

Emerging Therapeutic Options for Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus that often occurs in atopic persons. Management strategies include pharmacotherapy, dietary modification, and endoscopic therapy, although patients will often have a relapsing and remitting course. Currently, the primary pharmacotherapy for EoE consists of corticosteroids. Immunomodulators, leukotriene antagonists, biologics, and monoclonal antibodies are currently under study for treatment of EoE. The role of immunoglobulin E-mediated allergic reactions has been well documented and may provide insight into the etiology and effective therapy of EoE.

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated¹ “clinicopathologic disorder” that consists of symptoms of esophageal dysfunction and pathologic evidence of eosinophilic inflammation that is isolated to the esophagus, not responsive to proton pump inhibitors (PPIs), and not explained by another disorder.² Symptoms associated with EoE include a clinical spectrum of presentations from feeding difficulties in infants and abdominal pain or nausea in older children to gastroesophageal reflux disease (GERD)-like symptoms and dysphagia in adults. The typical patient with EoE is a male (3:1 ratio) with an atopic history. The prevalence of EoE appears to be increasing. A 2005 Swiss study estimated the prevalence of EoE to be 23 per 100,000 persons,³ while more recent studies have found a prevalence of 43 to 55 per 100,000 persons.⁴⁻⁶

Among patients with esophageal complaints, EoE is a significant burden. The condition is found in 4.9 patients per 1000 upper endoscopies⁷ and may account for 7.7% of patients with dysphagia and an identifiable cause⁸ and 4% of patients with refractory GERD-like symptoms.⁹

EoE does not have any pathognomonic features, but fixed rings and mobile rings (also known as trachealization and feline esophagus, respectively; Figure 1), white exudates, linear furrows, and mucosal friability (Figure 2) are associated with EoE. Additionally, a greater-than-typical force required to obtain a biopsy or “tug sign” has been reported.¹⁰ Although these are characteristic findings, a study of 102

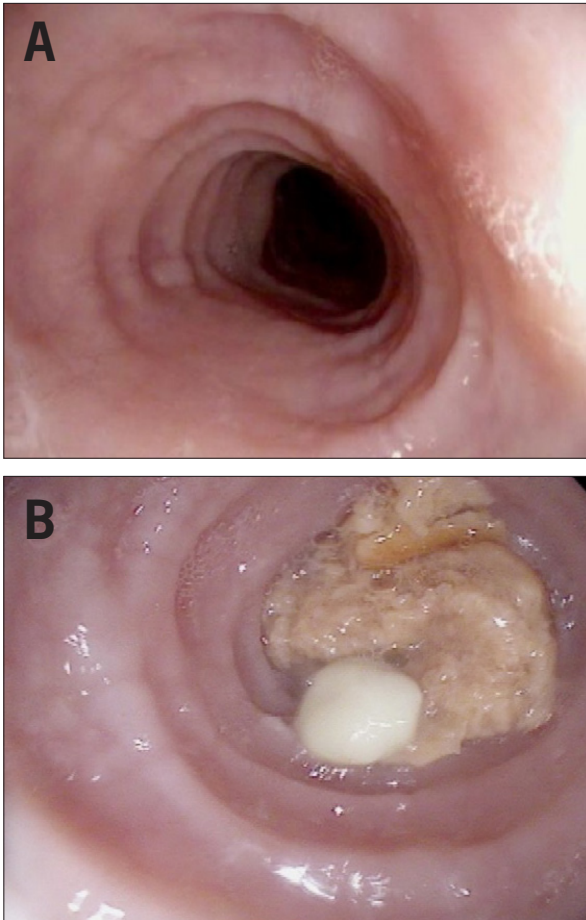


Figure 1. A 30-year-old man with allergic rhinitis and a history of food impaction presented to the emergency department complaining of food impacted in the esophagus. An upper endoscopy revealed concentric rings (A) and a bolus obstructing the midesophagus (B). Biopsies were consistent with eosinophilic esophagitis.

Images courtesy of Dr Showkat Bashir, The George Washington University.

patients found that 9.8% had biopsy-confirmed EoE with a normal-appearing endoscopy.¹¹ The finding of eosinophilic infiltration is the histologic hallmark of EoE; a finding of at least 15 eosinophils per high-power field is considered consistent with the diagnosis of EoE.^{1,2} However, EoE may be patchy and subject to sampling error, so multiple biopsies should be obtained.

Additional histopathologic findings may include eosinophilic microabscesses (Figure 3), superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, rete peg elongation, and subepithelial lamina propria fibrosis.^{1,12} Eosinophilic inflammation may result from exposure to allergens. In a murine model, eosinophilic inflammation developed in response to allergen exposure in a CD4+ T-lymphocyte-dependent manner.^{12,13}

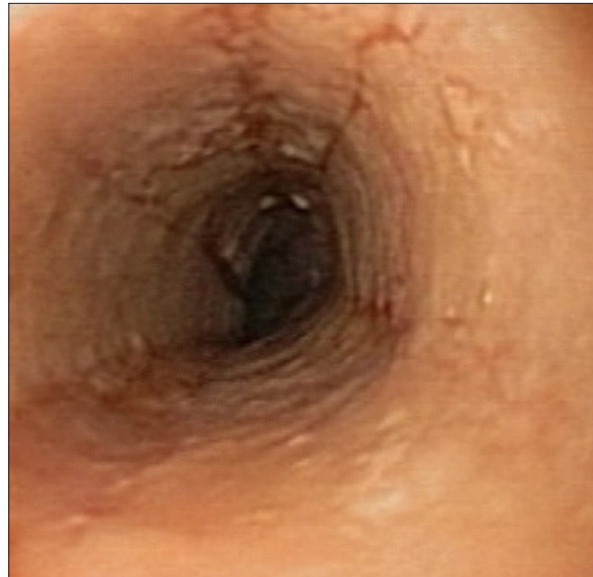


Figure 2. A 23-year-old man with a history of food impaction and episodic dysphagia requested evaluation. An esophagogastroduodenoscopy was notable for linear furrows as well as friable, “crepe paper” mucosa. Biopsies revealed numerous intraepithelial eosinophils.

