

Eosinophilic Esophagitis



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KEYWORDS

• Eosinophilic esophagitis • Dysphagia • Food allergy • Eosinophilia • Atopy

KEY POINTS

- Eosinophilic esophagitis is a disease with increasing prevalence over several decades.
- Pediatric and adult eosinophilic esophagitis differ in their clinical presentation, with dysphagia and food impaction being major symptoms for adults, whereas young children present with more vague symptoms.
- Strict elemental diet results in histologic remission in nearly all cases of eosinophilic esophagitis, pointing to the role of food allergy in disease pathogenesis.
- Therapy with topical steroids is effective in the treatment of eosinophilic esophagitis, but disease recurs with discontinuation of therapy.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a disease of the esophagus that is recognized in both children and adults.¹ It is characterized by significant esophageal eosinophilia with severe squamous epithelial hyperplasia generally occurring in association with upper gastrointestinal symptoms.¹ The gastric and duodenal mucosae are not affected. The diagnosis has been traditionally limited to patients who have persistent esophageal eosinophilia despite trial of treatment with a proton pump inhibitor (PPI), with the diagnoses of EoE and gastroesophageal reflux disease (GERD) considered to be mutually exclusive.¹ However new research over the past decade has shown there is an entity in which esophageal eosinophilia responds to high-dose PPI but without a presentation consistent with GERD. This condition has been termed PPI-responsive esophageal eosinophilia (PPI-REE), a new subtype of EoE.² Therefore, it has recently been recommended that lack of PPI responsiveness is not part of the diagnostic criteria for EoE.

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Because of the complexity of this disease, management remains an ongoing challenge for clinicians. A combination of pharmacotherapy, endoscopic interventions, and dietary restrictions is required, and many patients have experienced incomplete benefit.³ However, in the past decade, there is promise with the development of new biologic therapies.

DEFINITION OF EOSINOPHILIC ESOPHAGITIS

EoE is defined as a clinicopathologic condition that is immune or antigen driven. It is diagnosed with histology, endoscopic appearance, and clinical presentation. It is histologically defined by greater than or equal to 15 eosinophils per high-power field (eos/hpf) along with clinical symptoms of esophageal dysfunction. The definition of EoE is difficult because presenting symptoms are similar to those of GERD. Also, there is the entity of EoE without the presentation of GERD but that responds to PPIs, known as PPI-REE. With emergence of PPI-REE, persistent eosinophilia in the esophagus after 2 months of treatment with a PPI is no longer a criterion for diagnosis of EoE² (Box 1).

Note that esophageal eosinophilia is not exclusive to EoE.² Other diseases in which this occurs include Crohn disease, collagen vascular disease, drug-induced esophagitis, hypereosinophilic syndrome, GERD, and eosinophilic gastroenteritis (see Box 1). Because of the nonspecific nature of esophageal eosinophilia, the diagnosis of EoE may be delayed or missed. In a study of 200 adult patients diagnosed with EoE, the median delay in diagnosis was 6 years.⁴

Endoscopic Findings

There are identified endoscopic features that suggest the diagnosis EoE but are not specific and are not included in the criteria for diagnosis. The endoscopic features

Box 1
Definition of eosinophilic esophagitis

The diagnostic criteria of EoE include the following:

- Symptoms related to esophageal dysfunction
- Peak value of greater than or equal to 15 eosinophils/hpf on esophageal biopsy
- Exclusion of differential diagnoses for esophageal eosinophilia
- Differential diagnosis of esophageal eosinophilia
 - GERD
 - Eosinophilic gastroenteritis
 - Crohn disease
 - Connective tissue diseases
 - Hypereosinophilic syndrome
 - Infection
 - Drug hypersensitivity response

Data from Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology. 2018;155(4):1022-1033 e1010; and Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3-20 e26; quiz 21-22.

that were identified in a meta-analysis of 4678 patients with EoE included stacked circular rings, linear furrows, loss of subepithelial vascular pattern, strictures, whitish papules, and small-caliber esophagus.⁵

