Eosinophilic Esophagitis: A Newly Recognized Clinical Entity

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ABSTRACT

Eosinophilic esophagitis (EoE) is a newly recognized disease state with evolving criteria for diagnosis. While EoE is not fully understood, eosinophils suggest an immune-mediated pathophysiology. Children present with failure to thrive, gurgling, and other gastrointestinal symptoms. There are no treatments approved by the Food and Drug Administration at this time, although studies have been conducted.

Keywords: allergies, anti-IgE monoclonal antibodies, corticosteroids, dietary restrictions, eosinophilic esophagitis, eosinophils, food allergies, leukotriene D4 receptor antagonists, mast cell stabilizers, milk allergy, monoclonal antibodies

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CASE STUDY

A mother brought her 15-month-old child to the clinic with concerns of “gurgling sounds” coming from the child’s throat. The gurgling noises began at 12 months when breastfeeding was stopped and the child was started on formula. The noises lasted off and on throughout the day with no relation to food intake or activity.

This CE learning activity is designed to augment the knowledge, skills, and attitudes of nurse practitioners and assist in their understanding of the new clinical entity eosinophilic esophagitis (EoE).

At the conclusion of this activity, the participant will be able to:
A. Explain the definitive criteria for diagnosing EoE
B. Differentiate EoE from eosinophilic GERD
C. Demonstrate knowledge of the correct administration of fluticasone in tx EoE

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The authors do not present any off-label or non-FDA-approved recommendations for treatment.

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Physical exam revealed a pleasant child at the appropriate level of growth and development. His height and weight was at the 90th percentile. Gurgling sounds were absent during the visit.

The child was started on a proton pump inhibitor (PPI) and a barium swallow was ordered to rule out a structural abnormality. Results of the barium swallow were normal. At the 1-month follow-up visit, the child was still gurgling and had begun to tug at his throat. When the mother asked the child if his throat hurt, he shook his head no. Since his initial symptoms remained with the addition of tugging at his throat, an endoscopy with biopsies was performed. Biopsy results were consistent with diagnostic criteria for eosinophilic esophagitis (EoE).

**HISTORY AND DEFINITION OF EoE**

Eosinophils are a type of white blood cells that play a role in allergies and are associated with an inflammatory response. An immune globulin, IgE, is likely involved with the eosinophilic response, and receptors for IgE are present on the surface of the eosinophil cell. The esophagus is normally free of eosinophils. The presence of eosinophils in esophageal tissue is a non-specific finding. Esophageal eosinophilia occurs with many esophageal disease states, including gastroesophageal reflux disease (GERD). EoE is the recommended abbreviation for eosinophilic esophagitis to differentiate it from the abbreviation for erosive esophagitis (EE).

Although 1 of the earliest published articles regarding eosinophils in the esophagus was in 1949, EoE is a relatively newly defined disease for which little is known. The first definition of EoE, “...a primary clinicopathologic disorder of the esophagus characterized by esophageal and/or upper gastrointestinal (GI) tract symptoms in association with esophageal mucosa biopsy specimens containing ≥ 15 intraepithelial eosinophils per High Powered Field (eos/HPF) in 1 or more biopsy specimens and absence of pathologic GERD as evidenced by a normal pH monitoring study....” was based on the symptoms and histological findings.

As knowledge and clinical experiences grew, the definition of EoE was revised as “... a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.” This definition defines EoE as esophageal inflammation brought on by a high number of eosinophils. It also supports the belief that EoE involves the immune system and the body’s response to allergens. EoE is a chronic immune-mediated disease characterized by esophageal dysfunction clinically and inflammation histologically, despite normal pH monitoring of the distal esophagus or lack of response to high-dose treatment with PPI medications.