Image courtesy of Dr Lance Uradomo, University of Maryland School of Medicine.

Mucosal eosinophils are necessary but not sufficient for the diagnosis of EoE. Esophagitis due to GERD also may cause significant eosinophilic infiltration. Patients may respond clinically and histologically to PPI therapy. This condition has been termed PPI-responsive esophageal eosinophilia (PPI-REE).^{1,2}

Management strategies for EoE include pharmacotherapy, dietary modification, and endoscopic therapy. Short-term relief of symptoms such as dysphagia, nausea, or abdominal pain is the focus of medical and endoscopic therapy, but many patients with EoE will have a relapsing and remitting course. To achieve a more durable solution, patients, gastroenterologists, and allergists may collaborate to identify allergens and design a desensitization protocol or elimination diet.

Pharmacologic Options

No drug has yet earned a US Food and Drug Administration indication for the treatment of EoE. Various medications targeting several portions of the eosinophilic inflammatory cascade have been used with variable effect. As noted above, PPIs have been shown to decrease eosinophil concentration in the esophageal mucosa; a trial of PPI therapy is necessary to exclude PPI-REE. Topical and systemic corticosteroids have been used with success. Although there is a great deal of

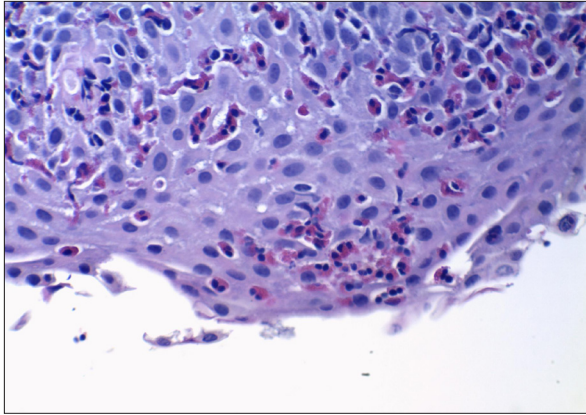


Figure 3. A 37-year-old man presented with recurrent dysphagia despite 8 weeks of proton pump inhibitor therapy. An upper endoscopy was performed. Biopsies revealed more than 15 eosinophils per high-power field and eosinophilic microabscesses, which were consistent with the diagnosis of eosinophilic esophagitis (hematoxylin and eosin stain, 40× magnification).

experience with corticosteroids, corticosteroid-sparing agents have been proposed as well. Early work in immunomodulators and targeted biologics has shown some promise, but further evaluation is needed.¹⁴

Proton Pump Inhibitors

The earlier understanding of esophagitis was that symptoms result from either GERD or EoE. Biopsies, however, may show mucosal eosinophils in either case.¹⁵ Significant overlap may exist between EoE and GERD. Patients with EoE may be predisposed to pyrosis and regurgitative symptoms. Likewise, GERD has been shown to cause eosinophilic infiltration.¹⁵⁻¹⁷ Biopsies may show significant eosinophil density in either case, and patients may respond to PPI therapy. In addition, patients with EoE may have concomitant GERD.¹⁸ Those with EoE appear to have increased expression of eotaxins, interleukin (IL)-5, and chemokine receptor-3. These cytokines and their receptors are involved in recruiting and activating eosinophils.¹ Eotaxin-3 has the strongest correlation. Measuring it in biopsy samples may help differentiate EoE from reflux esophagitis.^{19,20} Commercial eotaxin-3 assays are available.

Current guidelines describe PPI-REE as an entity distinct from EoE and not necessarily related to GERD.² Patients with PPI-REE have clinical, endoscopic, and histologic evidence suggesting EoE but experience symptomatic improvement and resolution of eosinophilia after a course of PPI therapy. Historically, EoE was diagnosed in many patients with PPI-REE initially treated with PPIs. Ngo and colleagues described a series of patients with EoE and their response to PPI therapy alone.²¹ Series have shown that a majority of adults²² with eosinophils in esophageal biopsies

have relief after PPI therapy; thus, these medications have become a first step in the management of eosinophilic inflammation in the esophagus.

