

Eosinophilic esophagitis: Review of nonsurgical treatment modalities

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ABSTRACT

Eosinophilic esophagitis (EoE) is a clinicopathological condition characterized by the combination of upper gastrointestinal symptoms such as dysphagia and even food impaction in association with histological findings of >15 eosinophils/high-powered field found in endoscopic biopsy specimens. EoE is considered an atopic disease with food and aeroallergen sensitivity. Current treatment options include elemental and elimination diets and topical corticosteroids. This study was designed to provide a review of the literature on the nonsurgical treatment modalities for EoE to understand the therapeutic challenges. A Medline and PubMed search was conducted using the key words eosinophilic esophagitis and treatment. EoE guidelines, randomized controlled trials, case studies, and evidence-based treatment articles in the English literature were selected. EoE patients can have symptomatic and pathological resolutions with dietary modifications and topical swallowed corticosteroids with continued therapy. However, these effects are not long-lasting and adverse reactions, both local and systemic, are possible. Newer targeted therapies using monoclonal antibodies against interleukin-5 (IL-5) appear to be well tolerated but various studies have not consistently shown symptomatic or histological improvement. Current therapies for EoE including specific diets and topical corticosteroids have shown only short-term symptomatic relief. Biological therapies such as anti-IL-5 agents are still under investigation. Long-term effects of treatments are not known and studies regarding safety of these therapies and specific dosing regimens are needed. Therapies targeting the molecules involved in the pathogenesis of EoE may be future options. Treatment should be individualized with careful consideration of patient's age, allergen sensitivity, lifestyle, and compliance.

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Eosinophilic esophagitis (EoE) is a clinicopathological condition characterized by the combination of upper gastrointestinal symptoms in association with histological findings of eosinophilic infiltration found on endoscopic biopsy specimens of esophageal tissue. EoE presents with symptoms varying by age from failure to thrive, vomiting, and food refusal in children to dysphagia, epigastric pain, and food impaction in adults.^{1,2} It is a chronic disease with a tendency for seasonal variations in symptoms that may be dependent on allergen exposure.³ Diagnosis of EoE is made by evaluation of clinical symptoms, mucosal biopsy showing ≥ 15 eosinophils/high-power field (HPF), and exclusion of other disorders such as gastroesophageal reflux disease (GERD) unresponsive to treatment with proton pump inhibitors.⁴

EoE is considered an atopic disease because many of these patients have evidence of food and/or aeroallergen sensitivities.⁵ Food antigen sensitization has been highly suspected as the pathogenic mechanism based on studies that establish improvement of symptoms

and pathological findings by the use of elemental diets. In individuals with documented food allergy, avoidance of these specific foods has been recommended.⁶ Dietary modifications including food avoidance and elemental diets have been used for the treatment of EoE.⁷ Treatment with topical corticosteroids has shown to improve esophageal eosinophilia and reduce esophageal remodeling.⁸ Newer targeted therapies using monoclonal antibodies against cytokines implicated in EoE have recently been investigated.

Patients with EoE present with symptoms that can significantly affect their quality of life. A retrospective study showed that 87 of 251 adult patients with EoE experienced food impactions requiring endoscopic removal.⁹ The aim of treatment for EoE should be symptomatic improvement with the goal of improving the patient's quality of life as well as pathological improvement with the goal of preventing long-term sequelae of chronic inflammation such as esophageal strictures. This article provides a detailed overview of the treatment modalities for EoE including advantages and disadvantages of each therapy.

DIETARY THERAPIES

Three dietary regimens have been shown to be effective in treatment of EoE: (1) elemental diet with an amino acid–based formula, (2) empiric elimination diets of common allergenic foods, and (3) elimination of foods based on various allergy testing.

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Elemental Diet

An elemental diet consists of a formula composed of amino acids and water. This particular diet has been studied mainly in children. The premise of the elemental diet is the complete elimination of dietary antigens that may trigger symptoms of EoE. In 1995, 10 children with persistent symptoms of GERD unresponsive to antireflux therapies with increased number of eosinophils (median, 41 eosinophils/HPF) on esophageal biopsy underwent treatment with amino acid-based elemental formula for 6 weeks. Eight of 10 subjects had complete resolution of symptoms and the other 2 subjects had partial symptomatic improvement. Follow-up endoscopies revealed a decrease of eosinophils from a median of 41/HPF to 0.5/HPF. Unfortunately, symptoms reappeared after resumption of a normal diet.¹⁰ A subsequent prospective study in 2003 placed 51 children with chronic GERD and ≥ 20 eosinophils/HPF on esophageal biopsy specimens on an elemental diet for 1 month. Significant improvement in vomiting, abdominal pain, and dysphagia were observed in an average of 8.5 days after beginning treatment in 49 patients. These 49 patients also had a decrease in median esophageal eosinophils from 33.7/HPF before the elemental diet to 1.0/HPF postdiet.¹¹ In a retrospective study of 381 pediatric patients, Liacouras *et al.* found that the removal of dietary antigens in the form of an elemental diet improved esophageal histology and clinical symptoms of reflux and dysphagia in 97% of patients. Once there is clinical and histological response, one new food is reintroduced per week starting from the least allergenic such as fruits and vegetables to the most allergenic such as dairy, soy, peanuts, and wheat.¹²

