



Best-Practice Eosinophilic Esophagitis: An Overview

SUMMARY

Eosinophilic esophagitis (EoE) is an emerging disease causing difficulty in swallowing, vomiting, refusal to eat, and poor weight gain. It is increasingly being recognized and diagnosed among infants and children by pediatricians, internists, allergists, gastroenterologists, and other physicians. Eosinophilic esophagitis is an allergic inflammatory disorder affecting the esophagus: a type of white blood cells called eosinophils build up in the esophagus that can damage the tissue, cause chronic inflammation, and even scarring. While the exact cause is unknown, food allergies appear to be a component of EoE. Symptoms generally resolve and the esophagus heals upon the identification and removal of the allergic foods from the diet. Therefore, nutrition therapies play an essential role in management of EoE.

SCIENTIST BIOGRAPHY

Jan Kajzer is a registered dietitian working in Pediatric Nutrition Science at Abbott Nutrition. Jan is a graduate of Miami University, Oxford, OH, The University of Dayton, Dayton, OH and The Ohio State University, Columbus, OH. Prior to joining Abbott Nutrition in 2009, Jan practiced as a clinical dietitian at Nationwide Children's Hospital in Columbus, OH. Her work at Abbott Nutrition focuses on the dietary management of food allergies.

HISTORY

The first report of eosinophilic inflammation of the esophagus in a patient with dysphagia (difficulty swallowing) and no gastroesophageal reflux disease (GERD) symptoms was published in 1977¹. Subsequently, several similar isolated case reports were published. In the 1980s, numerous reports linked intraepithelial eosinophils in esophageal biopsy specimens with GERD; however, some reports recognized that select patients with a dense eosinophilic infiltrate failed to respond to acid-suppression therapy¹. From the early 1980s through the mid-1990s, the significance of abundant esophageal eosinophils was underappreciated, and several investigators began to suspect that GERD may not be the cause of the dense eosinophilic infiltrate found in some patients.

A hallmark study by Kelly et al. in 1995 described a series of pediatric patients with GERD-like symptoms and eosinophil-predominant esophageal infiltration². These patients failed to respond to anti-reflux therapy; however, they responded well to dietary therapy with an amino acid-based diet, suggesting an allergic etiology. Further research has provided additional confirmation that patients with intractable GERD-like symptoms and dense eosinophilic esophageal infiltrates appear to have a unique non-GERD disorder that in some cases is allergy related (i.e., EoE).

EPIDEMIOLOGY

The epidemiology of EoE is still unclear given the poor prior awareness and recognition of the disease. In children and adolescents up to 19 years of age, current prevalence estimates range from 1 to 2 per 10,000 persons³. Interestingly, 97% of cases have been diagnosed since 2000⁴. These studies indicate that the incidence of EoE may be higher than for other well-recognized inflammatory GI disorders, such as Crohn's disease.

Based on recent literature, the prevalence of EoE is increasing⁵. However, a debate exists as to whether the new diagnosed cases represent a true increase in prevalence or just increased disease awareness. Results from a recent population-based long-term study have clarified this uncertainty and demonstrate that the accelerated EoE incidence does represent a true increase and is not merely the consequence of greater disease awareness⁶.

An emerging body of literature suggests that EoE has a strong familial association⁷. Approximately 10% of parents of children with EoE have a history of esophageal strictures, and about 8% have biopsy-confirmed EoE. Additionally, there are 27 or more multiplex EoE families with numerous affected members described thus far⁷. Eosinophilic esophagitis also has an increased sibling risk ratio relative to related atopic diseases, such as asthma⁷.

Evidence also suggests that there is both ethnic and gender variation in the prevalence of EoE. The majority of cases have been reported in Caucasian males^{1,8}. However, the certainty of this finding is questionable given that this patient population has been studied most extensively⁵. Therefore, additional population-based, epidemiologic studies are needed to investigate the true prevalence of EoE.

PATHOGENESIS

Although the pathogenesis of EoE is unclear, several hypotheses exist:

- Allergic and immune-mediated mechanisms, similar to those of other atopic diseases, have been implicated⁴. Evidence suggests that EoE is associated with T-helper cell (Th)-2 type immune responses. Increased levels of the Th2 cytokines interleukin IL-4, IL-5, and IL-13 have been found in the esophagus of patients with EoE⁵. These cytokines likely play an important role in the activation and recruitment of eosinophils to the esophagus.
- EoE may also be a mixed immunoglobulin IgE and non-IgE-mediated allergic response to food and environmental allergens⁵. IgE-mediated reactions are immediate hypersensitivity responses typically occurring shortly (within minutes) after allergen exposure. Conversely, non-IgE mediated allergic disorders are associated with a delayed response that can occur hours or days following exposure to an antigen.
- Interestingly, data suggest that acid reflux is not a causative factor in the majority of patients with EoE. However, because some patients do exhibit symptomatic, endoscopic, and histologic resolution of EoE following treatment with a PPI (i.e., PPI-responsive EoE); acid reflux may play a secondary role in this disorder⁴.

SYMPTOMS

Symptoms are often similar to GERD but symptoms may not resolve with the use of proton pump inhibitors (PPIs). As presented in the Table 1, there are age-related differences in symptoms¹.