Histologic Findings

The diagnosis of EoE requires 15 eosinophils/hpf in the esophageal mucosa. Multiple biopsies are required because the diagnosis may be missed with fewer biopsies. In a study of 102 patients with EoE, the probabilities of the diagnosis with 1, 4, 5, and 6 biopsies of having greater than 15 eosinophils/hpf were 0.63, 0.98, 0.99, and greater than 0.99, respectively.⁶

The pathologic features characteristic of EoE are separated into major and minor features. Major features include intraepithelial eosinophils at a concentration of greater than 15/hpf; eosinophilic microabscesses, which are groups of 4 or more eosinophils within the epithelium; surface layering, where eosinophils aggregate in the surface layers of the epithelium; surface sloughing of squamous cells and eosinophils; and eosinophil degranulation.⁷ Minor features include increased basal cell hyperplasia, lengthening of the lamina propria papillae, increased intraepithelial lymphocytes and mast cells, increased intercellular edema, and lamina propria fibrosis.⁷

Laboratory Evaluation

EoE has a strong association with atopy, and laboratory abnormalities associated with atopy are often found in patients with EoE, although they are not part of the diagnostic criteria. Patients with EoE may have slightly increased total immunoglobulin (Ig) E levels, and many patients with EoE have mild peripheral blood eosinophilia,^{8,9} with one center finding peripheral eosinophilia a much more common feature of pediatric EoE than adult EoE. A skin testing–based evaluation for specific food allergies and environmental allergies may also be considered in the evaluation of patients with EoE (discussed later).

CLINICAL FEATURES OF EOSINOPHILIC ESOPHAGITIS

Pediatric and adult EoE differ in their clinical presentations. In children, often the first presenting symptoms of EoE are feeding refusal or intolerance, which may be related to the inability of younger children to describe the feeling of dysphagia. Children with EoE also commonly have reflux symptoms, emesis, and abdominal pain. Failure to thrive, chest pain, and diarrhea are other presenting symptoms. Dysphagia and food impaction have been found to be more common in older children and adolescents.²

In adults, dysphagia with solid foods and food impaction are the two most commonly reported symptoms. Other symptoms include heartburn, reflux, and chest discomfort. Less commonly than in children, abdominal pain, diarrhea, and weight loss are reported in adult patients with EoE.

On initial history, patients may describe coping strategies that allow them to avoid some of the symptoms of EoE, such as washing down food with liquid, chewing food thoroughly, or avoiding foods that are associated with more dysphagia, such as meats.

Most children and adults with EoE have a personal history of other atopic conditions or a family history of either EoE or atopy.¹⁰

PATHOGENESIS

The pathogenesis of EoE is driven by various genetic, environmental, and host immune system factors and is not well understood. The presence of increased numbers

of eosinophils in the esophageal squamous epithelium is the hallmark of EoE, but increased esophageal eosinophil levels are also present in a multitude of other disorders.⁷

Food and possibly inhaled protein antigens trigger an adaptive T helper type 2 (Th2) cell-mediated response that involves interleukin (IL)-5 and IL-13.¹¹ IL-5 induces eosinophil growth and an activation factor that activates eosinophils to respond to eotaxin 3, which prolongs their survival. IL-13 also activates eotaxin 3 and calpain 14, known mediators of EoE. Eotaxin 3 gene is induced, which causes an influx of eosinophils into tissue.⁷

Approximately 75% of patients with EoE have evidence of allergy, with most having aeroallergen sensitization and a minority having food allergies.¹² There is evidence for seasonal variability of symptoms and diagnosis of EoE, suggesting these aeroallergen sensitizations are likely a contributing factor.

The complexity of EoE is primarily caused by the mixed picture of IgE-mediated and delayed Th2 responses.¹³ In a study by Straumann and colleagues,¹⁴ there were increased levels of eosinophils, T cells, and mast cells in esophageal mucosal biopsies compared with normal levels in stomach and duodenum. There was also increased expression of IL-5 and tumor necrosis factor- α in esophageal epithelial biopsy specimens. Also, there are increased levels of systemic and esophageal IgG4 in patients with EoE, suggesting its role in this disease as well.¹⁵ The high levels of IgG4 may play a role in blocking IgE responses and may explain the dissociation between the absence of positive skin tests and effective elimination diets.

