa is a non-specific finding which may be seen in several disorders, including GERD, infection, drug induced injury, and Crohn's disease. A recent review article describes 'major' and 'minor' histologic features associated with EoE [44].

These may help distinguish EoE from other entities, namely GERD, but are not pathognomonic for EoE. Major features include epithelial eosinophilia (>15 eosinophils/hpf), microabscesses, described as clustering of 4 or more eosinophils, and superficial layering of eosinophils. Minor criteria include basal cell hyperplasia, papillary lengthening, spongiosis (increased intercellular edema), and an increase in other inflammatory cells, particularly lymphocytes and mast cells (Fig. 3) [44].

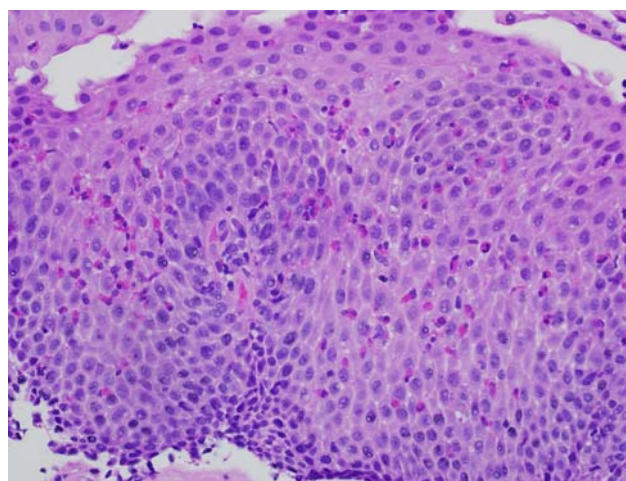


Fig. 3 Hematoxylin and eosin (H+E), $\times 200$, exhibiting squamous mucosa with basal zone hyperplasia, spongiosis, and markedly increased intraepithelial eosinophils with focal eosinophilic microabscess formation and widespread eosinophilic degranulation. Courtesy of Joel T. Moncur MD, PhD

Endoscopic Findings

The classic endoscopic findings in patients presenting with EoE are (1) concentric rings, otherwise referred to as felonization (Fig. 4); (2) longitudinal furrows or corrugation (Fig. 5); (3) white punctate exudative lesions or plaques; (4) avascular appearing mucosa; (5) friability described like crepe paper; and (6) occasionally a small caliber esophagus and even strictures can be seen in severe cases of EoE [45]. These findings are not pathognomonic but collectively suggest a diagnosis of EoE. The presence of Schatzki's rings has also been reported [46]. Up to 10% of patients may have normal endoscopic findings, and biopsies should be performed on all patients with symptoms suggestive of EoE despite a normal endoscopic examination [11, 40].

Role of Allergy Testing

As mentioned previously, allergies have been implicated in the pathogenesis of EoE. Furthermore, patients with EoE are more likely to have a history of atopic diseases [14, 21]. There is data to support that EoE is IgE mediated, which is reflected by the results of skin-prick testing (SPT). Atopic patch testing (APT) has also been applied to detect food allergies in children with EoE which supports a non IgE, cell-mediated response [47, 48]. Both SPT and APT have been successfully used to guide management in pediatric patients with EoE. However, the role of allergy testing in adults remains controversial, as it is not yet clear how the results of testing impacts management. Levels of eosinophils