Although an elemental diet has proven to be effective in reducing symptoms in these various studies, it has major disadvantages. The formula is not only expensive, but also unpalatable. Ingestion of large volumes of formula is required and must be fed through a nasogastric or gastrostomy tube to allow adequate caloric intake.¹¹ Moreover, the treatment is much less practical in adults with EoE.

A retrospective chart review comparing the three diets confirmed that an elemental diet was superior at inducing histological remission defined as < 15 eosinophils/HPF.¹³ Despite the advantages in reducing symptoms as well as eosinophilic inflammation shown by the use of an elemental diet, this treatment has not gained popularity for several reasons. Cost, impaired quality of life, and overall practicality are the main limiting factors for treatment with an elemental diet.

Six-Food Elimination Diet

An alternate option for dietary treatment of EoE is the elimination of six specific foods that are considered

to be the most allergenic, which include cow's milk protein, soy, eggs, wheat, peanuts/tree nuts, and seafood. In 2006, a retrospective pediatric observational study of 34 EoE patients who followed the six-food elimination diet showed that 74% of patients had clinical improvement along with a decrease in esophageal eosinophils.¹⁴ A prospective study of the same diet in 18 adults found that 94% had a symptomatic response, 78% improved histologically, and only one-third had complete histological resolution.¹⁵ A more recent study examined 50 adult patients with EoE who underwent the six-food elimination diet and showed improvement in both symptoms such as dysphagia and heartburn as well as a decrease in peak eosinophil counts to 8/HPF postdiet compared with 34/HPF prediet. However, after food reintroduction patients had return of EoE symptoms and statistically significant recurrence of esophageal eosinophilic infiltration.¹⁶ Although this diet provides an oral route for patients and is more palatable than an elemental diet, there are still disadvantages. It is not only difficult to refrain from these six foods, which may adversely affect the adherence to the diet, but there are also risks of protein and nutrient deficiencies.¹⁷

Overall this regimen is not as effective as an elemental diet in reducing the symptoms and improving eosinophilic inflammation and still carries the risk of impairing quality of life. Practicality and nutrient deficiencies are other limitations of this dietary intervention.

Elimination Diet Based on Allergy Testing

Patients with EoE often have history of food allergies as well as sensitization to foods on skin-prick testing and atopy patch testing.¹⁸ This dietary option involves the elimination of specific foods that provoke these allergic reactions based on skin-prick and patch testing. A large retrospective series of 146 children treated with an elimination diet based on the results of skin-prick and patch testing observed resolution of esophageal eosinophilia in 77% of patients. Egg, milk, and soy were identified most frequently with skin-prick testing and corn, soy, and wheat were identified most frequently with atopy patch testing.¹⁹ Although an elimination diet may offer a better quality of life compared with an elemental diet, the elemental diet has been shown to have a higher success of 97% compared with 77% in an elimination diet in regard to improvement of clinical symptoms and histology.¹² A retrospective cohort study of 98 patients with EoE showed histological remission in 96 and 81%, of patients on elemental and six-food elimination diets, respectively.¹³

An elimination diet has been shown to be less effective but can be more practical than an elemental diet.

Moreover, food allergy testing still has not been standardized and thus it is difficult to reproduce similar results in various studies.

Patient's lifestyle and an individual-based approach need to be considered when deciding to implement dietary therapies because patient compliance is necessary for successful treatment. Overall dietary therapies have been studied more in children than adults. Successful dietary treatment of EoE involves the collective efforts of patients, families, physicians, and dietitians.²⁰

PHARMACOLOGIC THERAPIES

Corticosteroids

Systemic steroids were the first pharmacologic treatment found to be effective in EoE. Multiple studies have shown that systemic steroids are effective in controlling EoE symptoms and esophageal eosinophilia.