EPIDEMIOLOGY

EoE was first described in 1977¹⁶ but it has only been in the last 25 years that the entity became more recognized by gastroenterologists and prevalence data began to be generated. Its estimated prevalence in the United States in an assessment of nationwide commercial insurance claims data from 2009 to 2011 was 56.7 cases per 100,000 persons, with similar rates in both children (50.5 cases per 100,000) and adults (58.9 per 100,000).¹⁷ High prevalence rates have been reported in the United States and Europe, whereas EoE seems to be less common in Asia.¹⁸

Multiple studies support the perception that the prevalence of EoE has been increasing. It is unclear how much of this increase in prevalence is caused by increased recognition versus increased development of the disease in patients.¹⁹ The annual incidence of new EoE diagnoses increased at the Mayo Clinic and its affiliates from 0.35 cases per 100,000 person-years during 1991 to 1995 to 9.45 cases per 100,000 person-years during 2001 to 2005.²⁰ A study from a single county in Switzerland found an increase in EoE prevalence from 3.1 cases per 100,000 inhabitants in 1989 to 1991 to 42.8 cases per 100,000 inhabitants in 2007 to 2009.²¹ In Denmark, there was a 19.5-fold increase in incidence from 1997 to 2012, in a time during which there was only a 1.9-fold increase in rate of esophageal biopsies performed.¹⁹

A survey suggested possible variation of prevalence within the United States, with a higher prevalence in northeastern states and lower prevalence in western states.²² This suggestion was supported by insurance claims-based data, in which United States EoE prevalence by region was most common in the Midwest (71.9 cases per 100,000) and least common in the west (30.9 cases per 100,000).¹⁷

Overall, male patients are more affected than female patients. Sixteen studies identifying 754 pediatric patients (mean age, 8.6 years) showed that 66% were male.²³ Data from 13 studies evaluating 323 adults (mean age, 38 years) identified that 76%

were male.²⁴ An analysis of insurance claims–based data indicated male predominance as well, with boys accounting for 70.1% of 3933 pediatric cases and for 63.3% of 12,472 adult cases of EoE.¹⁷

Little is known regarding risk factors for EoE. In a case-control study that included 115 patients with EoE and 225 controls, patients with EoE were significantly less likely to have ever smoked cigarettes or to actively use nonsteroidal antiinflammatory drugs.²⁵ Early-life exposures considered potential risk factors for EoE include antibiotics use in the first year of life, cesarean delivery, and preterm birth.^{26,27}

THE ROLE OF FOOD ALLERGY AND ENVIRONMENTAL ALLERGY IN EOSINOPHILIC ESOPHAGITIS

EoE has been considered a form of food allergy, because avoidance of food proteins in pediatric patients with EoE has been shown to control disease in most, although not all, children with EoE.

In 1995, Kelly and colleagues²⁸ provided strong evidence that immunologic response to food protein drives EoE. In this study, 10 children with EoE, resistant to standard antireflux medications, were placed on a trial of amino acid–based formula, and symptoms and endoscopic findings were compared before and after this elemental diet. Eight of 10 children experienced complete resolution of their symptoms and the remaining 2 reported significant improvement but not complete resolution. Endoscopic changes included a decrease in maximal esophageal intraepithelial eosinophils from a median of 41/hpf before the formula trial to 0.5/hpf after at least 6 weeks of elemental diet.

Since Kelly and colleagues²⁸ initial observation of the effectiveness of an elemental diet, subsequent studies have continued to support its effectiveness in children, and also in adults, with EoE. Liacouras and colleagues²⁹ presented a large retrospective case series of children with EoE. In this series, 172 patients attempted a completely elemental diet, of which 164 were compliant with the diet. Ninety-seven percent of those able to follow this diet showed significant improvement in esophageal eosinophilia (average 1.1 eos/hpf vs 38.7 eos/hpf before diet) and improved clinical symptoms. A meta-analysis of 13 studies of elemental diet in EoE (12 in children and 1 in adults) found that the overall effectiveness of strict elemental diet in achieving histologic remission of EoE was 90.8% (95% confidence interval, 84.7%–95.5%).³⁰