A retrospective analysis of children with EoE showed less responsiveness to PPIs; only 23% of such patients with EoE had symptomatic and histologic resolution.²³ Although patients initially respond well to PPIs, some patients in whom PPI-REE is diagnosed will ultimately experience symptomatic and histologic recurrence.²⁴

In vitro studies have demonstrated a mechanism of activity for PPIs in halting esophageal inflammation. T-lymphocytes produce IL-13 and IL-4. These cytokines are associated with the allergic response and stimulate production of eotaxin-3, a chemotactic signal for eosinophils. IL-13 and IL-4 increase the secretion of eotaxin-3 by esophageal squamous mucosa, but omeprazole blocks this production of eotaxin-3 in both GERD and EoE.²⁵

Recent work by Moawad and colleagues¹⁸ demonstrated that fluticasone and omeprazole had similar effects on reducing esophageal eosinophil concentrations. In their study, 42 adult patients were randomized to fluticasone 440 µg twice daily or esomeprazole 40 mg daily. Although all 4 patients with GERD who were randomized to esomeprazole achieved histologic response, such improvement was not evident in any of the 4 patients with GERD who were treated with fluticasone. The study concluded that esomeprazole resulted in superior clinical response and offered the greatest benefit to those with GERD and eosinophils in the esophageal mucosa.

In light of the frequent response to PPIs, a trial of these acid-suppressing medications is necessary to exclude PPI-REE, an entity distinct from EoE.^{1,2} An 8-week course of therapy (dosages between 20 and 80 mg per day of omeprazole for adults and 1 mg/kg twice a day for children) is recommended.^{1,2} Although PPIs may successfully treat patients' symptoms and resolve their eosinophilic inflammation, it is important to note that such patients do not meet the criteria for EoE and should instead be considered to have PPI-REE.^{1,2}

Corticosteroids

EoE is characterized by chronic inflammation and eosinophilic infiltration of the esophagus. Systemic corticosteroid therapy is an effective management strategy for both adults and children,²⁶ but this treatment is associated with undesirable adverse effects. Conversely, topical corticosteroids provide potent anti-inflammatory effects without the systemic adverse effects of oral corticosteroid medications.

Studies indicate that systemic and topical corticosteroids are similarly effective in reducing eosinophilia and symptoms. A pediatric study treated 40 patients with prednisone and 40 patients with topical fluticasone.²⁷ A normal esophageal biopsy was achieved in 81.3% of

children who completed the prednisone protocol. In the fluticasone arm, 50% of patients had a complete response. All prednisone-treated patients and 97.2% of those on fluticasone were free of their esophageal symptoms. Forty percent of the patients receiving prednisone experienced adverse effects (eg, hyperphagia, weight gain, and cushingoid features), and candidiasis developed in 15% of those treated with fluticasone.

Topical corticosteroid therapy for EoE has been widely studied. The most commonly evaluated topical corticosteroid therapies are swallowed aerosolized fluticasone and a viscous budesonide slurry. There is also early work with ciclesonide, a topical corticosteroid, used in allergic conditions, that reaches high concentrations in the mucosal epithelium,²⁸ and with orodispersible preparations of budesonide.¹⁴ Topical corticosteroids may decrease expression of IL-5 and eotaxins. Both IL-5 and eotaxins are involved in recruiting eosinophils, and IL-5 may be overexpressed in patients with EoE.²⁹

Alexander and colleagues randomized 42 patients to a 6-week course of swallowed fluticasone or placebo.³⁰ Use of the fluticasone treatment resulted in complete histologic response in 62% of patients, whereas none of the patients using a placebo inhaler had such a response. Staining for eosinophil-derived neurotoxin was also decreased. The topical corticosteroid did not produce a statistically significant decrease in symptoms.

Budesonide preparations (oral viscous slurries and liquid suspensions) are an alternative to swallowed aerosolized fluticasone (ie, essentially an alternate use of medication designed for pulmonary treatment). Budesonide has had similar results to fluticasone with respect to symptoms, endoscopic findings, and histologic response. A retrospective analysis of 20 children treated with 1 to 2 mg of oral viscous budesonide showed that 16 (80%) had a histologic response and 3 (15%) patients had a partial histologic response to budesonide.³¹ There was a statistically significant decrease in symptoms. Of those patients who became asymptomatic, 72% had had a complete histologic response to budesonide. Similar results were found in a randomized trial of PPIs with budesonide or placebo in children.³²

Budesonide also has been effective in adults. In a randomized, controlled trial of oral budesonide, 36 adult and adolescent patients were randomized to budesonide vs placebo.³³ A 2-week course of budesonide was effective in inducing histologic remission, improving endoscopic findings, and decreasing dysphagia symptoms. Esophageal eosinophilia was decreased by 91.9% in the budesonide arm compared with no significant change in the placebo arm. Mild, asymptomatic candidiasis was seen in 16.7% of the budesonide-treated patients.

In addition to inducing remission in a short-term study, a 50-week protocol showed that budesonide main-

tained histologic remission in 35.7% (5 of 14 patients) compared with 0 patients in the placebo arm.³⁴ In aggregate, the symptom score was stable in the budesonide group vs an increase in symptoms among placebo-treated patients. Notably, some patients with EoE were maintained in symptomatic remission with budesonide. Although the effects of budesonide were modest in the year-long trial, the dosage of 0.25 mg twice a day was rather low, and a higher dose may yield more impressive effects.

Topical treatment of the esophagus is challenging because gravity and peristalsis work to clear the esophagus of retained medication. Aerosol, solution, and viscous slurry formulations of fluticasone and budesonide have been effective in treating EoE. Viscous formulations of budesonide permit greater mucosal contact time and result in a greater decrease in esophageal eosinophilia compared with a nebulized form. Additionally, patients treated with viscous budesonide had improvement in endoscopic findings.³⁵ There was no difference in esophageal candidiasis (9%-18%) between the 2 preparations.