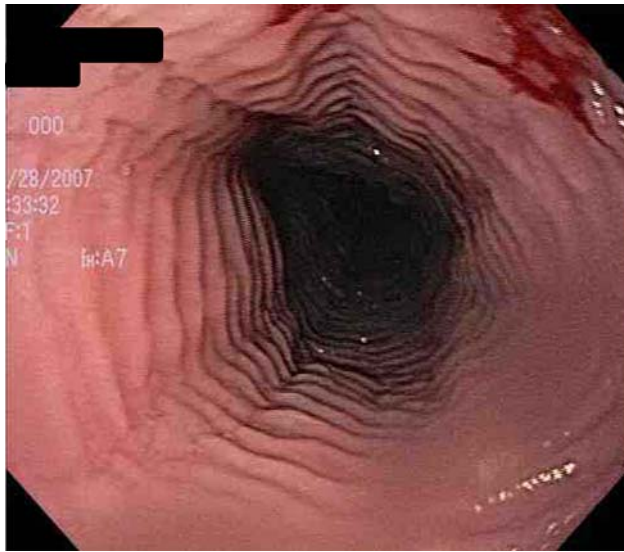


Fig. 4 Upper endoscopy imaging demonstrating multiple concentric rings in a patient with eosinophilic esophagitis

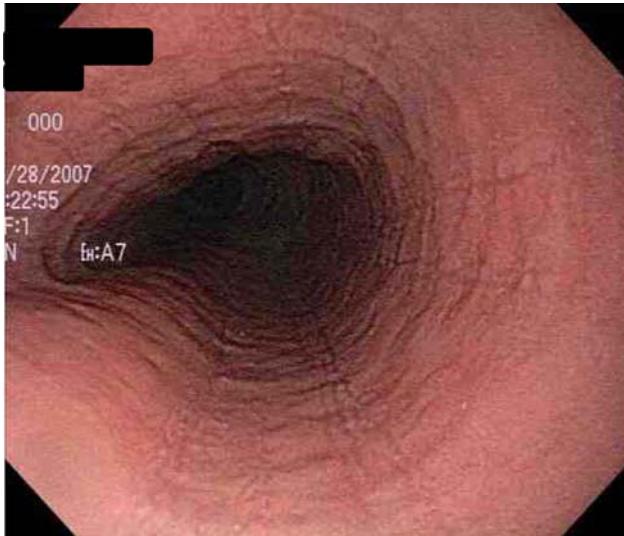


Fig. 5 Upper endoscopy showing esophageal furrows in a patient with eosinophilic esophagitis

and IgE can be measured upon presentation, but following them as a surrogate marker for disease activity may not be helpful.

Management

A number of treatment strategies exist, although only a few are based on randomized controlled studies and the majority are based on expert opinion from retrospective studies and case series. The difficulty in treating patients with EoE resides in the uncertainty of its etiology and the likelihood that multiple factors exist in its pathogenesis.

Current management strategies include dietary modifications, pharmacological therapy targeting allergy mediated disease, pharmacological therapy targeting acid suppression, and endoscopic dilation. The most current evidence for the treatment of EoE is summarized below. Each therapy discussed attempts to target a specific hypothesis for the pathogenesis of EoE (Table 1).

Dietary Treatment

Initial studies performed in the pediatric population suggested that food allergens may be implicated in the pathogenesis of EoE. In this population, the removal of a food stimulus has been shown to successfully resolve symptoms and improve histology. Three approaches have been proposed which include: (1) placement of the patient on a food antigen-free formula or an amino-acid-based diet; (2) the removal of food products which are most commonly associated with EoE (milk, soy, eggs, wheat, peanuts, and seafood); and (3) the elimination of foods which are likely to produce a reaction based on clinical history and allergy testing (skin prick and patch testing) [21].

Dietary therapy was first successfully reported in a study in which ten children were treated with an amino acid-based elemental diet for 6 weeks. Both symptom improvement and histologic changes were seen. Rechallenge with regular foods induced recurrent symptoms in 9 of 10 patients with milk, soybeans, wheat, peanuts and eggs being the most common inciting foods [49]. These findings were confirmed in a larger study by Markowitz et al. [50] where 51 patients with EoE were treated with elemental formulas for 1 month and showed a 96% response rate. However, due to poor palatability, the use of a strict amino acid-based formula required enteral feeding via a nasogastric tube in almost all patients. These earlier studies confirmed that elemental diet was an effective treatment option in children.

Spergel et al. [51] found that skin prick testing and patch testing in 24 EoE patients determined the offending agent in 75% of patients. Removal of the offending foods led to symptomatic and histologic improvement in the majority of these patients [47]. In another study, this group of authors also described 77% (112/146) of patients with EoE having histologic and clinical improvement with 6 weeks of dietary restriction based on allergy testing using SPT and APT.