Although food allergy plays an important role in EoE pathogenesis, food allergy testing does not always identify the causative food allergens. Elimination diets based on skin prick testing (SPT) for foods, either alone or in combination with atopy patch testing (APT), result in improvement in some patients with EoE but have much lower efficacy than strictly elemental diets. In 2002, Spergel and colleagues¹² reported on 26 children who underwent elimination diet based on SPT and APT. Following a diet based on avoidance of foods positive on SPT or APT, 18 had complete symptom resolution, 6 had partial improvement, and 2 were lost to follow-up. A recent meta-analysis of 14 studies of allergy testing–directed food elimination for EoE showed an overall 45.5% resolution rate, with a wide 95% confidence interval of 35.4% to 55.7%.³⁰ Spergel and colleagues³¹ have suggested that, because milk is the most common food allergy in patients with EoE and because of the high rate of false-negatives for milk SPT and APT in EoE, a combined empiric milk elimination plus allergy testing–directed elimination of other foods can increase the success rate of directed food elimination to 77%.

In 2006, Kagalwalla and colleagues³² proposed the concept of an empiric 6-food elimination diet (SFED) to eliminate the food proteins most commonly associated

with food allergies and/or EoE. This list included milk, soy, egg, wheat, all nuts, and all seafood. This list was suggested to avoid the limitations of insensitive allergy skin testing in EoE, while still being less restrictive and more palatable than a completely elemental diet. The remission rate with this intervention (defined as <10 eos/hpf on esophageal biopsy) was 74%. Follow-up studies by the same group retrospectively evaluated single-food reintroductions to identify the specific foods responsible for EoE disorder.³³ Children who achieved histologic remission after initial SFED sequentially reintroduced the excluded foods. If remission was maintained after a food reintroduction, then that food was retained in the diet. If there was an EoE exacerbation with a given food, then it was eliminated. Endoscopy was performed at least 6 weeks from the time each new food was reintroduced. This reintroduction process revealed that a single offending food was the cause of inflammation in 72% of these children, 2 foods were allergens in 8%, and 3 foods were causative in 8%. Eleven percent of patients tolerated reintroduction of all 6 foods without recurrence of their esophagitis. Subsequent studies in adults have shown similar results for the efficacy of SFED and successive reintroductions.³⁰

Multiple studies show that milk tends to be the most commonly identified trigger in EoE, with wheat, egg, and soy/legumes being other frequent culprits. Given the minor role of nut and seafood allergies in EoE, a modified 4-food elimination diet (FFED) has been proposed and studied. Molina-Infante and colleagues³⁴ showed that 54% of adult patients responded to an FFED diet eliminating dairy, egg, wheat, and legumes. In this same group, 72% of adults responded when an SFED was used as rescue therapy for those that did not respond to FFED. Kagalwalla and colleagues³⁵ found the FFED to be effective in inducing remission in 62% of a population with pediatric EoE.

Besides foods, there is also evidence that aeroallergen sensitization may act as a contributor to EoE. Many patients with EoE also have allergic asthma and/or allergic rhinitis and are sensitized to environmental inhalant allergens. There is evidence that EoE symptoms worsen in some patients during the spring and/or fall pollen seasons.^{28,36} In addition, a single-center retrospective study showed that time of initial EoE symptoms was correlated with times of peak grass pollen and ragweed pollen counts at local pollen counting stations.³⁷

A study by Sugnam and colleagues³⁸ evaluating food and aeroallergen sensitizations in children with EoE showed that younger patients with EoE showed more IgE and patch test sensitization to foods, whereas older children showed greater IgE sensitization to inhalant allergens. However, the causative nature of these positive tests was not explored in this study.