When patients are treated with corticosteroids, histologic abnormalities and symptoms will likely recur after the medication is withdrawn. Helou and colleagues identified patients who had been diagnosed with EoE and treated with a 6-week course of swallowed fluticasone.³⁶ At a mean follow-up of 3.3 years, 91% reported recurrence of dysphagia. The mean time to symptom recurrence was 8.8 months, and 69% required repeated fluticasone therapy.

Current recommendations support consideration of topical corticosteroid therapy for both children and adults with EoE.^{1,2} Although topical corticosteroids have proven effective in improving EoE histology, their ability to eliminate symptoms remains unproven in adults. Fluticasone can be given in dosages of 440 µg to 880 µg twice daily for adults and 88 µg to 440 µg 2 to 4 times a day for children (up to the maximum adult dose). Oral viscous budesonide dosages are 1 mg/day for children younger than 10 years and 2 mg daily for older patients. First-line pharmacologic therapy of EoE is an 8-week course of a topical corticosteroid.² Systemic prednisone (1 to 2 mg/kg) can be considered for cases of severe dysphagia, weight loss, or hospitalization.¹

Corticosteroids are effective in inducing and maintaining clinical and pathologic remission in EoE but are associated with significant adverse effects. Systemic corticosteroid therapy (eg, prednisone) can result in cushingoid features, secondary adrenal insufficiency, bone mineral density abnormalities, glaucoma, hyperglycemia, and other adverse effects. Topical corticosteroids, while avoiding these systemic effects, are associated with oropharyngeal and esophageal candidiasis, which may limit their use. These effects make a targeted, corticosteroid-sparing anti-inflammatory medication desirable.

Immunomodulators

Immune-suppressing medications have been used with success in chronic inflammatory diseases such as Crohn's disease and ulcerative colitis, but there is little experience with these medications in EoE. Netzer and colleagues reported a series of 3 patients with eosinophilic disorders of the esophagus (2 with classical EoE and 1 with eosinophilic gastroenteritis involving the esophagus) who were treated successfully with azathioprine or 6-mercaptopurine.³⁷ In each case, the patient was able to be weaned from corticosteroids only after alternate immunosuppression. These antimetabolites may interfere with proliferation of lymphocytes and decrease inflammation. As with corticosteroid therapy, their effect was not durable. Cessation of the medication was met with symptomatic or pathologic relapse. Sirolimus suppresses immune response by inhibiting T-lymphocyte activation. There is extensive experience with sirolimus in prevention of organ transplant rejection. A trial of sirolimus for corticosteroid-dependent or corticosteroid-refractory EoE is recruiting subjects.¹⁴

Leukotriene Antagonists

Montelukast inhibits eosinophil protease activity³⁸ and blocks the D4 leukotriene receptor,³⁹ limiting eosinophil chemoattraction. Its mechanism of action provides a plausible therapeutic option. If eosinophil chemotaxis and cellular activity are decreased, the degree and effect of esophageal eosinophilia also may be modulated. Case reports and small series have suggested that montelukast may have utility in treating esophageal and gastrointestinal eosinophilic disease.

Quack and colleagues presented a patient with eosinophilic gastroenteritis whose remission was induced by prednisone and maintained with montelukast.⁴⁰ A case series of 8 children with EoE who failed PPI therapy documented successful treatment with montelukast. One patient had a complete response, and 6 patients had improvement in symptoms. The results, however, were confounded by the use of additional therapies. Four patients, including the complete responder, had concomitant prednisone therapy, increased PPI doses, or both; 3 patients had clinical response to montelukast alone.

Attwood and colleagues described a series of patients treated with montelukast.⁴¹ Eight patients were given montelukast for induction or maintenance of remission. Seven patients (87.5%) had complete resolution of dysphagia. At 14 months, no patients had relapsed while on treatment, but 6 had recurrence of dysphagia within 3 weeks of stopping the medication. Montelukast did not reduce the eosinophil concentration in mucosal biopsies.

Although these retrospective series provide some enthusiasm for montelukast treatment, a prospective series failed to show clinical and pathologic remission.⁴² Eleven

patients with EoE achieved remission with a 6-month course of fluticasone. After endoscopy and biopsies documented remission, montelukast 10 mg/day was given. Symptoms returned in 4 patients after 2 months of montelukast, but corticosteroid therapy reduced the eosinophil concentration in esophageal biopsies. After the montelukast treatment, mucosal eosinophil concentrations increased to near precorticosteroid levels. Symptoms also improved on corticosteroid therapy. Although patients' symptom scores increased during the montelukast regimen, they did not return to precorticosteroid levels.

The American Academy of Allergy, Asthma & Immunology (AAAAI) does not recommend leukotriene antagonists, mast cell stabilizers (eg, cromolyn sodium), or biologics.¹ American College of Gastroenterology guidelines note that there are limited data to support the use of these medications.²

Biologics and Monoclonal Antibodies

IL-5 is a key molecule in the activity of eosinophils. Produced by Th2 lymphocytes, it triggers eosinophil proliferation and activation and facilitates eosinophil response to chemoattractant messengers. IL-5 is overexpressed in the esophagus of patients with EoE.¹⁵ Mepolizumab and reslizumab are humanized monoclonal antibodies against IL-5. Mepolizumab was used in 4 patients with hypereosinophilic syndrome.⁴³ It resulted in a marked decline in peripheral eosinophilia, which was maintained for 12 weeks after administration. Notably, a patient with EoE exhibited clinical and histologic improvement after mepolizumab therapy. By inhibiting IL-5-mediated eosinophil activation and migration, these antibodies may represent a corticosteroid-sparing approach to decreasing eosinophilic inflammation in the esophagus. This hypothesis has been evaluated in randomized trials in children and adults.