In 1998 Liacouras *et al.* treated 20 pediatric patients with oral methylprednisolone twice daily and after 4 weeks showed that eosinophils decreased from 34.2 to 1.5/HPF. Clinical improvement was attained in 95% of patients. Gastrointestinal symptoms and esophageal infiltrates reoccurred several months after steroids were discontinued.²¹ Systemic steroids can be used in severe cases for short-term use at a recommended dose of 1–2 mg/kg of prednisone. Systemic steroids are not recommended for long-term therapy of EoE given the reoccurrence of symptoms after discontinuation and the well-known adverse effects of prolonged use such as osteoporosis and weight gain.⁷ Use of topical steroids versus systemic steroids was compared by an open-label randomized prospective trial that showed that both medications achieved both histological and clinical responses. Histological responses were based on a grading system that consisted of the maximum numbers of eosinophils/HPF as well as basal cell zone thickness as a percentage of the epithelial thickness. The prednisone group achieved a greater degree of histological response, but the clinical remission was not sustained after either treatment. Symptoms returned within a mean of 5.5 weeks after discontinuation of prednisone and 8 weeks after discontinuation of fluticasone. Systemic adverse reactions were noted in 40% of patients treated with prednisone and in none of the patients treated with fluticasone. However, 15% of patients receiving fluticasone experienced esophageal candidiasis.²² Based on this study, the safety profile for topical steroids is more favorable than systemic steroids and the latter should only be used for a short term in severe cases of EoE.

Topical steroids for treatment of EoE was first studied in 1998 in a case series of four patients, which showed clinical improvement with swallowed fluticasone.²³ Topical fluticasone is delivered through a me-

tered-dose inhaler without a spacer, which is then swallowed instead of inhaled. Patients are instructed to not eat or drink for at least 30 minutes afterward. The first randomized, double-blind, placebo-controlled trial of topical steroids for EoE treatment was done in children and reported that 50% of patients treated with topical fluticasone for 2 months achieved histological remission defined by a peak eosinophil count of <1/HPFs compared with 9% who received placebo. In regard to clinical symptoms only, vomiting improved in the patients treated with fluticasone, but abdominal pain and dysphagia remained.²⁴ A prospective study of 30 adult patients by Lucendo *et al.* showed both significant improvement in symptoms as well as normalization of previous narrowing of the esophagus with 3 months of fluticasone at 500 µg twice daily.²⁵

Swallowed budesonide suspension has also been shown to be effective in the treatment of EoE in both pediatric and adult patients in randomized double-blind placebo-controlled trials. In a prospective pediatric study of 24 patients, 1–2 mg of budesonide mixed with sucralose to make an oral viscous suspension was given daily. In this study 87% of patients receiving viscous budesonide achieved histological resolution defined as <7 eosinophils/HPF whereas none of the patients receiving placebo had histological resolution.²⁶ Nebulized budesonide, which is then swallowed, was examined in a prospective randomized double-blind placebo-controlled study in a group of 36 adults that showed complete histological resolution defined as <5 eosinophils/HPF in 72% of patients taking budesonide at 1 mg twice daily for 15 days versus 11.1% resolution in patients receiving placebo.²⁷ Clinical improvement based on dysphagia scores were reported in both of the aforementioned pediatric and adult studies.^{26,27} Oropharyngeal and esophageal candidiasis can be seen in both topical fluticasone- and budesonide-treated patients. However, a long-term prospective study that used a smaller dose of budesonide at 0.5 mg daily for 50 weeks did not show evidence of candidiasis.²⁸ Unfortunately, as seen with dietary therapy, a retrospective study in 32 adult patients treated with topical fluticasone for 6 weeks showed that 91% had recurrent dysphagia at an average of 8.8 months after discontinuation of treatment. Sixty-nine percent of patients required additional course of treatment.²⁹

Based on the current literature, topical corticosteroids are an effective and practical mode of treatment for EoE. The main disadvantage is recurrence of symptoms and eosinophilic inflammation after cessation of treatment. Furthermore, studies in both pediatric and adult age groups addressing specific topical corticosteroid dosages and duration of treatment are needed.

Leukotriene Inhibitors

Inflammatory mediators such as cysteinyl leukotrienes have been thought to be chemoattractants for eosinophils and play a role in esophageal inflammation.³⁰ A prospective study of eight patients treated with the leukotriene antagonist montelukast by Atwood *et al.* found marked improvement in EoE symptoms but no histological improvement. Symptoms returned within 4 weeks of discontinuation of therapy in the majority of these patients.³¹ A subsequent prospective study showed that montelukast did not maintain steroid-induced remission of EoE.³² Based on the aforementioned studies and the current literature, the use of leukotriene inhibitors in EoE is not well supported.

Biological Agents

Several biological agents targeting various cytokines thought to play a role in EoE pathogenesis have been investigated.

Tumor necrosis factor α has been shown to be increased in active EoE.³³ Treatment with the anti-tumor necrosis factor α antibody infliximab was studied in a small open prospective trial of three patients, which showed neither reduction of esophageal eosinophils nor improvement of symptoms.³⁴ This is currently not an effective treatment for EoE.

