Recent Advances in the Treatment of Eosinophilic Esophagitis
Shauna Schroeder, Dan Atkins, Glenn T Furuta

Abstract

First described nearly 20 years ago, eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus characterized by eosinophilic infiltration of the esophageal epithelium. Over 50% of the current literature on EoE has been published in the last 3 years, signaling both a rising incidence and increased recognition of this disorder. Treatment options available for patients with EoE include dietary management and/or pharmacologic therapy. An individualized approach to treatment is preferred, with an emphasis on patient parental preference. The objectives of this article is to discuss the current and future treatment options for EoE.

Clinical Symptoms & Features of Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) has a spectrum of presenting symptoms, including feeding difficulties, failure to thrive, vomiting, epigastric and chest pain, dysphagia and food impactions. Clinical experience and increasing evidence suggests that these symptoms may develop chronologically. Whether this occurs because children are able to better express themselves with age or because eosinophilic inflammation leads to changes in functional phenotypes remains unclear. For example, young infants and toddlers often present with failure to thrive and feeding difficulties. These early feeding difficulties may be manifested as food refusal, low variety intake, poor acceptance of new foods, unstructured mealtimes, holding food in the mouth, splitting food out and prolonged feeding time. Preschool and school-aged patients commonly complain of abdominal pain or vomiting, whereas dysphagia is the primary complaint among adolescents. Dysphagia is often described as difficulty swallowing food, while some patients report food sticking temporarily in the throat or chest before moving into the stomach. A carefully taken history often reveals that these patients develop compensatory mechanisms such as eating slowly, taking small bites, chewing excessively, drinking after each bite or avoiding specific foods with denser textures that are problematic, such as meat or bread. Food impaction is the common complaint of the adolescent and adult patient populations. The food impactions can result from fixed esophageal strictures or esophageal dysmotility. A prospective study investigating the natural history of EoE in a follow-up study of 30 adult patients for up to 11.5 years showed that EoE as a primary and chronic disease was restricted to the esophagus, led to persistent dysphagia and structural esophageal alterations, but did not impact the nutritional state. No malignant potential was associated with this disease. This study described 29 out of 30 patients with EoE who almost exclusively reported acute and recurrent dysphagia with impaction of solid foods.

Pathophysiology of EoE

A number of basic studies support a role for atopy in the pathogenesis of EoE. For example, one mouse model of EoE demonstrated that exposure to ubiquitous allergens led to esophageal eosinophilia and that specific cytokines such as IL-5 are critical to the generation of this response. In addition, intratracheal delivery of IL-13 induced esophageal eosinophilia in a dose-dependent manner, a process that could be inhibited by anti-IL-13 antibody blockade. In another murine model, epicutaneous allergen sensitization potently primed for respiratory allergen-induced esophageal eosinophilia. Collectively, these experimental models of murine EoE have identified a connection between sensitization of extraintestinal organs and the development of esophageal eosinophilia.
The presence of atopy and Th2 allergic inflammatory responses in patients with EoE was proposed by Straumann et al. in 2001.[14] High eosinophil infiltration in the esophageal squamous epithelium was observed in patients with EoE but not in control subjects. Interestingly, increased T-cell and mast cell numbers were also found within the epithelium of these patients. The study also showed increased expression of IL-5 and TNF-α in esophageal epithelial biopsy specimens.[14]