Assaad and colleagues performed a prospective analysis of several doses of mepolizumab in children with EoE.⁴⁴ Fifty-nine patients received an infusion of mepolizumab 0.55, 2.5, or 10 mg/kg at Weeks 0, 4, and 8. Patients underwent an esophagogastroduodenoscopy at Weeks 12 and 24. At Week 12, 89% of patients had esophageal intraepithelial eosinophil counts less than 20 per high-power field. At Week 24, pathologic evidence of EoE recurred. Nausea, vomiting, and abdominal pain were the most common adverse events, but only 1 patient abandoned treatment because of the adverse symptoms.

A small, placebo-controlled trial in adults by Straumann and colleagues also showed improvement in EoE histology.⁴⁵ Eleven adults with active EoE were randomized to mepolizumab (2 doses of 750 mg given 1 week apart) or placebo. Those patients without histologic response to active therapy were given additional infusions at a higher dose. None of the patients achieved complete

histologic response (defined as <5 eosinophils per high-power field), but esophageal eosinophil counts decreased by 66% in the treatment group and 5% in the placebo group. Symptoms were not significantly different between the groups after treatment with mepolizumab or placebo. Mepolizumab did result in a significant decrease in transforming growth factor β 1 and tenascin expression. The decline in these markers may represent decreased inflammatory and remodeling activity.

Reslizumab, another humanized monoclonal antibody against IL-5, produced decreased esophageal eosinophil concentrations in pediatric patients with EoE.⁴⁶ Two hundred twenty-six patients were randomized and received 1 mg/kg, 2 mg/kg, or 3 mg/kg of reslizumab or placebo. Reslizumab treatment resulted in a 59% to 67% reduction in peak eosinophil count. Placebo-treated patients had a 24% decrease in peak eosinophil count. All treatment groups had improvement in the physicians' assessment of clinical response; there was no significant difference between the 2 groups.

Infliximab (Remicade, Janssen Biotech) is a chimeric antibody, which inhibits the activity of tumor necrosis factor alpha (TNF- α). In addition to T-lymphocyte-related cytokines, TNF- α is also increased in EoE. Straumann and colleagues conducted a prospective, open-label trial of infliximab in 3 adult male patients with corticosteroid-dependent EoE.⁴⁷ Infliximab did not result in symptomatic or histologic improvement.

QAX576 and RPC40406 are antibodies against IL-13 that could play a role in suppression of eosinophilic inflammation. Studies in patients with EoE have not yet been published.¹⁴

Omalizumab (Xolair, Novartis) is a monoclonal antibody targeted against human immunoglobulin E. Omalizumab is indicated in the treatment of asthma related to aeroallergens. Although the anti-immunoglobulin E antibody is effective in treating asthma, which is an eosinophil-, Th2 lymphocyte-, and IL-5-related disorder, it did not decrease esophageal eosinophil concentrations, and symptomatic improvement was not significantly different from that of placebo in a small, prospective, randomized, double-blind study.⁴⁸

OC000459 is a chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) antagonist that prevents prostaglandin binding and decreases eosinophilic inflammation in asthma. Patients with severe, corticosteroid-refractory or corticosteroid-dependent EoE (defined as dysphagia with almost all solids) were randomized to OC000459 or placebo. An 8-week course of therapy produced a small improvement in physicians' assessment of EoE and a modest reduction in esophageal eosinophil density,⁴⁹ suggesting that the agent may have more significant effects if used in higher doses or in patients with less severe disease.

An effective, targeted, corticosteroid-sparing therapy would reduce eosinophilic inflammation and esophageal symptoms while avoiding the potential adverse effects of corticosteroids. Further research is needed in the area of monoclonal antibodies.

Therapy Targeting Food Allergy

Earlier assessments that EoE and allergy are related only in pediatric populations have been supplanted by more recent evidence. As many as 37% of adults with EoE have a history of food allergy,³ and 61% have allergic diathesis of some type.⁵⁰

Food allergies are common in patients with EoE. A retrospective analysis established that 81% of patients with EoE referred for allergy testing had a positive result.⁵¹ Because high rates of asthma, allergy/anaphylaxis, eczema, and atopy exist among patients with EoE, the AAAAI recommends that such patients consult an allergist or immunologist. Fifty percent of adults with EoE test positive for a food allergen,⁵¹ and allergy testing by serum immunoglobulin E or skin prick is appropriate to identify comorbid food allergies in these patients.¹ Unfortunately, the tests are not sufficiently sensitive and specific; they reliably identify clinically relevant culprit foods only 13% of the time.⁵²

Airborne allergens also have been implicated in EoE. Studies have noted a seasonal variation in new diagnoses,^{6,50} suggesting that outdoor allergens play an etiologic role. Aeroallergens were shown to induce EoE in a murine EoE model.⁵³

Immunotherapy

Injection of purified allergen has become a mainstay of therapy for severe respiratory and cutaneous allergies. Similar desensitization has been reported in patients with environmental allergies and EoE.^{54,55} For those with a specific, identifiable allergen, immunotherapy could be an effective and durable mode of controlling EoE. Enthusiasm must be tempered, however, against the possibility that immunotherapeutic techniques may trigger EoE. This phenomenon has been used purposefully in the induction of esophageal eosinophilia in experimental mice¹³ and reported as a complication of human immunotherapy.⁵⁶ Further research is needed to determine the safety and efficacy of this technique.