It has recently been noted that a small but significant subset of patients with EoE who have failed SFED are sensitized to fresh fruits and vegetables, suggesting an oral allergy syndrome-like cross-reactivity with plant allergens, such as profilins and birch pollen.³¹

TREATMENT OF EOSINOPHILIC ESOPHAGITIS

Conventional Pharmacologic Therapies

For treatment of EoE, topical steroids (ie, swallowed fluticasone or budesonide) achieve successful remission in up to 80% of patients, although 10% of patients are refractory to this treatment, and, when steroids are discontinued in patients once controlled, disease nearly always recurs. Although no topical steroid formulations are approved specifically for EoE, recommended dosing of fluticasone from consensus guidelines (swallowed through a metered-dose inhaler) is 440 to 880 mg twice daily for adults or 88 to 440 mg twice to 4 times daily (to a maximal daily adult

dose) for children. Recommended dosing of budesonide (swallowed as a viscous suspension) is 1 mg daily for children less than 10 years old or 2 mg daily for older children and adults.³

Prednisone may be useful if topical steroids are not effective.³⁹ However, it is recommended that systemic steroids be used only in emergency cases, such as to treat severe dysphagia and weight loss, or for treatment during hospitalization. Because of the potential for significant side effects and the availability of other treatments that are effective in most cases, the long-term use of systemic steroids is not recommended for EoE.³

The role of PPI therapy in treatment of EoE has evolved over time. Originally, the diagnosis of EoE was dependent on a failure of PPIs to resolve symptoms related to esophageal dysfunction. The role of PPI treatment failure in the diagnosis of EoE was readdressed at the AGREE (A Working Group on PPI-REE) conference in 2017 involving experts from 14 countries.² It was concluded that there is significant overlap between PPI-REE and EoE, and that GERD and EoE are not mutually exclusive.

Dietary Interventions

The 3 main approaches in dietary management are (1) a strictly elemental (amino acid formula-based diet; (2) empiric food elimination, based on most common allergic triggers (ie, milk, wheat, egg, soy, nuts, and seafood); and (3) allergy test-directed elimination, based on positive allergy skin prick test and/or patch test results.

Each dietary approach offers different pros and cons for patients with EoE (**Table 1**). Although elemental diets with amino acid-based formulas are highly effective, they are unpalatable and are better tolerated by infants than by older children with EoE. The frequent need for nasogastric tube or gastrostomy placement and the high cost of elemental formula are also negatives of the strict elemental diet. In general, elemental diet is mainly an option for treating EoE in children with multiple food allergies, failure to thrive, and severe disease in which a strict diet with multiple eliminations is ineffective. Directed elimination diets, based on skin test and/or atopy patch test results, offers better long-term tolerability for most patients. Skin tests and patch tests have variable sensitivity and specificity for different food triggers, and atopy patch tests are not standardized. Ability of testing-directed elimination diets to achieve histologic remission of EoE was estimated at only 45.5% in a meta-analysis,³⁰ but recently a modified approach of elimination guided by SPT and APT combined with empiric milk elimination has been suggested to achieve a response rate of 77%.³¹

Empiric elimination diets, in the form of SFED or FFED, have good efficacy, are more tolerable for many patients compared with elemental diet, and avoid the need for gastrostomy-tube placement. However, with the elimination of 4 or 6 major food categories (dairy, egg, legumes, wheat, and in the case of SFED also nuts and seafood), achieving appropriate nutrition is still challenging and requires the involvement of an experienced nutritionist.

Molina-Infante and colleagues⁴⁰ have evaluated the effectiveness of a step-up empiric dietary strategy in pediatric and adult patients with EoE, as an alternative to a traditional SFED. Patients with EoE unresponsive to PPI therapy underwent a 2-food elimination diet (milk and gluten-containing grains). Nonresponders were offered an FFED (2-food elimination diet plus elimination of egg and legumes) and subsequent nonresponders were placed onto a 6-food-group elimination diet (FFED plus withdrawal of nuts and seafood). Remission was achieved in 43%, 60%, and 79% of patients with the 2-food elimination diet, FFED, and SFED, respectively.

Table 1 Comparison of dietary therapies for eosinophilic esophagitis		
Diet	Pros	Cons
Elemental formula	Effective in nearly all patients	High cost Requires NG or PEG tube in most patients Decreased QOL Negative psychosocial impacts
Six food elimination	Effective in many patients Some foods may be able to be reintroduced	Moderately high cost Potential nutritional deficits Serial EGD may be needed to assess response to food removal and reintroductions
Guided elimination	Often requires fewer food avoidances (depends on number of positive tests)	Extensive allergy testing required Less effective in many studies than other interventions Nutritional deficits may occur if many foods are removed

Abbreviations: EGD, esophagogastroduodenoscopy; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy; QOL, quality of life.