Studies in mouse models have also shown that Th2 signaling is required for the induction of esophageal eosinophilia. In these studies, mice genetically deficient in signal transducer and activator of transcription 6 (STAT 6), IL-13, IL-4 and IL-5 all have impaired induction of eosinophilia in response to allergen exposure.[15, 16] Furthermore, IL-13-deficient mice have reduced levels of allergen-induced experimental eosinophilia.[15] IL-13 is overexpressed in the esophagus of patients with EoE and selectively induces the eosinophil-activating chemokine eotaxin-3 by a transcriptional mechanism in the esophageal epithelial cells.[17, 18] One study characterized an EoE transcriptome showing 574 dysregulated genes in EoE patients compared with normal individuals. The gene with the greatest overexpression was eotaxin-3, which was highly correlated with eosinophil number in the biopsies.[1] Other dysregulated genes included periostin (induced by IL-13 and overexpressed in EoE tissues) and filaggrin (downregulated by IL-13 and decreased in EoE tissues).[16] Periostin is a fascin domain-containing extracellular matrix molecule that regulates eosinophil adhesion and promotes eotaxin-induced eosinophil recruitment.[19] Filaggrin is a skin structural barrier protein and its loss of function is associated with increased skin permeability and susceptibility to atopic dermatitis in humans.[20] Atopic sensitization in mice[21] and is also associated with EoE. Notably, IL-13 downregulates filaggrin expression in skin keratinocytes,[22] providing a potential mechanism by which food antigen-elicited Th2 cell adaptive immunity might impair esophageal barrier function, perhaps propagating local inflammatory processes and increasing antigen uptake by cells in the esophagus. These processes might be particularly important owing to the increased levels of activated mast cells and B cells and evidence for in situ production of immunoglobulins in the esophagus of patients with EoE, demonstrated by histology and transcriptome analysis.[18, 23, 24] A recent study by Bianchard et al. demonstrated that numerous epidermal differentiation complex (EDC) genes, such as filaggrin and SPRR3, were downregulated both in IL-13-stimulated esophageal epithelial cells and in EoE biopsies specimens compared with healthy controls.[25] Whereas the filaggrin loss-of-function mutation 2282del4 was overrepresented in EoE compared with control individuals (6.1 vs. 1.3% respectively; p = 0.0172), the decreased filaggrin expression was uniformly seen in all EoE cases in vivo. These results show that the epithelial response in EoE involves a cooperative interaction between IL-13 and expression of EDC genes.[25] The genomic analysis of EoE describes variants at chromosome 5q22 encompassing thymic stromal lymphopoietin (TSLP) involved in EoE. TSLP is overexpressed in esophageal biopsies from individuals with EoE compared with unaffected individuals. These recent data implicate the 5q22 locus in the pathogenesis of EoE and identify TSLP as the most likely candidate gene in the region.[27]

Effector roles of eosinophils are an active area of investigation. The eosinophil, with granule products such as major basic protein (MBP)-1, is known to alter smooth muscle contractility through the activation of M2 muscarinic receptors.[24] Eosinophils may also participate in tissue remodeling and fibrosis in a variety of eosinophil-associated diseases, such as hyper-eosinophilic syndromes, asthma, eosinophilia myalgia syndrome, eosinophilic endomyocardial fibrosis, idiopathic pulmonary fibrosis and scleroderma. Eosinophils are implicated in fibrogenesis through secretion of fibrogenic growth factors (TGF-β, PDGF-BB, IL-1β and eosinophil-derived granule proteins such as MBP, and eosinophil peroxidase). Eosinophils are thought to be the chief source of TGF-β in pediatric patients with EoE.[28]

Treatment

While treatment of EoE is complicated by a number of different factors, consensus would support that symptom reduction/resolution should be a primary goal in the care of patients by practicing clinicians. In addition, particularly for the pediatric patient, maintenance of growth and development are key features of successful
treatment.

The more complicated question is that of mucosal healing. To date, many practitioners are inclined to use mucosal healing as a benchmark of treatment. This is based on the rationale that resolution of inflammation will prevent complications, such as esophageal stricture. The evidence to support this is based on basic studies examining mechanisms by which eosinophils can contribute to remodeling and fibrosis. This is also supported by clinical studies that show a positive impact of medical treatment on markers of fibrosis. The incidence of esophageal stricture in patients with EoE is not certain. Longitudinal studies, identification of pathophysiological mechanisms and appropriate biomarkers will lead the way towards understanding the diagnostic pathways appropriate for EoE patients in this regard. Presently, mucosal healing remains an end point for research studies and for many practices, including ours.

Potential treatments include pharmacologic therapy, dietary management and mechanical dilation. Current experimental approaches include biological treatments such as anti-IL-5 and anti-IL-13 antibodies.