Diet

Because of the allergic nature of EoE, investigators have pursued evaluation of dietary modification as a potential treatment. In this analysis, the more promising results are found in studies of pediatric populations as opposed to studies of adult populations. Pediatric series have demonstrated significant clinical and histologic improvement.

Elimination of dietary allergens resulted in improvement in symptoms and esophageal eosinophilia in 98% of children.⁵⁷ Dietary interventions based on allergy testing or food exposure testing include: elemental diet (the most restrictive type of diet), the 6-food elimination diet, and a more targeted dietary restriction based on allergy testing (eg, patch or skin prick testing). According to American College of Gastroenterology recommendations, dietary therapy may be considered first-line therapy in pediatric and adult EoE.²

Elemental Diets Elemental diets consist of a medical food product composed of an amino acid–based formula. The absence of complete proteins reduces the risk of allergic reaction. These diet formulations have been shown to be effective in some studies, but adherence to such diets is often difficult. Because many patients find elemental diets unpalatable, feeding tubes are often necessary to administer the diets. In addition, the elimination of “regular food” may be undesirable to patients.

When a cohort of children was treated with an amino acid formula, 97% had clinical and histologic improvement.⁵⁷ These diets, when adhered to, also may provide histologic improvement in adults. A recent study by Peterson and colleagues⁵⁸ demonstrated endoscopic and histologic improvement in adult patients. Patients were treated with the elemental diet and surveyed with upper endoscopy and biopsy every 2 weeks. Of the 18 patients who completed the trial, all but 1 showed improvement in endoscopic features of EoE: linear furrows and decreased exudates. Strictures, however, failed to improve on the diet. There was also a significant reduction (approximately 80%) in eosinophils, with 9 (50%) patients demonstrating a complete histologic response and 4 patients demonstrating a near-complete response.

Unfortunately, the elemental diet did not improve symptoms in adults. There was no significant decrease in dysphagia, regurgitation, or pyrosis. Moreover, adherence to the elemental diet proved difficult because of patient weight loss, deviation from the diet with consumption of normal food, and study dropout.⁵⁸ The unpalatable or intolerable nature of the elemental diet, combined with its expense, limits its utility for large groups of patients.

The Six-Food Elimination Diet A less restrictive approach, based on consumption of normal foods, is the 6-food elimination diet. Six foods have been identified as common causes of allergic response: cow-milk protein, soy, wheat, egg, peanut, and seafood. Empiric elimination of potential allergens has been associated with clinical and histologic improvement in children⁵⁹ and adults.^{52,60} Adhering to the 6-food elimination diet resulted in a reduction in esophageal eosinophilia in 73% of children. Lucendo and colleagues⁶⁰ described

a protocol of reintroduction of food types (eg, legumes, nuts, and milk proteins) followed by histologic assessment for esophageal eosinophilia. Patients who responded to the elimination diet and continued to avoid triggers of EoE remained in clinical remission for up to 3 years.⁶⁰ Gonsalves and colleagues also noted clinical, endoscopic, and histologic response to a 6-food elimination diet.⁵²

Restrictive Diets Spergel and colleagues established restrictive diets for 146 pediatric patients with EoE.⁶¹ Patients had skin allergy testing to guide dietary restriction and esophageal biopsies for evaluation of response. More than 75% of these pediatric patients had clinical and histologic response to an elimination diet. Skin prick and patch testing may accurately identify the necessary dietary changes in 70% of children. Skin prick or patch testing proved to be less useful in adults, identifying only 13% of culprit foods.⁵²

The prevalence of EoE is increased among pediatric⁶²⁻⁶⁴ and adult⁶⁵ patients with celiac disease. It has been hypothesized that these patients may have wheat or gluten allergy as a trigger for their EoE in addition to their gluten-sensitive enteropathy. However, data on treatment of concomitant celiac disease and EoE are limited. Studies have evaluated the response to a gluten-free diet. Although findings of celiac sprue improve, EoE response is less impressive. Abraham and colleagues reported a series of 9 children with celiac disease and EoE.⁶⁶ One patient treated with a PPI and gluten-free diet had a partial response on esophageal biopsy. Those on gluten-free diet alone continued to have evidence of EoE. The possibility of nonceliac gluten sensitivity or wheat allergy should be considered in patients with EoE. Those with celiac sprue should abstain from gluten exposure, but this may not be sufficient to alleviate esophageal symptoms.