**PREVALENCE**

EoE is found worldwide. It is estimated that the prevalence of EoE is 52/100,000 in the US, with the Mid-Atlantic and New England states having the highest prevalence. EoE affects males more than females and is prevalent across all ages. EoE usually presents during childhood; the peak age of diagnosis is within the first 3 years or at 30-40 years old. The incidence of EoE appears to be increasing, but there is controversy regarding this claim. The increase could mean an increase in the disease, but it can also mean health care providers are becoming more aware of the disease and therefore performing more esophageal biopsies.

**PATHOPHYSIOLOGY**

The exact pathophysiology of EoE is a mystery. Eosinophils infiltrate the esophagus and cause damage that can lead to development of strictures, narrowed esophagus, and food impaction. It is uncertain how and why the eosinophils accumulate in the esophagus. Two areas that predominate the investigations of EoE are allergies and genetics.

**Allergies**

The role of allergies in EoE is perplexing. Individuals with EoE do not develop anaphylactic shock when eating a food. But withholding the causal food or replacing food with a specific elemental formula diet eliminates the eosinophils in the esophagus and reverses the inflammation of the esophagus in most cases. Additional support for allergies as the fundamental cause is supported by the results of treating EoE with swallowed inhaled steroids.
This treatment also eliminates the eosinophils in the esophagus in most patients. Studies are also demonstrating the role of airborne allergens. Some studies are suggesting that EoE in children is caused mostly by food, whereas EoE in adults is caused mostly by airborne allergens. Seasonal variation has been seen in diagnosis.

**Genetics**
The majority of patients with EoE are white and male, thereby supporting a role of genetics. There also appears to be a high rate of atopy with parents and siblings who are being diagnosed with EoE. Molecular analysis is being conducted at several levels, with differences found between patients with EoE and patients without. Current investigations are also exploring the role of eosinophils, mast cells, transformation growth factor—β1 (TGF-β1), lymphocytes, and cytokines in the inflammatory process, as these cells are also found in EoE.

**CLINICAL PRESENTATION**
Symptoms of EoE are similar in children and adults, but there are also some age differences. Common symptoms of infants include irritability, feeding refusal, and failure to thrive. Children display feeding disorder, vomiting, abdominal pain, and dysphagia. However, symptoms vary, as with the case study above when the child’s chief complaint was gurgling and later tugging at his throat. Cough, hoarseness, and throat clearing were also found in children. Children can have food impaction but not as commonly seen as in adults. In children 5 years and older, dysphagia and anorexia/early satiety are correlated with EoE.

Symptoms for adults include dysphagia, food impactions, feeding dysfunction, chest pain, and upper abdominal pain. Feeding dysfunction can lead to coping mechanisms, such as avoiding highly textured food, extensively chewing food, and cutting foods in small pieces. Interestingly, some patients have no symptoms but still present with histological findings consistent with EoE. It is important to note that many patients with EoE also have a history of eczema, allergic rhinitis, and asthma.

**PHYSICAL EXAMINATION**
Physical examination is usually normal. An infant with failure to thrive will present with obvious symptoms of growth failure, and most children and adults may also have allergy symptoms such as rhinitis.

**DIAGNOSIS**
Diagnosis of EoE includes endoscopy, with biopsies from the proximal and distal esophagus showing a minimum of 15 eosinophils/hpf. Biopsies are necessary because the esophagus may appear normal. Other findings of the esophagus that may support but do not diagnose EoE include fixed or transient esophageal rings, whitish exudates, longitudinal furrows, edema, and diffuse esophageal narrowing. Allergy testing in the form of skin pricking and patch testing are also recommended to assist with identifying possible allergens.

**CLINICAL TRIALS OF MEDICATIONS FOR EoE**
Treatment goals for EoE have focused on alleviating symptoms, reducing inflammation, and identifying and eliminating possible food triggers.