**Pharmacological Therapy**

**Role of Proton Pump Inhibitors**

**Rationale** To date, the exact significance of esophageal eosinophilia requires careful clinical consideration. Traditionally, this finding has been attributed solely to peptic injury, but with the advent of EoE, a second potential etiologic entity is recognized. Some patients may exhibit clinical features of both gastroesophageal reflux disease (GERD) and EoE and therefore clinical judgment must be used to help decide on the appropriate treatment after carefully balancing the risks and benefits.

In this light, proton pump inhibitors (PPIs) play two important roles for managing patients with esophageal eosinophilia. First, they can be used to exclude peptic injury as a cause for this histological finding, by treating patients to see if their symptoms resolve and histology normalizes, the so-called proton pump responsive esophageal eosinophilia. Second, some patients with well-defined EoE may have an element of peptic disease and require acid blockade for symptom relief. A common scenario is the patient with EoE who develops heartburn when on well-established EoE nutritional or steroid treatment. There may be a component of poor esophageal acid clearance secondary to motor alterations associated with eosinophilic inflammation. These patients, who primarily have EoE, can also have a peptic component that is responsive to PPIs.

**Studies** The presence of esophageal eosinophilia in pediatric GERD was first described by Winters et al. in 1982. They correlated the presence of esophageal eosinophilia (>1 eosinophil/high power field [HPF]) with markers of reflux esophagitis (abnormal pH studies, manometry and endoscopy) in 46 children. Since then, others have suggested that the interaction between GERD and EoE can be complex, and that the notion of establishing a clear distinction between the two disorders may be too simplistic. Spechier et al. suggest four situations in which peptic injury might be associated with esophageal eosinophilia that justify use of PPIs: GERD causes esophageal injury that results in a mild eosinophilic infiltration; GERD and EoE coexist but are unrelated; EoE contributes to or causes GERD; or GERD contributes to or causes EoE.

**Summary** The diagnosis of EoE should be made by endoscopy and biopsy only after the patient has been treated with a PPI for at least 4–8 weeks and other causes have been excluded. The lack of a clinicopathological response to PPI therapy in patients who have isolated esophageal eosinophilia is virtually diagnostic of EoE. PPI therapy may be useful in patients with well-established EoE who develop peptic symptoms later during the course of this disease.

Although PPIs are highly effective for reducing gastric acid secretion and healing reflux esophagitis, recent speculation suggests that gastric acid suppression could contribute to the development of food allergies. Normally, digestion of dietary proteins begins upon exposure to acid and pepsin in the stomach. If dietary
proteins escape gastric digestion, immunologic sensitization to some proteins may occur, leading to the theoretical risk of contributing to the development of food allergy. It is important to recognize that no reports have documented that the use of PPIs have led to the development of EoE.

Corticosteroids

**Rationale** As seen in a number of other allergic diseases, eosinophilia is relatively responsive to the administration of corticosteroids. Proposed mechanisms by which corticosteroids impact eosinophilia include induction of apoptosis, downregulation of chemotactic factors and inhibition of other pro-eosinophilic mediators.[31]

**Studies: Role of Systemic Steroids** A number of studies have shown that both systemic and topical corticosteroids significantly reduce symptoms and decrease esophageal eosinophilia in patients who have EoE.[34,36] In 1998, Liacouras et al. demonstrated that systemic administration of 1.5 mg/kg of methylprednisolone significantly improved esophageal inflammation in children.[36] Symptoms resolved in 10 out of 20 patients within 8 days of initiating therapy. Systemic corticosteroids have significant side-effect profiles and adverse effects such as poor growth, adrenal suppression, mood disorder, bone marrow suppression and osteopenia. As a result, systemic steroid treatment should be reserved for patients who present emergently with severe dysphagia, acute weight loss or the inability to tolerate oral intake. There may be a place for corticosteroid use prior to esophageal dilation. The dose is typically 1.2 mg/kg (maximum 60 mg/day) of prednisone; symptoms should improve within 7-10 days. Typically, relapses occur when medications are stopped.[37]