Endoscopic Therapy

Dysphagia is a frequent complaint among patients with EoE.³⁶ Although not specific to EoE, endoscopic findings, such as concentric rings, fixed strictures, and luminal narrowing, are common. As with peptic and other strictures, the narrowing seen in EoE presents a therapeutic target that has led to the practice and study of esophageal dilation for relief of dysphagia related to EoE. Early experience with dilation for EoE included instances of bleeding and perforation.^{67,68} These findings limited the use of endoscopic therapy to patients who have severe symptoms and/or have failed pharmacologic therapy. Subsequent series have shown that dilation by balloon or bougienage can be safe and effective. A review of published reports regarding dilation in EoE estimated the incidence of perforation to be 1 in 671 dilations.⁶⁹

Schoepfer and colleagues performed a retrospective analysis of 10 patients who had failed topical cortico-

Table. Emerging Therapeutic Options for Eosinophilic Esophagitis

Therapeutic Option	Proposed Mechanism	Comments
Proton pump inhibitors	Reduce mucosal production of eotaxin-3, which leads to decreased eosinophil homing	<ul style="list-style-type: none"> – Reduction in eosinophil density – Symptoms and eosinophil infiltration recur with withdrawal of medication – Used in treatment of proton pump inhibitor–responsive esophageal eosinophilia
Topical corticosteroids	Fluticasone and budesonide reduce production of interleukin-5 and eotaxins	<ul style="list-style-type: none"> – Induction of histologic remission – Symptoms may remain stable – Recurrence of inflammation after withdrawal of medications – Complications: candidiasis
Systemic corticosteroids	Reduce production of interleukin-5 and eotaxins	<ul style="list-style-type: none"> – Induction of histologic remission – Symptoms may remain stable – Recurrence of inflammation after withdrawal of medications – Complications: cushingoid features, weight gain, hyperglycemia, hypertension
Leukotriene antagonists (montelukast)	Inhibit eosinophil protease activity, block leukotriene receptor	<ul style="list-style-type: none"> – Might contribute to maintenance of remission – Not currently recommended
Monoclonal antibodies	Antibodies to interleukin-5 decrease eosinophil homing, activation, proliferation	<ul style="list-style-type: none"> – Experimental – May induce remission, but symptoms recur after completing therapy
Immunotherapy	Reduces allergic response to specific allergens	<ul style="list-style-type: none"> – Biologically plausible – Reduces burden of allergy and risk of anaphylaxis
Dietary restriction	Limits exposure to known or potential allergens	<ul style="list-style-type: none"> – Improved biopsies in adults and children

steroid therapy for strictures related to EoE.⁷⁰ Patients underwent esophageal dilation using Savary dilators (to 12-19 mm in 1 to 5 sessions). None of the patients experienced esophageal perforation. Although 70% had some postprocedural odynophagia, it was self-limited and lasted only 1 to 3 days. At a follow-up appointment 2 to 6 months after completion of the dilation sessions, all patients were free from dysphagia.

A cross-sectional study of patients treated with esophageal dilation demonstrated favorable results at 14 to 40 months of follow-up. Eight of 10 patients were asymptomatic, with the remaining 2 patients reporting only seasonal or occasional dysphagia. Although dilation provided symptomatic improvement, it did not affect the underlying inflammatory process or eosinophilia.^{71,72}

A larger, retrospective analysis of 207 patients treated with esophageal dilation with or without antieosinophilic medications also showed the techniques to be effective and safe. Although 73% reported odynophagia, all were willing to have repeat dilations. There were no perforations or significant bleeding events reported. Two-thirds of patients reported that improvement in dysphagia symptoms lasted at least 1 year.⁷² The use of

esophageal dilation for EoE-induced dysphagia appears to be safe and effective. Nonetheless, it does not address the underlying eosinophilic infiltrative changes. As a result, most patients still require the aforementioned medical and/or allergist interventions for long-term maintenance care.

Balloon dilation also may be an effective technique for dilation in EoE. Madanick and colleagues described a series of patients who underwent esophageal dilation using a “pull-through” technique with a controlled-radial expansion balloon.⁷³ Use of a through-the-scope balloon allows direct visualization of the esophagus during the dilation maneuver, whereas bougienage requires serial, blind passes of a device while sensing resistance. In this series of 13 patients, resistance was encountered in 85%, and a tear was achieved in 69%. The technique provided improvement in dysphagia in 69% and had no serious complications.

The best strategy for initial management of EoE-associated dysphagia is not proven. To date, there has not been a randomized, prospective assessment of dilation vs medical therapy. Kavitt and colleagues⁷⁴ devised a model to determine the cost-effectiveness of 2 strategies: swallowed fluticasone followed (if necessary) by esophagogastroduo-