Several anti-inflammatory and anti-allergic therapeutic classes have been evaluated in EoE. These medication classes include corticosteroids, leukotriene antagonists, mast cell stabilizers, and monoclonal antibody therapy against IL-5 and IgE. However, few studies have been conducted in a prospective, randomized, double-blinded manner, and most study sizes have been too small and homogenous to extrapolate results. The small study size has also been a major limitation to conclude statistical significance of treatment options. Additionally, despite being effective in other inflammatory and allergic disease states, not all medications have demonstrated benefit in the treatment of EoE. One other consideration is that eosinophils may be only a marker for inflammation and that reduction of eosinophils may not significantly affect symptoms or progression of the disease. A brief discussion of selected clinical trials follows.

**Dietary and Food Studies**
Food has been implicated as a trigger for EoE. Studies have identified milk as a major food allergen.
Other common foods identified include soy, eggs, and wheat. These studies imply that certain foods may trigger EoE, but the specific food type will vary from patient to patient.

**Corticosteroids**

**Methylprednisolone.** In 1 of the earliest studies in pediatric patients with EoE, oral methylprednisolone was shown to reduce symptoms and improve histology in most patients at 4 weeks. Most patients had symptom relapse if therapy was withdrawn.

**Fluticasone.** In a small, nonrandomized, retrospective study, investigators assessed subepithelial fibrosis before and after fluticasone therapy in pediatric patients; the inhalation dosage form was administered orally. They found an association of decreased fibrosis and clinical symptoms after fluticasone therapy. Investigators in a small, prospective, randomized trial compared fluticasone to esomeprazole and assessed clinical response in adults. Patients received 440 mcg of fluticasone or esomeprazole 40 mg daily. The investigators found no difference in the response between the treatment groups in improvement in dysphagia or esophageal eosinophil infiltration, nor did they find improvement before and after treatment within each group. However, dysphagia and esophageal eosinophil infiltration did trend toward improvement in both groups.

It is proposed that the low systemic bioavailability of oral fluticasone suggests locally mediated effects rather than systemic effects. However, systemic levels in this patient group have not been studied after swallowing the inhalation dosage form, and therefore whether the administration is local (topical) or systemic has not been definitively determined. Caution should be exercised in interpreting those studies stating the results are from topical administration. Children who have not responded to swallowed fluticasone may respond to other oral corticosteroids, which are believed to achieve a more systemic response. A study of fluticasone in adults demonstrated improvement in histological features but no improvement in symptoms.

**Budesonide.** A randomized, double-blind, placebo-controlled trial of budesonide 1 mg twice daily for 15 days was evaluated in adolescent and adult patients with EoE. After 15 days the eosinophil load, mast cells, and tumor necrosis factor alpha (TNFα) were significantly reduced. Additionally, subjective scores for dysphagia of solid foods were decreased significantly with budesonide therapy.

In a retrospective analysis of safety, symptoms, endoscopic, and histologic findings among 20 children treated with oral viscous budesonide, investigators determined that the majority responded to budesonide therapy. Of the 20 children, 16 were responders, 1 was a partial responder, and 3 were nonresponders. There are reports that patients who have not responded to swallowed fluticasone have responded to oral viscous budesonide.

**Proton Pump Inhibitors**

PPIs play a role in the differential diagnosis of EoE by helping to eliminate eosinophilia esophagitis related to GERD as a diagnosis. However, GERD may be present concurrently EoE. Up to 75% of EoE patients may be prescribed a PPI despite the fact that they are not expected to affect the immune-related inflammatory response. Despite the lack of effect on the immune system, there have been reports of beneficial treatment of EoE with PPIs. However, in a prospective, randomized trial of adult EoE patients, a PPI was compared to swallowed fluticasone. No clinical benefit was found in the pre- and post-treatment PPI patients.