**Studies: Role of Topical Corticosteroids** In an effort to minimize systemic steroid toxicity, fluticasone and budesonide have been used as topical preparations for the treatment of EoE. The overall goal of administering these preparations is to decrease the corticosteroid to adhere to the squamous epithelium and provide an anti-inflammatory effect. In 1998, Faubion et al. reported successful clinical response of four children to the administration of topical, swallowed fluticasone spray at a dose of up to 880 g twice daily.[33] Following this, Teitelbaum et al. recorded a favorable clinical and pathological response of 13 children to 8 weeks of topical fluticasone with a concomitant reduction in CD3 and CD8 lymphocytes.[23] Noel et al. conducted a retrospective analysis of 20 pediatric patients with EoE who received swallowed fluticasone.[39] All nonallergic patients, as defined by negative skin-prick testing (SPT), responded clinically and histologically to swallowed fluticasone. By contrast, 20% of the allergic patients demonstrated no response, while another 20% only exhibited a partial response to swallowed fluticasone. In 2006, Konikoff et al. completed the first placebo-controlled trial of fluticasone in pediatric patients with EoE.[40] They randomly assigned 36 patients to receive either placebo (n = 18) or swallowed (n = 18) fluticasone (440 g twice daily). Clinical symptoms and histological changes were evaluated. After treatment, half of the patients treated with fluticasone achieved full histological remission compared with one patient who achieved remission in the placebo group. Surprisingly, 10% of children receiving placebo went into remission. Similar findings have been observed in adults.[41] Results from a recent study by Caldwell et al. suggest that swallowed glucocorticoid treatment (FP) directly affects esophageal gene expression in patients with EoE.[42] In particular, increased Fkbp51 mRNA transcript levels identify glucocorticoid exposure in vivo and distinguish FP responders from untreated patients with active EoE and patients without EoE. In addition, Fkbp51 reduces glucocorticoid-mediated inhibition of IL-13 signaling in epithelial cells in vitro, suggesting that Fkbp51 might influence FP responsiveness.[42]

In an effort to provide an alternative, more easily administered topical steroid, Aceves et al. developed an oral viscous suspension of budesonide.[43,44] Overall, 16 out of 20 EoE children treated with oral budesonide (1 mg/day for those <10 years of age, 2 mg/day for those >10 years of age) mixed with 5 g of sucralose showed a clinical and histopathological response to therapy. No significant adverse effects occurred, and morning cortisol levels remained within normal limits.

One potential side effect of orally administered topical steroids is oropharyngeal or esophageal candidiasis, which
occurs in less than 10% of patients. Another theoretical risk is bone mineral loss, for which the risk is unknown. A meta-analysis of the risk of inhaled corticosteroids found that fluticasone might lead to bone mineral loss at total daily doses higher than 750 g. This risk may not be as great with swallowed topical steroids because they may not be as well absorbed and are rapidly metabolized by the first-pass metabolism through the hepatic circulation.[49]

Summary Systemic and topical corticosteroids effectively resolve acute eosinophilic inflammation in EoE. Systemic corticosteroids may be used in acute, emergent cases when patients have severe dysphagia requiring hospitalization because of weight loss and dehydration at a dosage of 1 2 mg/kg/day (50 mg/day as maximum) via parenteral or enteral routes. Long-term use of systemic corticosteroids is not recommended because of the adverse effects including osteoporosis, poor growth and adrenal suppression. Topical steroids, including swallowed fluticasone and budesonide suspension, do not have the same severity of toxicities as systemic corticosteroids. Suggested starting doses range from 440 to 880 g per day for children and 880 to 1760 g per day for adolescents and adults divided twice daily.[46] All efforts are made to maximize the contact time of the aerosolized particle with the esophageal mucosa. As such, patients should be instructed to administer the metered-dose inhaler without the use of a spacer. The metered-dose inhaler should be inserted into the mouth with the lips sealed around the device, sprayed into the back of the throat without inhaling and rinsing the mouth should not be performed. Patients should not eat or drink for at least 30 min after taking the medication. Treatment can continue for 6–8 weeks.[31] Long-term maintenance studies with these medications have not been performed. When systemic and topical steroid preparations are discontinued, inflammation generally recurs.

Immunomodulators

Rationale As previously described, oral corticosteroids can have deleterious effects with long-term use. Some patients can become steroid-dependent on corticosteroids for EoE management. As in other inflammatory gastrointestinal diseases, immunomodulators (azathioprine [AZA] and 6-mercaptopurine [6-MP]) have been used to modify intestinal inflammation.

