Case-based review

Eosinophilic esophagitis (EE) is a newer disease entity that has been diagnosed with increasing frequency over the past 10 years. The first reported case of EE was in 1977 in an adult patient with food allergies, gastroesophageal reflux disease (GERD) symptoms, and esophageal eosinophilia [1]. The definitive link between food allergies and EE was shown by Kelly and colleagues [2] in 1995, when they described 10 patients with isolated esophageal eosinophilia unresponsive to acid blockade who improved with an elemental formula. In fact, 8 had complete normalization of esophageal eosinophilia after 6 weeks. Their findings introduced the role of food allergy in EE [2].

Since the mid-1990s, there has been a dramatic rise in the number of patients diagnosed with and the number of papers published on EE. EE has now been reported in every continent except for Africa, including every state in the United States and most of Western Europe. Several reports have suggested that the prevalence of EE is increasing in both pediatric patients and adults. Noel et al [3] described an incidence of EE of 1 in 10,000 children along with a fourfold increase in prevalence from 2000 to 2003. Similarly, Straumann and Simon [4] reported an incidence of 6 in 100,000 adults with increasing prevalence. In addition, Liacouras et al [5] described a 35-fold increase between 1994 and 2003 in newly diagnosed EE cases in Philadelphia, and Cherian et al [6] described a 18-fold increase in cases between 1995 and 2004 in Western Australia.

The First International Gastrointestinal Eosinophil Research Symposium (FIGERS), joining together allergists, gastroenterologists, and pathologists, recently provided clinicians with recommendations for the diagnosis and treatment of EE [7]. This group defined EE as a “primary clinicopathological disorder of the esophagus.” Diagnosis is made by esophageal biopsy with the finding of 15 or more eosinophils per high-power field (HPF) in 1 or more specimens. In addition, gastroesophageal reflux must be aggressively managed prior to endoscopy with high-dose proton pump inhibitor (PPI) or

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the patient must have evidence of normal pH probe in his/her distal esophagus. This recommendation was due to the fact that Ngo and colleagues [8] described 3 patients who had up to 52 eosinophils per HPF resolve with reflux medications. Other than gastroesophageal reflux, clinicians must keep in mind that eosophageal eosinophils can be seen in other disease entities including eosinophilic gastroenteritis (increased eosinophils throughout the gastrointestinal tract), Crohn’s disease, collagen vascular disease, hypereosinophilic syndrome, drug associated, and, at times, infections (Table 1).

**CASE STUDY**

**Initial Presentation**

A 5½-year-old, previously well Caucasian boy presents with persistent emesis of 3 months’ duration and gastroesophageal reflux symptoms.

**History**

The patient is vomiting 2 to 3 times a day without bilious or blood in the emesis. His past medical history is significant for mild “spitting up” as an infant. He has also history of mild allergic rhinitis that controlled with over-the-counter antihistamines. There is a family history of allergic rhinitis in his mother and father. His paternal grandfather has a history of multiple esophageal dilations, and his father has had GERD symptoms “for years.”

**Physical Examination**

The patient’s physical examination is remarkable for weight at the 30th percentile and height at the 40th percentile, unchanged over time. HEENT examination is remarkable for pale nasal turbinate edema. Cardiovascular, lung, abdomen, and skin examinations are unremarkable.

- What is the initial approach to the evaluation of this patient?

The etiology of persistent vomiting must be evaluated in a stepwise manner. Infectious causes, gastroesophageal reflux, anatomical issues, food allergy, and EE are included in the differential diagnosis. The use of cultures, pH probe, upper gastrointestinal series, and allergy testing may be employed in the evaluation. It is important to ensure that the patient is not losing weight or dehydrating from his persistent vomiting. Our patient’s workup included a normal upper gastrointestinal evaluation with small bowel follow-through (eliminating anatomic concerns) along with negative stool cultures (decreasing possibility of common infectious agents).

**Initial Treatment and Further Workup**

The patient is treated with a PPI for 2 months without relief of symptoms. He then undergoes an upper endoscopy with biopsy of 4 discrete locations in the esophagus showing patchy infiltrate. There is a maximal count of 40 eosinophils per HPF in 1 biopsy, 20 in another sample, 30 in third sample, and 10 in the fourth sample. There was no significant inflammation in the duodenum or antrum.

- Do these findings confirm a diagnosis of EE?

The endoscopy shows the typical patchy appearance of EE with isolated eosinophilia to the esophagus. However, up to one third of endoscopies are normal in appearance; thus, biopsy is of utmost importance. A count of greater than 15 eosinophils per HPF in at least 1 specimen despite acid suppression with a PPI for 1 to 2 months and the exclusion of other causes confirms the diagnosis [7]. Gonzales and colleagues [9] have shown that 5 discrete biopsies are necessary for sufficient power to rule out EE.