**Anti-Interleukin-5 Monoclonal Antibodies**

**Reslizumab.** Reslizumab is a monoclonal antibody that binds irreversibly to IL-5 and prevents IL-5 from activating eosinophils and other clinical effects. In a multi-center, randomized, double-blinded trial in children and adolescents 5 to 18 years old, subjects were randomized to receive either sterile saline or varying dosages of reslizumab infusions about every 28 days for 4 doses. Reslizumab reduced esophageal eosinophil counts significantly compared to saline (placebo); however, there were no significant differences for the assessments of clinical symptoms and quality of life. Both the placebo and the reslizumab group experienced an improvement in clinical symptoms and quality of life scores.
Mepolizumab. Mepolizumab is a monoclonal antibody that binds irreversibly to IL-5. In a multicenter, randomized, double-blinded study, 59 children received varying dosages of an infusion of mepolizumab every 4 weeks for 3 doses. No placebo group was included. Mepolizumab improved eosinophil load in some patients, and the clinical markers trended toward improvement. However, these improvements did not achieve statistical significance. A larger sample size might have detected a difference between pre- and post-treatment results.30

Anti-IgE Monoclonal Antibodies
Omalizumab is a monoclonal antibody against IgE that is indicated for treatment in moderate to severe asthmatic patients. Two case reports in patients who had several allergy-associated disease states, including food allergies, concluded that clinical symptoms improved, but histological features of EoE did not.31

Leukotriene D4 Receptor Antagonists
Leukotriene D4 is a known facilitator of allergic and immune mediators. Montelukast, an orally administered medication, is a receptor antagonist of leukotriene D4 and is commonly used in other disease states that have an allergic/immune component, such as asthma. In a prospective, nonrandomized study of adult patients who were receiving fluticasone for 6 months, montelukast was initiated at 10 mg daily concurrently with fluticasone as adjunct therapy to see if the fluticasone dosage could be reduced. Evaluation of montelukast at month 3 indicated a reversal of the histological and clinical improvement achieved by fluticasone. Four of 11 patients had to be withdrawn from the study at month 2 because of serious deterioration of clinical status.32

Mast Cell Stabilizers
In a small study of 14 pediatric patients, cromolyn 100 mg was administered 4 times a day for 1 month without clinical or histological improvement.33

TREATMENT
No treatments for EoE have been approved by the Food and Drug Administration. Clinicians must evaluate the outcomes of clinical trials as they become available and incorporate the results into their clinical practice. Below is a discussion of treatment options based on the limited information that is available.

Dietary Restrictions
Dietary restrictions, usually the first step, involve strict use of an amino-acid-based formula, eliminating 1 or more food based on allergy testing, or eliminating a most likely food usually based on a diet journal.9 After a certain time frame of eliminating the food, usually 4-8 weeks, the esophagus is biopsied.15 Unfortunately, this involves frequent esophageal biopsies that require general anesthesia. The most effective diet therapy is the elemental diet, which reduces the eosinophilic response in most patients.9,11

Corticosteroids
Clinical trials to date indicate that corticosteroids have been the most consistent and efficacious treatment and therefore are the cornerstone of treatment. Corticosteroids that are presumed to have lower systemic absorption are reasonable to be tried first to minimize systemic adverse effects. While it is reasonable to assume that fluticasone and budesonide have lower systemic levels than oral methylprednisolone or prednisone, no clinical studies have been conducted to detect differences in systemic levels among the corticosteroids in EoE treatment. There is no evidence that 1 corticosteroid has greater beneficial effects or less adverse effects.

Fluticasone. Fluticasone is a reasonable first option and is thought to have low systemic levels as a result of low bioavailability when absorbed from the gut. Fluticasone is administered by spraying the inhalation dosage form into the mouth and instructing the patient to swallow the spray. If the patient responds inadequately to fluticasone, then changing to a corticosteroid to achieve a higher systemic concentration is reasonable, such as oral viscous budesonide or oral methylprednisolone. “Topical” fluticasone refers to swallowed fluticasone and does not mean application to the skin. Dosage:

- 2 to 4 years old: 44 mcg swallowed twice daily34
Medications to Avoid

**Leukotriene D4 Receptor Antagonists**

Therapy with montelukast resulted in a reversal of histological and clinical improvement seen with fluticasone. This class of agents, which also includes zafirlukast, should be avoided in patients with EoE. These medications should be avoided until clinical trials indicate they are safe and effective for EoE.