Study Azathioprine treatment has been successfully used in some patients with steroid-dependent eosinophilic gastroenteritis.[47] A study by Netzer et al. reports three patients with severe steroid-dependent EoE and was able to demonstrate that therapy with AZA (2.5 mg/kg) is capable of maintaining long-term remission while avoiding the clinical effects of steroids.[48] AZA and 6-MP act by inhibiting purine synthesis, which ultimately affects DNA/RNA synthesis. These medications also inhibit the proliferation of T and B lymphocytes, which leads to a decreased production of cytokine T lymphocytes and plasma cells.[46] in EoE, increased esophageal infiltrations with CD3+ T cells, CD8+ T cells, CD1a+ dendritic cells and mast cells have been reported.[14,49] AZA and 6-MP delay the recruitment and/or proliferation of lymphocytes into the esophageal epithelium, leading to decreased antigen processing in the esophagus and decreased inflammation.[49]

Summary There is one published study to date using immunomodulators (AZA/6-MP) as a maintenance medication in adult patients with steroid-dependent EoE.[48] Currently, there are no published data concerning the use of cyclosporine, tacrolimus or methotrexate as maintenance medication in EoE. Although there may be a place for immunomodulators as a maintenance therapy, they need to be compared with other EoE therapies in clinical trials.

Biologics

Rationale IL-5 is a cytokine produced by Th2 cells and mast cells. It is the key mediator in eosinophil activation and has been demonstrated to regulate various processes associated with eosinophils.[50] These include antigen-induced eosinophilia, bone marrow release of eosinophils, eosinophil tissue survival and eosinophil activation. In murine models, esophageal eosinophilia has been shown to be IL-5 dependent, and IL-5 has been shown to stimulate B-cell growth and increase immunoglobulin secretion. In addition to Th2 cytokines, TNF-α is upregulated in EoE[18] and is highly expressed by epithelial cells of the esophagus in patients with active EoE.[49]
Studies Based on these properties, neutralizing antibodies against IL-5 have been generated to lower eosinophil blood and tissue levels with the goal of impacting diseases characterized by Th2 environments and eosinophilia, such as asthma and EoE.\textsuperscript{[9,51]} In 2004, Garrett et al. treated four patients who had idiopathic hyper-eosinophilic syndrome with anti IL-5 antibody.\textsuperscript{[52]} Each patient was treated with 10 mg/kg (maximum 750 mg dose) of mepolizumab with a single intravenous injection for 3 consecutive months. Anti-IL-5 significantly reduced peripheral eosinophils and symptoms in all four patients. One patient had severe dysphagia and marked esophageal eosinophilia that decreased following treatment. No adverse events were identified. Stein et al. conducted an open-label study using intravenous mepolizumab in four adult patients with EoE, one of whom had esophageal narrowing.\textsuperscript{[53]} Patients received three doses of intravenous anti-IL-5 antibody, at monthly intervals, without change in other therapy and underwent esophageal biopsy at weeks 0, 8 and 20. Blood eosinophil percentages were decreased significantly, as were the number of eosinophils. These results suggest that biologic compounds are a promising new therapy for patients who have EoE.\textsuperscript{[53]} Straumann et al. studied 11 adult patients with active EoE who were randomized to receive either 750 mg of mepolizumab (n = 5) or placebo (n = 6). The effect of mepolizumab was assessed clinically, endoscopically, histologically and via blood and tissue biomarkers.\textsuperscript{[54]} Results showed a significant reduction in the mean esophageal eosinophilia in the mepolizumab group (54%) compared with the placebo group (5%) after 4 weeks of therapy and the treatment was well tolerated. Symptoms were not significantly changed, although a trend toward improvement was seen between 4 and 13 weeks. The expression of remodeling molecules, tenascin C and TGF-β, was reduced.\textsuperscript{[55]}