Interleukin (IL)-5 plays a key role in eosinophil proliferation, differentiation, and activation and thus humanized monoclonal antibodies against IL-5 have recently been studied.³⁵ Mepolizumab, a humanized monoclonal antibody against IL-5 has been used clinically in the treatment of various eosinophilic disorders. An open-label randomized and placebo-controlled phase II trial in 2006 showed a decrease in esophageal eosinophilia and clinical improvement in four patients after three monthly infusions of 750 mg of mepolizumab, which was given in addition to topical steroids and restricted diets.³⁶ This study was followed by the first double-blind, placebo-controlled trial in 2010, which studied 11 adult patients who were randomized to mepolizumab or placebo. The treatment group received two i.v. infusions of 750 mg of mepolizumab and those who did not receive complete remission after 8 weeks received 2 additional doses of 1500 mg of mepolizumab. Mepolizumab was well tolerated by patients at the various dosages. Although there was a decrease in esophageal eosinophils in the treatment group compared with the placebo at 4 weeks, none of the subjects had complete resolution and there was no additional improvement after subsequent doses. There was a reduction in expression of molecules associated with esophageal remodeling (tenascin-C and transforming growth factor β) in the treatment group after 13 weeks, but no significant improvement in symp-

toms compared with placebo.³⁷ A multicenter, double-blind, randomized, prospective study of 59 children with EoE defined as peak esophageal eosinophil count of >20 /HPF showed a reduction in peak and mean eosinophil counts to <20 /HPF in 18 of 57 and 51 of 57 children, respectively, but no significant reduction in clinical symptoms after treatment with mepolizumab.³⁸ The decrease in esophageal eosinophils is not always concordant with improvement of clinical symptoms as is evident in the mepolizumab studies.

Reslizumab, another humanized monoclonal antibody against IL-5, has been recently studied in a double-blind randomized, placebo-controlled trial in children. In this prospective study, 226 patients were randomly assigned to receive 1, 2, or 3 mg/kg of reslizumab infusions or placebo. Peak eosinophil counts were decreased in 59, 67, and 64% in the 1, 2, and 3 mg/kg treatment groups, respectively, whereas a 24% reduction in eosinophils was seen in the placebo group ($p < 0.001$). Both the treatment and the placebo groups showed symptom improvement based on physician global assessment scores and thus no relationship was found between the reduction in esophageal eosinophil counts and assessment scores. Reslizumab, like mepolizumab, was also generally well tolerated with limited side effects such as headaches and cough, which were similarly seen in the placebo group.³⁹

These biological agents have been well tolerated by patients with relatively low side effects. However, variable diagnostic criteria for EoE have been used by these studies and none of the studies have shown prolonged symptomatic relief. Long-term clinical trials are required for assessment of efficacy and safety of these therapies.

With the advancement of our knowledge about the role of various chemokines and cytokines in the pathogenesis of EoE, treatment can be geared toward these specific molecules. Overexpression of IL-13 and eotaxin 3 has been shown in EoE and these may serve as future biomarkers to monitor disease activity.^{40,41} These molecules could also be potential targets for future biological agents. In addition, advancement of knowledge about the role of micro-ribonucleic acid in allergic conditions and EoE may offer potential treatment options that could target the underlying pathogenesis.⁴²

CONCLUSIONS/FUTURE DIRECTIONS

Patients with EoE can benefit from various treatment modalities leading to improvement in clinical symptoms. They respond to dietary modifications, which require long-term therapy and may adversely affect their quality of life. Additional studies are needed to assess quality of life and compliance issues with dietary treatments. Currently, swallowed corticosteroids are the mainstay of treatment for patients with EoE.

Compared with dietary modifications, this treatment may offer a better quality of life, but symptomatic and pathological resolutions are not long-lasting and local and systemic adverse reactions are possible. Future studies are needed to determine ideal dosing regimens for both initiation and maintenance therapy. Therapies combining dietary modifications and topical swallowed corticosteroids are other potential treatment modalities. Although individual practices may have experiences with these modalities, there is no evidence regarding long-term effect of such therapies. Biological agents appear to be well tolerated but there is still no evidence of sustained clinical or histological improvement.

Several challenges exist in studying treatment modalities for EoE. Nonidentical criteria used to diagnose EoE makes it difficult to compare studies. There is a lack of correlation between symptoms and pathological features of EoE. In addition, there is a deficiency of knowledge about the natural history of EoE, different EoE phenotypes, and absence of a noninvasive marker for monitoring disease activity. Further elucidation of these issues can help facilitate assessment of efficacy of treatments in the future.

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