Food reintroduction is a key aspect of the long-term management of EoE. Following remission with any of the major dietary interventions, foods should be gradually reintroduced, with observation for recurrence of symptoms of EoE and consideration of serial repeat endoscopies. Spergel and Shuker⁴¹ suggest reintroducing the least allergic foods first, such as fruits and vegetables, whereas the most allergenic foods (milk, egg, wheat, and soy) are left to last.

Esophageal Dilation

For symptomatic patients with strictures, esophageal dilation is an option if medical or dietary therapy have failed, but it does not address the underlying inflammation in EoE. Because of the low rate of esophageal strictures in children with EoE, most esophageal dilations have been performed in adult patients with EoE. Early reports of outcomes of esophageal dilation for EoE suggested high complication rates, with 5% of patients experiencing esophageal perforation and 7% requiring hospitalization for chest pain.⁴² However, more recent data suggest that the rate of perforation is much lower. A 2017 meta-analysis of 37 studies found that perforation and postprocedure hospitalization occurred in only 0.03% of dilations for EoE.⁴³

Biologics

Anti-IL-5 monoclonal antibodies and other biologics targeting Th2 inflammation seem promising as therapy for EoE because of their low side effect profile but, to date, none have become US Food and Drug Administration approved for treatment of EoE. Anti-IL-5 therapies were some of the first to be investigated for use in EoE. These products were chosen because IL-5 is a key cytokine critical for survival of eosinophils. A trial of reslizumab, an anti-IL-5 humanized monoclonal antibody, in pediatric patients with EoE showed significant decrease compared with placebo in peak eosinophil count per high-power field on esophageal biopsy (but counts were still above the levels consist with histologic remission) and there was no significant difference of Physician Global Assessment scores compared with placebo.⁴⁴ Two trials of another anti-IL-5 monoclonal antibody, mepolizumab, in EoE failed to reach their primary outcome

measures of significant histologic remission rate (reduction of esophageal eosinophils to $<5/\text{hpf}$).^{45,46}

Recent trials of biologics directed at IL-13 and at the IL-4R α subunit (a component of both the IL-4 and IL-13 receptors) have shown significant reductions in esophageal eosinophilia and improvement in symptoms of EoE. A phase II, randomized, double-blind, placebo-controlled, parallel-group clinical trial was undertaken to evaluate the efficacy and safety of RPC4046, an anti-IL-13 monoclonal antibody in adult subjects with EoE.⁴⁷ Significant improvement from placebo was seen in eosinophil count per high-power field on esophageal biopsy, as well as EoE endoscopic reference score and the clinician's global assessment of disease severity score.

A double-blinded, randomized, placebo-controlled, phase II trial was recently completed to evaluate long-term safety and clinical efficacy of dupilumab, a monoclonal antibody against IL-4R α , for use in EoE. Initial positive results of this study have been presented in abstract form but are not yet published.⁴⁸

The outcomes of these recent trials of biologics targeting IL-4 and/or IL-13 seem more promising than those reported in previous trials of biologics targeting IL-5, but the ultimate success of these therapies remain to be determined in upcoming phase III trials. In addition, in several trials to date, it seems that outcomes improve when conventional therapy, such as PPIs or topical steroids, was given in conjunction with a biologic.

SUMMARY

EoE is a newly defined condition that has dramatically increased in prevalence in the last several decades. It may occur at any age, but the clinical presentation in young children is often more vague than the classic solid food dysphagia and food impacting that are the major presenting symptoms of EoE in adults and adolescents. Successful therapies exist, including medications and dietary modifications, but disease typically recurs when the successful intervention is discontinued. Although no biologic therapies are currently approved for the treatment of EoE, clinical trials are ongoing and these therapies that specifically target aspects of Th2-mediated inflammation may play a role in the treatment of EoE in the future.

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