Kagalwalla et al. [52] removed the six most common food allergies (dairy, eggs, wheat, soy, peanuts, seafood) and demonstrated a 74% clinical and histological efficacy in 35 patients. Liacouras et al. [14] found improvement in symptoms in nearly 65% (247/381) of pediatric patients with EoE treated with both elemental and elimination diets.

Table 1 Medical treatments for eosinophilic esophagitis

Treatment	Mechanism of action	Best evidence	Population studied	Adverse events	Recommendation
Elemental diet	Antigen free formulation of food	Markowitz et al. [50] 51/51, histologic and clinical improvement, retrospective	Pediatric	Difficult to tolerate, may require NG tube placement	Consider as first line in pediatric population
Remove commonly associated foods	Remove the 6 most common foods associated with EoE (milk, soy, eggs, wheat, peanuts, seafood)	Kagalwalla et al. [52] 26/35, histologic and clinical improvement, retrospective	Pediatric	None significant	Not as effective as elimination diet, but better tolerated. Reasonable first line in pediatric population
Elimination diet	Eliminating potentially causal foods based on allergy testing	Spergel et al. [51] 112/146, histologic and clinical improvement, retrospective	Pediatric	None significant	Not as effective as elimination diet, but better tolerated. Reasonable first line in pediatric population
Topical steroids	Locally acting steroid sprayed and then swallowed into esophagus	Konikoff et al. [60] 10/20 histologic resolution, prospective randomized controlled study	Pediatric	Oral thrush, esophageal candidiasis	Recommend as a first line agent in adults and pediatric population
Systemic steroids	Systemic anti-inflammatory medication	Schaefer et al. [62] 30/32 histologic resolution, prospective randomized uncontrolled study	Pediatric	50% relapse rate; Side effects from systemic steroids	In both pediatric and adults, recommended in severe cases or refractory cases
Cromolyn	Selective leukotriene receptor antagonist	Attwood et al. [63] 6/8 symptomatic improvement, case series	Pediatric	Minimal adverse effects (nausea and myalgias)	Not supported by current literature
Biologic agents	Monoclonal antibody to IL-5, a cytokine that stimulates eosinophil production	Stein et al. [66] 4/4 refractory cases histologic and clinical improvement, phase II study	Adult	Not completely known	Experimental
Montelukast	Inhibits degranulation of mast cells	Liacouras et al. [61] 0/14 cases had any improvement, retrospective	Pediatric	None significant	Not recommended
Proton pump Inhibitors	Decrease peptic acid exposure to esophagus allowing tight junctions to heal	Ngo et al. [69] 3/3 histologic resolution, case series	Adult, Pediatric	Minimal adverse effects of short-term PPI use	Recommend as a first line agent in adults and children
Dilation	Mechanically stretch esophagus. Does not treat underlying pathophysiology	Schoepfer et al. [75] 10/10 symptom improvement in steroid refractory cases, retrospective	Adult	Perforation, mucosal tears, post procedure chest pain	Recommend gentle dilation (24–30 Fr) in patients with strictures or refractory dysphagia in adults

Dietary therapy has proven to be an effective therapy in children and some clinicians have advocated using this as the first step in management in this population [50, 53]. This therapy is fairly rigorous and needs to be tailored to specific families and resource availability. There are, however, no data to recommend this form of therapy to adult patients with EoE. Therefore, in clinical practice, allergy testing and elimination diet are rarely attempted in the adult population, especially due to an unrealistic goal of restriction diet in an adult and the poor tolerance to elemental diets.