Infliximab is a chimeric IgG1 monoclonal antibody and is a potent inhibitor of TNF-α. Blocking TNF-α activity with infliximab demonstrated high efficacy in the treatment of several chronic inflammatory diseases, including Crohn's disease,\textsuperscript{[56]} rheumatoid arthritis\textsuperscript{[57]} and asthma.\textsuperscript{[58]} Straumann et al. conducted a prospective translational study with the purpose of evaluating the efficacy of infliximab monotherapy in three male adult patients with severe corticosteroid-dependent EoE. All three patients tolerated treatment with infliximab well, and no relevant adverse events occurred; however, the therapy was not able to induce a resolution of the eosinophilic tissue infiltration, nor did it markedly reduce symptoms. One out of three patients achieved a partial response, one experienced a mild flare-up and the third was refractory to the TNF-α blockade.\textsuperscript{[59]}

Summary & Recommendation In the future, novel biologic agents may present a unique therapeutic alternative for some patients with EoE. Their use is currently undergoing clinical investigation.

Dietary Management

Elemental Diet/Elimination Diet

Rationale Since eosinophils are associated with allergic reactions, early hypotheses proposed food allergens as the instigating factor in EoE. Since then, a number of clinical studies support a role for food allergies in the pathogenesis of EoE.\textsuperscript{[60]} The first evidence that protein allergens may induce EoE came from Kelly et al., who treated children with an elemental diet or amino acid-based formula.\textsuperscript{[60]} All children experienced symptom resolution and improved histology. No murine models have yet been developed that are based on protein hypersensitivity leading to esophageal eosinophilia, and thus this hypothesis has escaped further study. The role of allergy evaluation in the adult population has also been elucidated. In a recent paper, allergy evaluation had a high yield in adult EoE as 81% of referred patients had one or more allergens identified and 50% had one or more skin tests positive to foods. Therefore, allergy evaluation should be considered in adult patients with EoE.\textsuperscript{[54]}

Studies of Elemental Diet The elimination of food allergens can be achieved by different approaches and has been primarily used in children. For instance, the removal of all food allergens, an elemental diet, which is the most extreme approach, can lead to resolution of symptoms and histological changes in EoE.\textsuperscript{[36]} A directed elimination based on the results of allergy testing with SPTs and atopy patch testing (APT) in combination with the clinical history is effective in children.\textsuperscript{[62,63]} Another approach that avoids any form of allergy testing is the empiric elimination of the eight most common food allergen groups (milk, soy, egg, wheat, shellfish, fish, tree
nuts and peanuts).\[64\]

The elemental diet requires the replacement of all solid food with a nutritionally complete elemental formula. Kelly et al. studied ten children (aged 8 months to 12.5 years of age) who had persistent reflux symptoms but who had not responded to GERD treatments, including six who had prior Nissen fundoplications.\[60\] All ten patients had fewer symptoms on an amino acid-based formula, with eight patients reaching complete histological resolution. Symptoms returned when food was reintroduced into the diet, with milk causing symptoms in seven patients, soy in four patients, wheat and peanut in two patients, and egg in one patient. In larger studies involving over 160 patients at The Children's Hospital in Philadelphia (PA, USA), more than 98% of the patients demonstrated resolution of symptoms and normalization of biopsies when treated with an amino acid-based diet.\[65,66\] The most frequently encountered barriers to success with an elemental diet are linked to compliance; this approach often requires the use of a nasogastric tube for formula administration.\[67\]

**Studies of Directed Elimination Diet** Allergy testing has been used as a method to identify allergenic culprit foods in children with EoE. Two methods used to test for IgE-mediated food allergies include serum food allergen-specific IgE immunoassays and SPT. IgE-mediated reactions are characterized by classical symptoms of allergic disease resulting from the effects of mediators released and generated by crosslinking of IgE on the surface of mast cells. Classic IgE-mediated reactions are not typically thought to be the sole etiology of EoE. Because tests that accurately identify foods responsible for delayed allergic reactions are not available and because the exact immunologic mechanisms for EoE have not been elucidated, some studies and practitioners report the successful use of these forms of testing to identify the food allergens that are clinically relevant for a specific patient with EoE. In EoE, the positive predictive value (PPV) of SPT for milk, egg, beef and peanut was greater than 75%, but the PPV of SPT for oat, rice, potato, peanut, chicken and barley ranged from 33 to 43%.\[62\] Many patients with EoE do not present with the clinical picture of IgE-mediated reactions, thus leading to the use of APT to look for foods causing non-IgE-mediated reactions. APT is thought to provide evidence for a T-cell-mediated reaction. APT is performed by placing the food in its native state in contact with the skin under an aluminum Finn Chamber for 48 h on the patient's back. The chamber is removed and the reaction is examined for induration and papules 24 h later. One center's experience with APT in children with EoE showed that the PPV for APT was 94% for beef, 83% for milk, 60% for most foods and 48% for oats.\[26\] The negative predictive value was more consistent and generally was in the mid-80% to mid-90% range for all foods except for milk, which was 59%. These findings suggest that if a food is negative on skin testing and APT, it is probably not responsible for the EoE.

