

Esophagitis: Allergic and Eosinophilic

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Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus that has been more recently described in the pediatric population. EoE is characterized by clinical symptoms of esophageal dysfunction in the setting of immune and antigen-mediated eosinophilic infiltration of the esophageal mucosa. Based on the most recent consensus guideline, three primary components are required for diagnosis: clinical symptoms of esophageal dysfunction, pathologic evidence of esophageal eosinophilia by biopsy with a peak count of greater than 15 eosinophils in a high-power field (hpf), and evidence that eosinophilia is limited to the esophagus and not due to other causes of eosinophilic infiltrations.

The prevalence of EoE in the pediatric population is believed to be rising but currently is estimated at 1.6 to 40 per 100,000 children. EoE tends to be more common in Caucasians and is predominantly found in males (3:1). The exact cause of the gender and race distribution is unknown. EoE has been reported in all age groups, beginning as early as young infancy, after solid food introduction, and spanning into later adulthood. EoE has a strong association with atopic diseases; up to 80% of children have evidence of asthma, allergic rhinitis, atopic dermatitis, or food allergies at the time of EoE diagnosis.

Diagnosing EoE can be challenging because symptoms are nonspecific, mimic other diseases, and can be highly variable among individuals and different age groups. Specifically, symptoms of EoE are often clinically indistinguishable from gastroesophageal reflux disease (GERD) in children. Young infants and toddlers commonly present with nonspecific feeding difficulties, refractory spitting up or vomiting, and feeding refusal, and thus often experience poor weight gain. School-age children most commonly report vomiting and abdominal pain and occasionally have food refusal or dysphagia. Adolescents and adults report gastroesophageal reflux, dysphagia, chest pain, and food impaction, which frequently is the primary presenting symptom in an acute setting. Other symptoms may include abdominal pain, anorexia, and early satiety. The age difference in symptoms is likely due both to the developmental ability to describe symptoms and the progression and severity of the disease with time. Esophageal strictures are a major complication of untreated EoE, and the risk of stricture formation increases with the delay in diagnosis.

Patients with symptoms concerning for esophageal dysfunction should be referred for further evaluation via upper endoscopy. As stated previously, an eosinophil count greater than 15/hpf is required in at least a single esophageal biopsy to meet the histopathologic diagnostic criteria. Multiple biopsies from both the proximal and distal esophagus should be examined to increase the diagnostic yield. Other associated pathologic findings may include eosinophilic microabscesses, superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, and lamina propria fibrosis. Because eosinophilic

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infiltration in EoE is limited to the esophagus, biopsies from the antrum of the stomach and duodenum should be obtained at initial endoscopy to help to exclude other more widespread causes of gastrointestinal eosinophilia such as Crohn disease, infectious esophagitis, hypereosinophilic syndrome, achalasia, and celiac disease. In addition to pathologic findings, gross findings on endoscopy can include esophageal rings, edema, white exudates, linear furrows, and esophageal narrowing or stricture. However, gross findings are not essential for diagnosis, and the esophagus may appear normal on visual inspection, even in the setting of EoE.

Recently, substantial attention has focused on a subgroup of patients believed to have EoE based on symptoms and initial presence of greater than 15/hpf eosinophils on biopsy in whom esophageal eosinophilia and symptoms resolved following management with high-dose proton pump inhibitors (PPIs). This entity has become known as PPI-responsive esophageal eosinophilia (PPI-REE) and has resulted in the updated recommendation in the 2011 guideline that all patients undergo an 8-week trial of high-dose PPI (1 mg/kg per dose twice daily) to exclude PPI-REE before being diagnosed with EoE. Whether PPI-REE is a distinct entity, should be considered as a subgroup of EoE, is on the spectrum of GERD, or is some combination of the four remains unclear and is an active area of investigation.

The immunopathogenesis of EoE is complex, involving a Th2 inflammatory response triggered by food antigens in the esophagus, resulting in eosinophilic infiltration and activation. Accordingly, treatment strategies are aimed at mediating this response. Following a confirmed diagnosis of EoE, the two generally accepted potential therapeutic options are either food elimination or topical corticosteroid treatment. Dietary elimination can either be:

- Complete, with replacement of solid food intake with an amino acid-based formula
- Targeted, with food removal based on individual perceived food triggers and potentially the results of allergy testing
- Empiric, with elimination of the six most common allergens associated with EoE: dairy, soy, eggs, wheat, peanuts/nuts, and fish/shellfish

Alternatively, if dietary elimination is not successful or is not a viable option for a patient, topical corticosteroid

treatment has been found to be effective. Although widely used as first-line medical therapy and reported in the literature, topical corticosteroids are not currently approved by the U.S. Food and Drug Administration for the treatment of EoE in children. The two commonly used preparations are swallowed aerosolized fluticasone propionate and oral viscous budesonide. Refractory cases of EoE may require systemic immunosuppressive therapy. Unfortunately, due to the chronic nature of EoE, studies generally have shown that regardless of treatment chosen, many patients experience relapse of symptoms and pathologic findings with reintroduction of eliminated foods or discontinuation of corticosteroids. Thus, treatment must continue indefinitely in many cases.

In summary, clinical features associated with EoE are nonspecific, related to underlying esophageal dysfunction and inflammation, and closely mimic GERD and other clinical entities. Both clinical and pathologic evidence of eosinophilic esophageal infiltration must be present and other clinical entities with similar presentations excluded to confirm the diagnosis of EoE.

COMMENT: EoE was first described in the late 1970s, with more frequent recognition and reports of the disease beginning in the early 1990s. The prevalence is highest in the United States and Western Europe, and children present more commonly with inflammatory components compared with adults, who often present with fibrosis of the esophagus. As noted by the authors, no one biomarker can make the diagnosis, and active research is dedicated to finding validated symptom assessment tools and reliable biomarkers to limit the number of endoscopies needed to identify patients. The primary clinician is a critical member of this multidisciplinary team in identifying symptoms and making the needed referrals to the gastroenterologist, allergist, and nutritionist. The respective input of members of this multidisciplinary team is needed to develop individualized therapy for each patient. The primary clinician also has a critical role in assisting and supporting patients and their families in adapting to this chronic, often relapsing disease through their longitudinal relationship.

– Janet Serwint, MD
Consulting Editor, *In Brief*

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