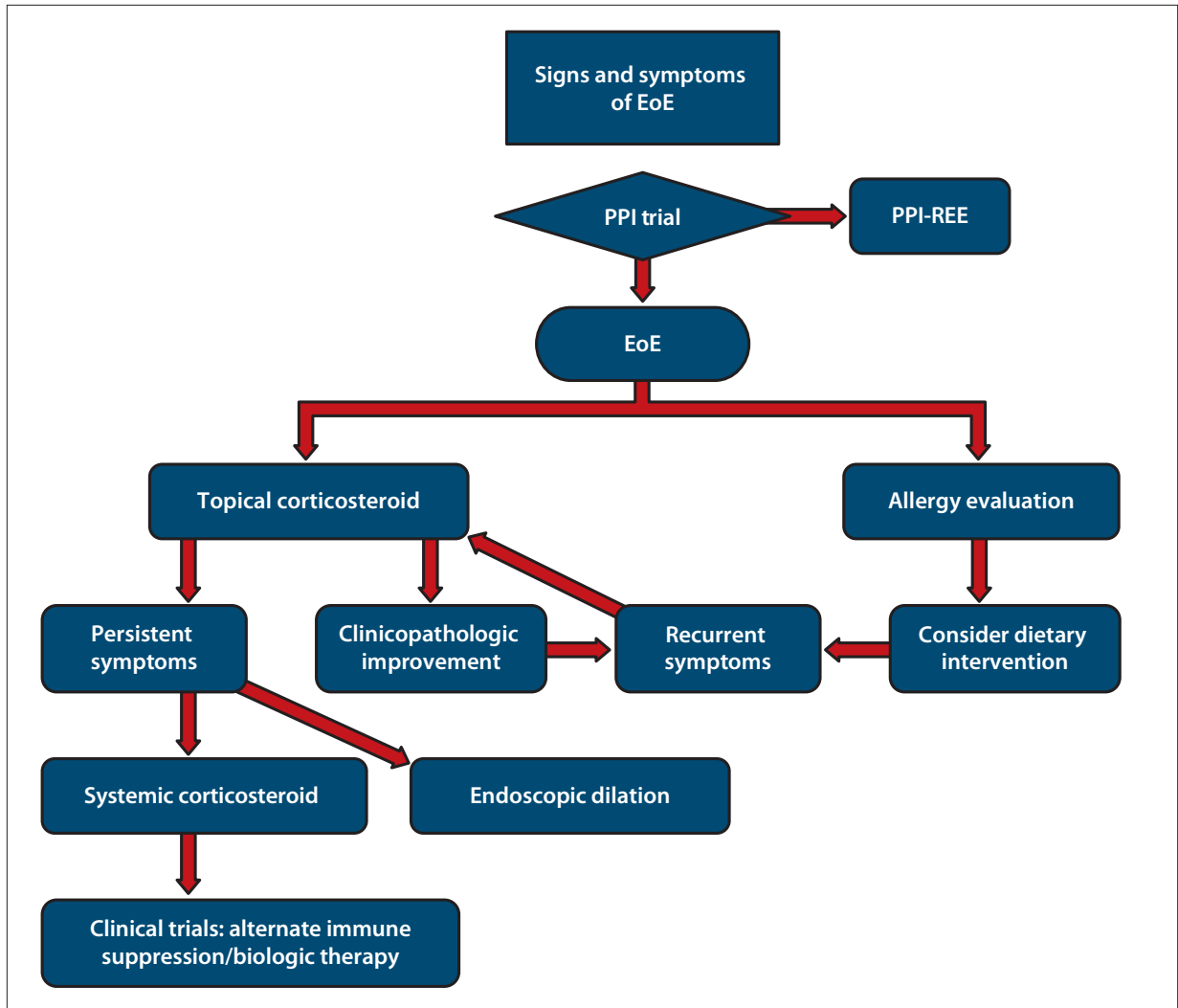


Figure 4. An algorithm for the management of eosinophilic esophagitis.

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; PPI-REE, proton pump inhibitor–responsive esophageal eosinophilia.

denoscopy (EGD) and dilation; and EGD and dilation followed by swallowed fluticasone if dilation was inadequate. Accounting for the probability and cost of managing complications, including candidiasis, bleeding, and perforation, the researchers determined that the EGD-first strategy would cost \$1171 per patient compared with \$1078 per patient in the fluticasone-first strategy.⁷⁴

Controversies and Questions

Several challenges face clinicians applying EoE literature to their practice. Chiefly, there is a lack of consensus on proper endpoints for EoE therapy. In addition, many studies are retrospective and small or include confounding variables that hinder their interpretation. Studies have been performed with adult, pediatric, or mixed popula-

tions and may not be easily generalizable to an individual patient. Finally, earlier series were performed prior to established definitions of PPI-REE and may include these patients among their cohorts. In the case of EoE, as with other challenging clinical situations, early research has raised new questions while also laying the groundwork for more robust trials.

Symptom control is of great importance for patients and can be assessed without invasive procedures. It is a common endpoint in therapeutic trials but is a necessarily confounded one. Patients with longstanding dysphagia may have established patterns of dietary modification to limit their swallowing difficulties. Patients in a placebo arm are, therefore, receiving a treatment in the form of avoidance of difficult-to-swallow foods.⁷⁵ This may result in an underestimate of the efficacy of the intervention

arm. Eosinophil density, concentration of eosinophil-related cytokines, and other histologic outcomes provide “hard” outcomes but may not correlate with symptoms from one patient to another.

Summary

EoE is a chronic inflammatory condition of the esophagus often occurring in atopic individuals. In the proper clinical setting, esophageal biopsies showing significant eosinophil concentration confirm the diagnosis of EoE. Some patients will respond to PPI therapy and, thus, receive a diagnosis of PPI-REE.

Patients with EoE will often have a relapsing and remitting course of symptoms, including feeding difficulties, abdominal pain, nausea, GERD symptoms and dysphagia. Patients may achieve temporary relief of symptoms using various medical or endoscopic therapies, such as topical or systemic corticosteroids or esophageal dilation (Table). An algorithm depicting EoE treatments is given in Figure 4. Unfortunately, EoE is likely to recur after cessation of treatment. The role of immunoglobulin E-mediated allergic reactions has been well documented in both children and adults. It points to the etiology of the disease but also provides a therapeutic target. Addressing the allergic underpinnings of EoE in collaboration with an allergist or immunologist may provide greater long-term control of the disease through the use of a targeted dietary modification or immunotherapy aimed at allergen desensitization.

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