**Nonpharmacologic Procedures**

Esophageal dilation has been evaluated in EoE. Dilation provides temporary symptomatic improvement in patients with esophageal strictures. There are different methods for dilation, and the procedure is complicated by the presence of fibrosis of the esophageal wall.

**Prognosis**

Because of the newness of the disease, there is a paucity of information on the long-term prognosis of EoE. The limited studies show a consensus that EoE is a chronic disease with relapses and remissions. Otherwise, the outcome of EoE varies widely. Studies are contradictory in demonstrating the development of food tolerance. Some patients appear to develop a tolerance to the food, but other patients do not. If a food or foods are identified and there is strict avoidance, remission is sometimes seen. Very few patients progress to eosinophil gastroenteritis or eosinophilic colitis. Complications of EoE can include strictures, food impaction, narrow esophagus, and esophageal rupture. There has been no evidence of EoE leading to esophageal cancer.

**Role of NP**

An important role for the nurse practitioner (NP) is identifying possible patients with EoE. Obtaining a thorough family and patient history is critical, especially with infants and children. If EoE is suspected, the patient needs to be referred to a gastroenterologist. A multidisciplinary center is best because of the team approach. A major referral center is also up to date on the latest methods of diagnosis and treatment. Along with a gastroenterologist, the patient will be

- 5 to 10 years old: 110 mcg swallowed twice daily
- 11 years and older: 220 to 440 mcg swallowed twice daily

**Budesonide.** Oral viscous budesonide is an effective treatment and is reported to be effective in some patients for whom swallowed fluticasone has failed. Oral viscous budesonide is prepared by dissolving a 0.5-mg respule in five 1-gm packets of sucralose (Splenda) for a total volume of 10 to 15 mL. Dosage: 0.5 to 1 mg twice daily.

**Methylprednisolone.** In pediatric patients, oral methylprednisolone has been shown to reduce symptoms and improve histology at 4 weeks. Most patients have symptom relapse if therapy is withdrawn. Generic methylprednisolone is less expensive than inhaler corticosteroids. Methylprednisolone tablets or solution may have fewer local effects and may have more systemic adverse effects than swallowed budesonide or swallowed fluticasone; however, that theory has not been established. Dosage: 0.75 mg/kg administered orally twice daily.

**PPIs**

Despite the lack of effect on the immune system, most EoE patients are prescribed a PPI. The dosage is relatively high compared to dosage for “heartburn.” Dosages vary depending on the PPI administered. Dosages for esomeprazole: adults, 20 mg twice daily; children, 1 mg/kg twice daily (up to the adult dosage).

**Mast Cell Stabilizers**

Cromolyn sodium failed to demonstrate any benefit in patients with EoE and cannot be recommended at this time for EoE. Nedocromil (Tilade) is a member of this class of medications.

**Interleukin-5 Monoclonal Antibodies**

While IL-5 inhibitors have reduced eosinophil counts, they have failed to demonstrate an improvement in the quality of life and other clinical markers. Neither reslizumab nor mepolizumab can be recommended at this time.
evaluated by an allergist, pathologist, and nutritionist or dietitian. This team works together to develop a plan that is best for the individual patient.

The NP must monitor the growth and development of children with EoE. This is especially important with children on any type of elimination diet. Children are at risk to be nutritionally compromised.

An evaluation of quality of life of the patient and family needs to be included in the care. A food elimination diet can be difficult to understand and follow. A dietitian can supply the information, but the NP may need to assist with adherence to the diet. This change affects not only the patient but also the entire family. For example, holidays for most families revolve around eating. The NP may also need to assist with the emotional toll.

The positive side is the ongoing research to try to determine the cause and cure for EoE. There are also many resources about EoE available to patients and families on the internet and at multidisciplinary centers. Another responsibility of the NP should be to guide the patient and family in accessing evidence-based sources of information. N3

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