- What are common clinical presentations of EE?

This young boy with chronic emesis and GERD-like symptoms and a familial history represents a classic presentation of EE in a school-age child. The patient is growing and otherwise doing well but has as an increase in gastrointestinal symptoms. A review of family history shows other male members with similar symptoms. EE is more common in males and has a strong familial component.

The history of spitting up as an infant might have been an early symptom of EE or simple newborn GERD. Up to 80% of newborns have physiologic normal GERD, which resolves by 18 months of life. But many cases of EE start in the newborn period as GERD-like symptoms.

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**Table 1. Differential Diagnosis of Eosinophilic Esophagitis**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Eosinophilic esophagitis</td>
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<tr>
<td>Crohn’s disease</td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
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<tr>
<td>Parasitic disease</td>
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<tr>
<td>Candida infection</td>
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<tr>
<td>Hypereosinophilic syndrome</td>
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<tr>
<td>Viral infections</td>
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<td>Drug allergy</td>
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Symptoms of EE vary by age. Young infants and toddlers typically present with GERD or failure to thrive due to the assumed pain with eating. School-age children typically present with abdominal pain or persistent GERD symptoms. The most common symptoms in adolescents and adults include dysphagia and food impaction [3,7,10]. These symptoms are more unusual and should immediately suggest the possibility of EE as the diagnosis.

Seventy to 80% of patients with EE have atopy, like our patient with allergic rhinitis. His nasal turbinate edema is a classic physical finding.

- What is the general approach to management of EE?

Management of EE involves elimination/control of eosinophils with either medications or diet (Table 2). The etiologies of EE are primarily due to food allergies and very rare cases of pollen association.

**Medications**

Medical treatment involves treating the symptoms but not the cause of the disease. At present there are no approved medications for the treatment of EE. However, the use of “topical” corticosteroids has been shown to be successful. The patient typically swallows inhaled corticosteroids used for asthma in moderate to high doses (given without use of spacer and avoiding foods/liquids for 30 minutes). The goal of this therapy is to deposit steroids in the esophagus, leading to apoptosis of the eosinophils and reduction of symptoms. These methods have been shown to have a varying rate of success. Konikoff et al [11] completed a randomized, double-blind, placebo-controlled trial of 36 pediatric patients with EE who either refused or failed dietary modification. The intervention arm swallowed fluticasone for 3 months. They reported improved symptom control and less eosinophils/HPF in biopsy in 50% of the patients [11]. The success rate was 50% compared with an 80% to 90% success rate in the open-label trials with fluticasone or budesonide [7,12].

Cromolyn was utilized in 14 patients without symptomatic or histologic improvement [5]. Based on this and other studies, although cromolyn sodium has no significant adverse effects, it was not found to be effective and is not recommended. Leukotrienes are known to attract eosinophils leading to inflammation and tissue eosinophilia. When leukotriene receptor antagonists were used, symptoms appeared to decrease without improvements in endoscopy findings [13]. Omalizumab, anti-IgE, in a case study had no effect on eosinophilic esophagitis indicating a non-IgE mechanism of disease [14]. At this point, these drugs cannot be recommended for EE.

| Table 2. Treatment Strategies for Eosinophilic Esophagitis |
|-----------------|-----------------|
| **Strategy**     | **Success Rate** |
| Elemental diet   | 85%–96%         |
| 6-food elimination | 50%–75%       |
| Directed diet    | 70%–80%         |
| **Medical**      |                 |
| Oral corticosteroids | 100%           |
| Swallowed fluticasone | 50%–80%   |
| Swallowed budesonide | 80%           |

**Dietary Approach**

The second approach to management of EE is treating the cause of the disease. An elemental diet has been successful in both pediatric and adult patients with success rates approaching high 90% [5,15]. However, due to poor palatability of these formulas, it is difficult for patients to remain on these formulas. A more directed approach of eliminating the particular food antigen is possible. There are 2 possible ways to remove the food antigen: (1) removing the most common food allergens, or (2) removing the allergens based on allergy testing. The first method has been primarily studied by Kagalwalla et al [16] in children and Gonsalves et al [9] in adults. They have found by using a “6-food” elimination diet (no milk, soy, egg, wheat, seafood [fish and shellfish], or peanuts [peanuts and tree nuts]), esophageal eosinophilia is significantly reduced. In their pediatric trial, they started 35 children on the “6-food” elimination diet and 25 children on an elemental diet. Resolution defined as less than 10 eosinophils/HPF was noted in 88% of the children on the elemental diet and 74% of the children on the elimination diet [16]. In adult trials, the success rate is reported to be 50% with the elimination diet and low 90% for the elemental diet (personal communication, Gonsalves).