Pharmacological Therapy Targeting Allergy Mediated Disease

Topical Corticosteroids

The idea that EoE represented a locally acting allergic reaction in the esophagus was the impetus for investigators to search for a method to deliver a locally acting anti-inflammatory therapy. The topical application of either swallowed steroids or viscous budesonide to the esophageal mucosa has been studied and has been well accepted as an effective therapy, at least in the short-term, for EoE. In this manner, patients theoretically would benefit from the anti-inflammatory effects of steroids, but not the systemic risks, especially in patients who may require repeated doses. Both fluticasone and beclomethasone have been used successfully in multiple studies. Fluticasone is given via a metered dose inhaler without a spacer, and patients are instructed to swallow the medication rather than inhaling it. It is recommended that patients avoid food for 2–3 h after taking the medication and rinse their mouth with water to prevent developing oral thrush or esophageal candidiasis, well-known side effects of these inhalers.

The majority of the literature documenting efficacy of swallowed fluticasone comes from pediatric studies. Faubian et al. [54] showed symptomatic improvement in four patients treated with either fluticasone 880 µg/day or beclomethasone 84 µg/day for 6 weeks. Teitelbaum showed clinical and histologic improvement from 8 weeks of inhaled fluticasone two puffs twice daily (44 µg/puff for ages 2–4, 110 µg/puff for ages 5–10, and 220 µg/puff for ages 11 and older) in 100% (13/13) of patients [55]. Arora et al. [56] noted successful use of 6 weeks of swallowed fluticasone 220 µg/puff twice daily for the treatment of EoE in 21 adults, all of which had resolution of dysphagia. Three years after the original study, 6 of 10 patients contacted described recurrence of dysphagia symptoms. All had retreatment with swallowed steroids and 7 of 10 required repeat endoscopy [57].

In another study in a pediatric population, Noel et al. [58] found an immunologic and histological response to swallowed fluticasone 440 µg/puff twice daily in 20 children

with EoE. Ten patients had food allergies by SPT and ten patients were non-allergic. All of the patients (10/10) without allergies were responders to fluticasone and 6 of 10 patients with allergies responded to treatment. Additionally, 80% (16/20) of pediatric patients receiving oral viscous budesonide (1–2 mg/day) mixed with 5 g sucralose had clinical response to therapy. This may be helpful in children who are neurologically impaired or any patient not able to perform an inhaler puff-and-swallow sequence [59].

The best evidence for this therapy and the only double-blinded placebo-controlled trial was performed by Konikoff et al. [60] This study documented the efficacy of swallowed fluticasone propionate (440 µg twice daily) in a pediatric population for 3 months. Significantly more patients in the fluticasone group achieved histological remission (<1 eosinophil/hpf) on follow-up biopsies compared to the placebo group (50% vs. 9%, $P = 0.047$). In addition, there was a significant reduction in CD8 T-lymphocytes and mast cells in the post-treatment biopsies. Improvement was most striking in the proximal esophagus. Interestingly, the non-responders had positive skin prick testing. Patients treated with swallowed fluticasone have improvement in endoscopic, histologic, and immunologic parameters associated with EoE. These data show that topical steroids appear to be an effective short-term therapy; however, long-term usefulness remains unproven and frequent relapses are noted in multiple studies.

Systemic Corticosteroids

In children, systemic steroids (methylprednisolone: 1.5 mg/kg/day divided into twice daily dosing) have been shown to relieve symptoms and improve histology at 4 weeks, although most patients have symptom relapse upon withdrawal of the medication [61]. Recently, Schaefer et al. [62] published an open-labeled prospective randomized trial comparing the efficacy of swallowed fluticasone to oral prednisone to treat pediatric patients with EoE. Forty children were randomized to each arm. Study patients received 4 weeks of induction therapy followed by 8 weeks of weaning protocol. Induction doses included 1 mg/kg/dose twice daily of methylprednisolone (maximum, 30 mg twice daily) and twice puffs twice daily of fluticasone (110 µg/puff for 1–10 years of age and 220 µg/puff for 11–18 years of age). Histologic improvement was achieved in 94% (30/32) and clinical resolution was seen in 100% (32/32) of patients in the oral steroid arm at 4 weeks. However, 45% of children had relapse of symptoms at the 24-week time point. Results were confounded by the fact that restrictive diets to avoid food allergens were concomitantly used in this patient population.