**Studies of Empiric Elimination Diet** In an effort to avoid allergy testing completely, Kagawallawa et al. removed the eight most common food allergen groups (milk, soy, egg, wheat, shellfish, fish, tree nut and peanut) from the diets of 35 pediatric patients.\[64\] Approximately 74% of the 35 patients who received the eight-food group elimination diet demonstrated improvement. The children treated with this elimination diet showed clinicopathologic improvement (80.2 ± 44 eosinophils per HPF before elimination vs 13.6 ± 23.8 after elimination). The study also compared the results of the empiric food elimination diet to the results obtained in 25 patients treated with an elemental diet consisting of an amino acid-based formula with no other added foods. The comparison revealed that, although both diets significantly improved the clinicopathologic features of the disease, the elemental diet was more effective in respect to the number of patients who responded (22 out of 25) and regarding the residual number of eosinophils per HPF (13.6 in the eight-food group; 3.7 in the amino acid formula group).\[64\]

**Summary** Dietary therapy is effective in resolving symptoms and improving the histopathology associated with EoE. When deciding on the use of a specific dietary therapy, the patient's and parent's goals and quality of life need to be assessed and considered. Nutritional evaluation by registered dietitians is strongly encouraged to ensure that proper calories, vitamins and micronutrients are provided. Typical vitamin and micronutrient deficiencies occur from avoidance of specific foods. For example, milk avoidance places patients at increased risk for vitamin D, calcium, phosphorus and vitamin B12 deficiencies. Wheat products are typically enriched and
fortified with iron, niacin, riboflavin, thiamine, folate and fiber.

**Endoscopic Management**

**Esophageal Dilation**

**Rationale** The pathogenesis of EoE is uncertain, but it is known that eosinophils contain mediators associated with tissue remodeling and the development of fixed fibrosis. An undetermined portion of patients with EoE develop fixed esophageal narrowing that is unresponsive to diet or medical management and requires esophageal dilation to regain function.

**Studies** No prospective studies are yet available to guide the clinician in precisely when and how to perform esophageal dilation in patients with EoE. In other esophageal diseases, the major complications of esophageal dilation are perforation and bleeding, which have been reported in approximately 0.5% of dilations performed for esophageal strictures. In addition, bacteremia may accompany dilation in 20-45% of cases, although clinically recognizable infectious complications, such as endocarditis and brain abscesses, are rare.[68]

Previous reports suggested that esophageal mucosal fragility and tissue remodeling might predispose patients with EoE to esophageal tears and perforations.[66] For example, Sgouros summarized the results of esophageal dilation in 64 EoE patients from 11 published reports.[73] A total of 83% of patients experienced immediate symptomatic improvement. Extensive mucosal tears were observed in the majority of cases, and 9% experienced severe chest pain treated with analgesics and hospitalization. Dilation was complicated by esophageal perforation in one patient (1.5%). Long-term follow-up was only available in 12 patients, all of whom experienced symptomatic recurrences after 3-8 months.