Table 1: Common EoE Symptoms

Infants	Food refusal, failure to thrive, feeding intolerances/feeding aversions, reflux
Children	Vomiting, dysphagia, abdominal pain, heartburn, regurgitation, feeding refusal/feeding aversions
Adolescents/Adults	Dysphagia, food impaction, heartburn, reflux

DIAGNOSIS

Liacouras et al. published diagnostic guidelines which state, “Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”⁸. It is the combination of clinical symptoms, pathologic results characterized by one or more biopsies showing eosinophil-predominant inflammation (≥ 15 eosinophils in peak high-power field [HPF]) isolated to the esophagus and exclusion of other GI disorders (i.e. GERD, infection, Crohn’s disease)⁸.

PHARMACOLOGIC THERAPY

Systemic steroids, topical steroids and PPIs are common pharmacologic therapies used for EoE, but there are important factors that must be considered with long-term use in any of these options.

Systemic Oral Steroids: One of the first treatments that demonstrated efficacy in patients with EoE was systemic oral steroids. Approximately 95% of patients using systemic steroids can experience both clinical and histologic improvement; however, 90% have symptom recurrence upon treatment discontinuation⁵. Moreover, because prolonged use of systemic steroids are associated with serious side effects, such as bone abnormalities, poor growth, and adrenal suppression, long-term use is not recommended¹.

Topical Steroids: The main pharmacotherapy for treatment of EoE is topical steroids delivered to the esophagus. These agents have a substantially better safety profile than systemic steroids and are 50% to 80% effective in improving symptoms and histology of EoE⁵. The main side effects associated with topical steroids are superficial oropharyngeal and esophageal candidiasis⁸. As with systemic steroids, symptoms and pathologic changes often recur after discontinuation of topical steroid therapy. Therefore, long-term treatment will be required for many patients with EoE; however it is important that the lowest effective dose be used with appropriate follow up.

Proton Pump Inhibitors: The efficacy of PPIs in reducing EoE symptoms is comparable to that observed with topical steroids⁹. Additionally, PPIs may be effective in patients with EoE and concomitant GERD, and in those with PPI-responsive EoE. Importantly, although PPIs may be used as co-therapy to partially alleviate some symptoms, they should not be considered a primary treatment option.

NUTRITION MANAGEMENT

There are three types of diets that have been shown to be effective in the dietary management of EoE:

6-Food Elimination Diet: This approach to nutritional management is to remove the six most common food allergens (wheat, dairy, eggs, soy, seafood [fish & shellfish], peanuts and tree nuts) from the diet. An advantage of diet is that allergy testing is not required to determine which foods to remove from the diet¹⁰. In a retrospective study of 35 children with EoE, treatment with 6-food elimination diet (SFED) resulted in 74% clinical and histologic improvement¹¹. In this study, cow’s milk, soy, wheat, egg, peanut/tree nut, and seafood were the only foods excluded while all other solid foods were allowed. Recently, this treatment approach was validated by a prospective study in which 78% of patients had histologic improvement¹².

Directed Elimination Diet: Another nutritional approach to treating EoE is to remove selective foods from the diet based on results of food allergy testing. Research shows that 57% - 77% of subjects experienced improvement in clinical symptoms and histologic results^{1,13}.

The main disadvantage of an elimination diet is potential nutritional deficiency¹⁴. As the number and type of foods removed from the diet increases, so does the risk of nutritional deficiency. Risk of dietary inadequacy can also be influenced by the child's initial nutritional status and the presence of additional risk factors (e.g., refusal of foods/selective eating/texture aversion). The elimination of certain food groups such as dairy, meat, and grains creates more substantial nutritional challenges than the removal of others foods. Therefore, the number and type of calories, protein, and micronutrients remaining in the diet should be carefully monitored so that supplementation with vitamins, minerals, or amino acid-based formula is introduced as needed.

Amino Acid-Based Diet: An amino acid-based diet requires replacement of all solid foods with a nutritionally complete amino acid-based, hypoallergenic formula. Kelly and colleagues were the first to successfully use an amino acid-based diet for the dietary management of children with GERD-like symptoms resistant to acid-suppression². Since this landmark publication, several studies have evaluated dietary management with an amino acid-based diet in children with EoE and studies show remission rates ranging from 88% with a hypoallergenic, amino acid-based formula^{1,15}.

The amino acid-based diet remains the most effective dietary management option, resulting in both clinical and histologic remission in children with EoE. There is a greater likelihood of achieving mucosal healing with this approach compared with other dietary strategies or steroid treatment¹⁰. The disadvantages of this approach include poor taste, patient compliance, and impaired quality of life (QoL) due to removal of regular foods. Additionally, many children require either nasogastric or gastrostomy tubes to deliver adequate nutrients, which can lead to patient discomfort and parental distress. Moreover, amino acid-based formulas are costly, which may place a significant financial burden on families who either do not have health insurance or whose insurance plans do not cover these formulas.

CONCLUSION

Consensus recommendations state that dietary therapy should be considered as an effective therapy in all children diagnosed with EoE^{1,8}. Which diet to use should be based upon disease severity, patient's lifestyle and QoL, and family resources. It is strongly encouraged that a registered dietitian is consulted to ensure that proper calories, vitamins, and micronutrients are maintained.

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