These two studies showed that systemic oral steroids may have good efficacy in the pediatric population. However, symptom relapse is common upon discontinuation of

prednisone. Furthermore, systemic steroids carry the risk of severe side effects to include cushingoid features, weight gain, hyperphagia, osteoporosis and severe infections. There are no reported trials of oral steroid use in adults. Steroids may be considered in severe or refractory cases of EoE, but several courses may be required over time.

Leukotriene Receptor Antagonists

Eosinophils and mast cell degranulation induce tissue damage, which is mediated by cysteinyl leukotrienes. Leukotriene receptor antagonists, such as montelukast, have been shown to selectively block D4 receptors on eosinophils and dampen the inflammatory action of the eosinophil. This has only been studied in a small series of patients. Attwood et al. [63] treated eight adult patients with EoE for 14 months in an open-label study with montelukast 100 mg daily. Clinical improvement of symptoms was seen in 6 of 8 patients after several weeks of therapy; however, there was no change in esophageal eosinophilia noted. Once the medication was discontinued, the majority of patients had relapse in symptoms. This finding was repeated in a small case series of pediatric patients with EoE [64].

Biologic Agents

IL-5 has been found to be a major contributor in the eosinophil-inflammatory process in the esophagus, as first proposed by Mishra et al. [22]. Mepolizumab is a monoclonal antibody against IL-5, which has been shown to be safe, effective, and able to reduce eosinophil counts in the esophagus when used in patients with hypereosinophilic syndrome [65]. A recent small phase II study evaluated the use of mepolizumab in patients with severe EoE refractory to alternative medications and had encouraging results [66]. In this study, four adult patients with EoE received three IV infusions of mepolizumab (750 mg monthly). There was improvement in dysphagia and histology (ninefold decrease in eosinophil counts) in all patients. On post treatment endoscopy, less narrowing of the esophagus was noted as well. No major side effects were experienced. Larger studies are needed to address both the efficacy and safety concerns before there is general acceptance of this treatment regimen.

Other biologic agents have been studied as well for the treatment of EoE. A recent study described the effects of omalizumab, a humanized anti-IgE monoclonal antibody, for the treatment of eosinophil associated gastrointestinal disorders (EAGD). Seven of the nine subjects with EAGD had esophageal eosinophilia. All subjects were treated with subcutaneous injections of omalizumab (85–375 mg per dose) every 2 weeks for a total of eight doses. Concurrent treatment with steroids (budesonide or prednisone) was present in five patients, PPI treatment (omeprazole,

esomeprazole, lansoprazole) in five patients, and montelukast in one patient. Although the medication was well tolerated, there was a 25% increase in esophageal eosinophilia following treatment [67].

In a pilot study, Inflixamab, a chimeric monoclonal IgG1 antibody, was used to treat three adult patients who were refractory or dependent on steroids. Subjects were treated with 5 mg/kg by intravenous infusion at weeks 4 and 6. No clinical or histologic improvement was observed post treatment [68].

Mast Cell Inhibitors

Cromolyn sulfate, which is FDA approved for the treatment of asthma and allergic rhinitis, inhibits degranulation of mast cells and prevents release of histamine and leukotrienes after contact with antigens. Since several patients with EoE have a history of atopic diseases and mast cells are involved in the pathogenesis, the use of cromolyn sulfate was studied in pediatric subjects with EoE. Fourteen patients received 100 mg oral cromolyn four times a day for 1 month without any clinical or histologic improvement seen [14].

Pharmacological Therapy Targeting Acid Suppression

Proton Pump Inhibitors

Some allergists and gastroenterologists have entertained the possibility of a complex interaction between GERD and EoE [17]. Peptic acid is known to damage esophageal cells expanding the tight junctions between them. This may allow aeroallergens and food allergens to be deposited in these tight junctions and lead to an inflammatory cascade with an end result of esophageal eosinophilia. Ngo et al. [69] reported successful clinical and histologic improvement in one case series of three patients (one adult and two pediatric patients) with an 8 week course of omeprazole 10–20 mg twice daily. Another retrospective case series describing 8 of 17 patients with EoE presenting with food impaction had symptom improvement on PPI therapy, but histology was not obtained post treatment [41].