The alternative dietary approach is to remove foods based on allergy testing. There are 3 standard methods for food testing: skin prick testing, in vitro–specific IgE, and atopy patch tests. Other food testing, in particular IgG to foods, is not clinically relevant and has not been shown to be useful for any food allergy conditions. Specific IgE (most commonly known as RAST testing, an outdated term) has been useful for any food allergy conditions. Specific IgE (most commonly known as RAST testing, an outdated term) has not been successful in EE. There was a response rate of near 0% when foods are eliminated based purely on in vitro–specific IgE [17].

The use of skin prick test only had a slightly better success rate of about 50%. This strongly suggests that the food allergy in EE is not strictly IgE-mediated, consistent with the results with omalizumab. Based on this finding, we started to use atopy patch testing for EE [18]. Atopy patch testing is designed to look for non–IgE-mediated food reactions,
presumably T-cell-mediated. We have found the combination of both skin prick testing and atopy patch testing looking for both IgE- and non-IgE-mediated disease has been highly successful in the treatment of EE. We have found that a food that was negative on both skin prick testing and atopy patch testing was unlikely to cause EE, with a predictive value of 90% or more for all foods except milk [19]. We have found the combination of skin prick testing and atopy patch testing can resolve EE symptoms and normalize biopsies in 80% of patients [18–20].

**Aeroallergens**

We have seen 1 case of strictly aeroallergen sensitization in a 20-year-old girl with EE whose symptoms varied with the pollen seasons [21]. Onbasi and colleagues [22] conducted an interesting study performing endoscopy and biopsies in 3 populations: normal, patients with gastroesophageal reflux, and patients with allergic rhinitis. They found about 21% to 25% of patients with either GERD or allergic rhinitis had esophageal eosinophilia (mean number of eosinophils/HPF, 1.7 and 5.5, respectively). This level of esophageal eosinophilia is not enough to make the diagnosis of EE but emphasizes the need for a careful diagnosis. Therefore, before we perform any endoscopy, our patients are treated with a PPI and nasal corticosteroid.

**What is the prognosis?**

EE is a chronic disorder. If any treatment, medical or dietary, is stopped, symptoms return and esophageal eosinophilia recurs, with very rare exceptions. Longitudinal studies in adults over a 12-year period do not show resolution [23]. Similar in pediatrics, long-term studies show resolution in less than 5% of patients [10,13,24]. These patients were all diagnosed at an early age and were treated aggressively with avoidance of the allergens.

**Follow-up**

The patient is found to be positive to milk and egg on skin prick test and potato and beef on atopy patch tests. He has these 4 foods removed from his diet with resolution of his emesis in 10 days. Repeat endoscopy 2 months later shows rare eosinophils in esophagus, while remaining on the PPI and nasal steroids. He had been started on nasal steroids as he had pale nasal turbinate edema, a cardinal physical sign of allergic rhinitis.

If a patient that has persistent symptoms of GERD that do not respond to PPI therapy, has dysphagia, or food impaction, he/she should be referred for workup of possible EE. Patients with this complex disorder are best managed by a team of physicians and nutritionists who are experts in this disease. This team should include an allergist, gastroenterologist, and a nutritionist all working closely together.

**Summary**

EE is an allergic disorder of the esophagus due to the combination of both IgE- and non–IgE-mediated food allergies. The diagnosis of EE is rising due to a combination of increased recognition and prevalence. The treatment options for EE are either medical or dietary, with treatment selection based on the individual patient and his/her preferences. Treatment currently is most likely lifelong. Similar to many other atopic disorders, patients do not typically outgrow EE.

**References**


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CME EVALUATION: Diagnosis and Treatment of Eosinophilic Esophagitis

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. The number of eosinophils per high-powered field needed to make a diagnosis of eosinophilic esophagitis (EE) is
   A. 0
   B. 5
   C. 15
   D. 40
   E. 100

2. A common presentation of EE in an infant is
   A. Food impaction
   B. Dysphagia
   C. Abdominal pain
   D. Persistent gastroesophageal reflux disease (GERD) despite medications
   E. GERD

3. Which medication has the best success in the treatment of EE?
   A. Oral cromolyn
   B. Montelukast
   C. Proton pump inhibitor
   D. Swallowed fluticasone
   E. Cetirizine

4. The dietary approach that has the highest success rate in the treatment of EE is
   A. Removal of foods based on skin testing
   B. Removal of foods based on in vitro testing
   C. Removal of foods based on skin testing/patch testing
   D. 6-food elimination diet
   E. Elemental diet

5. Foods cause the majority of cases of EE.
   A. True
   B. False
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5. What changes will you make in your practice as a result of reading this article?  
   __________________________________________________
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6. What topics would you like to see presented in the future?  
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