A recent study by Straumann and Hirano aimed to define the effectiveness, safety, and patient acceptance of dilation in EoE.[71] In a retrospective review of 681 EoE patients, two cohorts were defined. Cohort 1 consisted of patients treated with dilation alone, whereas cohort 2 included patients treated with a combination of dilation and anti-eosinophilic medication. In total, 207 EoE patients were treated with esophageal dilation: 63 in cohort 1 and 144 in cohort 2. Dilation led to a significant increase in esophageal diameter and improvement in dysphagia in both cohorts. After dilation, dysphagia recurred after 23 ± 22 months in cohort 1 and 20 ± 14 months in cohort 2. No esophageal perforation or major bleeding occurred. Among patients who were prospectively surveyed, 74% reported retrosternal pain after dilation; however, all agreed to repeated dilation if required.[71] Eosinophil peak infiltration, eosinophil load, and EoE-associated histological signs were not significantly affected by esophageal dilation. The conclusion of the study was that esophageal dilation is highly effective in providing symptom relief and can be performed safely. However, patients report post-procedural discomfort and dilation does not lead to improvements in underlying inflammatory processes or esophageal tissue remodeling.[71]

**Summary** Esophageal dilation may be useful in patients with diagnostic findings of esophageal narrowing or strictures and clinical symptoms of partial obstruction. Risks include mucosal tearing and perforation. Whether pretreatment with medical or dietary therapy for EoE improves outcomes of dilation is not certain but may be helpful.

**Summary**

Medical, nutritional and mechanical treatments relieve the symptoms of EoE, but it remains uncertain whether any treatment can prevent the complications of the disease. In this regard, the therapeutic endpoints for clinicians to judge treatment efficacy must be individualized and balance risk, benefits and quality of life. Proposed endpoints include resolution of symptoms (symptomatic resolution), elimination of esophageal eosinophilia (histological remission), and resolution of endoscopic abnormalities (endoscopic remission).
Five-year View

Eosinophilic esophagitis is associated with food allergies but the exact underlying pathophysiology remains to be elucidated; this may lead to a variety of treatment modalities in the future. As novel therapeutic targets become identified, directed therapies may be better defined.

Sidebar

Key Issues

- Eosinophilic esophagitis (EoE) presents with a constellation of symptoms including feeding difficulties, abdominal pain, dysphagia, food sticking sensation and food impactions. While the pathogenesis of EoE remains under investigation, these symptoms may be related to esophageal dysmotility or remodeling changes.
- To date, the pathogenetic mechanisms leading to esophageal inflammation in EoE relate to a dysregulated allergic response in the esophageal mucosa. Defects in the epithelial barrier (flaggrin), alterations in mucosal immune regulation (thyroid stromal lymphopoietin, IL-13) and increased expression of eosinophil chemoattractants (eotaxin-3) may all contribute to inflammation and esophageal dysfunction.
- Symptom reduction is a common goal of treatment. While the impact on histological response remains under debate by some, improvement of inflammation is a key end point for many and for research studies.
- Treatment includes pharmacologic therapy, dietary exclusions and mechanical dilatation. As more research identifies the impact of esophageal remodeling and fibrosis, new treatments targeting this feature of EoE will be critical.
- As research leads us to novel therapeutic targets, we must continue to address the question of what is worse the disease or the treatment.

References


19. Il-13 is overexpressed in the esophagus of patients with eosinophilic esophagitis (EoE) and selectively induces the eosinophil-activating chemoattractant eotaxin-3 by a transcriptional mechanism in the esophageal epithelial cells.


29. The interaction between gastroesophageal reflux disease and EoE can be complex and the notion of establishing a clear distinction between the two disorders may be too simplistic.


• To address the diagnostic criteria and treatment of EoE, a multi-disciplinary task force of 31 physicians formulated consensus recommendations based on a systematic review of the literature and expert opinion.


- The effect of mepolizumab was assessed clinically, endoscopically, histologically, and via blood and tissue markers. There was a significant reduction in the mean esophageal eosinophilia in the mepolizumab group compared with placebo. Expressions of remodeling molecules were reduced and a trend towards symptomatic improvement was observed.


- Esophageal dilation is highly effective in providing symptom relief and can be performed safely in patients with EsE. However, there is no histological evidence of improvement in these patients and there are often reports of post-procedural discomfort.

Papers of special note have been highlighted as:

- of interest
Financial & competing interests disclosure
Glenn T Furuta is a consultant to Meritage Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.