A recent study looked at the response of PPI (omeprazole, esomeprazole, lansoprazole) on 43 pediatric patients with EoE. Seventeen patients (40%), seven of which had abnormal pH monitoring, were responders, defined as <5 eosinophils/hpf on repeat esophageal biopsies. PPI doses were similar between responders and non-responders [70].

Although there is minimal evidence in the literature supporting the use of PPI in adults with EoE, this is still regarded as an accepted first-line therapy. Anecdotally, many of our patients with EoE are ‘PPI-responsive’ and this has been experienced at multiple other centers.

Dilation

Esophageal dilation has been used to treat complications of EoE, such as strictures, but only provides transient symptom improvement. Both controlled radial expansion (CRE) or through the scope (TTS) balloons and bougies have been used for dilation. CRE balloons can be used to dilate a dominant or focal stricture which can limit esophageal wall disruption with reduced shear force injury. Also, this method allows direct visualization of the mucosa with termination of the dilating session if mucosal tearing is visualized. There have been a number of case series describing successful dilation using balloon and bougie dilators (47–100% efficacy), primarily in adult populations [2, 3, 71–76]. The most recent of these studies by Schoepfer et al. [75] reported successful dilation in 10 of 10 adult patients with EoE refractory to topical steroids. There are a few studies that have used a combination of PPI therapy and dilation with similar efficacies in improving dysphagia (54–84%) [76, 77].

Dilations should be performed carefully and gradually due to the fragility of the esophageal mucosa and possible fibrosis of the esophageal wall. Complications of esophageal dilation in patients with EoE include deep mucosal tears, perforation, and an increased need for post endoscopic analgesia [39]. Complication rates reported by Cohen et al. [78] include 7 of 36 mucosal lacerations (19.4%), 3 of 36 perforations (8%), and one emesis-induced rupture (3%). These complication rates are higher compared to the experience at our institution.

Our group has dilated over 35 adult patients with EoE with balloon and bougie dilators over the last 2 years without any major complications to include perforations. Complications can be minimized if appropriate caution is taken when dilating patients with EoE. Our recommendation is to begin small and gradually increase depending on the degree of resistance when passing the dilator. Generally, we will begin with an 8–10 mm bougie. If resistance is met upon advancing the dilator, we will use two consecutive dilators in increments of 1 mm for that session. However, if very mild or no resistance is encountered on initial dilation, we then use three consecutive dilators in increments of 1 mm. Occasionally, we bring patients back who continue to have symptoms for another bougie session. Although esophageal dilation may not address the underlying disease process and has complications associated with it. We recommend it as an adjunct in patients with strictures who continue to have difficulties with swallowing after medical therapy or those who present with a strictured esophagus upon initial presentation. Furthermore, dilations may be helpful even when no dominant strictures are seen. There are no studies to date comparing dilators for the treatment of EoE.

Conclusions

Eosinophilic esophagitis is a chronic condition and an important cause of dysphagia and food impactions in adults. Its diagnosis remains controversial, but it is currently accepted to be a clinical diagnosis with dense (>15 eosinophils/hpf) esophageal eosinophilia. Several biopsies should be taken from the proximal and distal esophagus to maximize diagnostic yield. The role of allergy testing is controversial; however, many centers are exploring its use in adults. Topical steroids and proton pump inhibitors continue to be accepted as first line therapy in adult patients with EoE. Dietary treatment appears to be more effective in inducing remission in the pediatric population and is currently being studied in adults with EoE at some centers. The use of biologic agents requires further investigation. Cautious dilation is generally safe and may be performed with either balloon dilators or bougies in patients with strictures or refractory symptoms. Data on maintenance therapy remains limited, and the majority of patients appear to have relapses in symptoms. Multiple factors are involved in the pathogenesis of EoE, and thus evaluation and management is best approached by a multidisciplinary team of a gastroenterologist, allergist, and nutritionist.

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