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Edited by:
Hillel Naon, M.D.
Acting Division Head, Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, University Southern California, Keck School of Medicine, Los Angeles, USA

Review Article

Eosinophilic Esophagitis: A Clinicopathological Review

Vrinda Bhardwaj*, Rula Harb and Hillel Naon

Division of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital Los Angeles, USC Keck School of Medicine, USA

Abstract

Eosinophilic esophagitis (EoE) is a chronic, atopic inflammatory disorder of the esophagus. With the escalating prevalence in children and young adults, revised guidelines have been established. Its pathogenesis has been associated with T helper Type 2 (Th2) inflammatory response. Diagnosis is based on a comprehensive evaluation including patient's clinical manifestations and characteristic histologic findings on esophageal mucosal biopsies. The management of EoE involves dietary approaches and pharmacologic agents. This article provides a practical overview of recent literature pertaining to the epidemiology, pathophysiology, diagnosis, treatment, and prognosis of EoE.

***Corresponding author**
Vrinda Bhardwaj, Children's Hospital Los Angeles, 4650 W Sunset Boulevard, Mailstop # 78, Los Angeles, CA -90027, USA, Tel: 323-361-5924; Fax: 323-361-3718; E-mail: vbhardwaj@chla.usc.edu

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ABBREVIATIONS

EoE: Eosinophilic Esophagitis; GERD: Gastro-Esophageal Reflux Disease; TIGERS: The International Gastrointestinal Eosinophil Researchers; ICD: International Classification of Diseases; (TH 2): T Helper Type 2; IL: Interleukin; GWAS: Genome-Wide Association Studies; TSLPR: Thymic Stromal Lymphopoietin; PPIs: Proton Pump Inhibitor; HPF: High Power Field

INTRODUCTION

Eosinophilic esophagitis (EoE) is an atopic inflammatory disease of the esophagus that has become increasingly recognized in children and adults over the last decade [1]. The disorder is sometimes referred to as "asthma of the esophagus" given that it shares many clinical and pathophysiologic characteristics with asthma [2]. EoE is characterized by isolated eosinophilic infiltration of the esophageal mucosa [3]. The identification of EoE as a disease occurred following investigations into treatment resistant patients with gastro-esophageal reflux disease (GERD) [4]. The similarity in presentation of EoE and GERD necessitates the correlation of clinical and pathological findings and the establishment of diagnostic criteria differentiating the two disorders, to ensure accurate diagnosis and management [5].

With the escalating prevalence of children and adults with EoE and emerging clinical and basic research, several unmet needs have been identified that were not addressed in the 2007

Consensus Recommendations [6]. In an effort to develop a more robust set of clinical guidelines, The International Gastrointestinal Eosinophil Researchers (TIGERs) convened a multidisciplinary group of clinical experts to review and revise the previous recommendations. In the 2011 Consensus Recommendations, a conceptual definition was developed to provide a global view of this disease: "Eosinophilic esophagitis represents a chronic, immune/antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" [7]. This definition is based on the growing clinical experiences and the research studies indicating the chronic nature of EoE [8]. Since 2007, an ever-growing body of clinical and basic evidence has also identified the role of immune/allergic mechanisms that underlie the disease [9]. It is now clear that many patients have atopic features and respond to dietary eliminations and steroids [10].

The increasing number of recognized cases of EoE has resulted in a dramatic expansion of the medical literature surrounding the disease. This article provides a practical overview of recent literature pertaining to the epidemiology, pathophysiology, diagnosis, treatment, and prognosis of EoE.

EPIDEMIOLOGY

The estimation of the prevalence of EoE at the US national level was made possible after the 2008 approval of an International Classification of Diseases, 9th Revision (ICD-9) code for EoE (530.13). Using this, estimated prevalence of EoE in the United States, among children and adults between the ages of 0 and 64 years, is ~ 57 per 100,000 [11]. In children/adolescents up to 19 years of age, current prevalence estimates range from 1 to 4 per 10,000 persons [12]. Recent literature suggests that the prevalence of EoE is increasing [13]. Pediatric gastroenterologists usually see more new patients with EoE than new patients with Crohn's disease [14]. However, despite the increase in esophagogastroduodenal biopsies between 1982 and 1999, a retrospective study examining 666 patients found the incidence of EoE to be relatively stable during this time period [8]. Hence, there is a debate as to whether the new cases of EoE being diagnosed represent a true increase in prevalence or rather increased recognition of latent disease [1].

Evidence also suggests that there is both ethnic and gender variation in the prevalence of EoE, with the majority of cases reported in Caucasian males. However, this finding is also uncertain since this is the patient population that has been most extensively studied [15,16]. Further population-based, epidemiological studies are needed to investigate the true prevalence of EoE.

The Pathophysiology of EoE

Although the pathogenesis of EoE remains unclear, evidence suggests that the disease is associated with T helper type 2 (Th2) immune responses, which are typical of other atopic conditions [1]. In particular, elevated levels of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-13, as well as mast cells, have been found in the esophagus of EoE patients [17-19]. These cytokines appear to play an important role in the activation and recruitment of eosinophils to the esophagus.

EoE is also believed to be a mixed immunoglobulin IgE and non-IgE medicated allergic response to food and environmental allergens. [20,21]. IgE- medicated reactions are immediate hypersensitivity responses that usually occur within minutes after exposure to an allergen. The non- IgE medicated allergic disorders are characterized by a delayed onset (hours or days after exposure to the antigen) and potentially more chronic symptoms [1]. The majority of patients with EoE have been found to have positive skin prick test (detects IgE- mediated reactions) and atopy patch test (identifies non-IgE-mediated reactions) to foods and /or aeroallergens.

Accumulating evidence has shown a strong familial association in EoE [12]. Several candidate genes for EoE have been identified. CCL26/eotaxin-3 gene, based on genome-wide association studies (GWAS), is the most highly expressed gene in EoE, being up-regulated between 50- and 100-fold in EoE patients [22]. However, this disease-associated allele has only been found in 14% of cases [23], highlighting the contributions of other risk variants. More recently, a significant gene locus at 5q22.1 has been identified and replicated in European cases of EoE [23]. The two genes that map to this locus are TSLP and WDR36. TSLP encodes a cytokine similar to IL-7 produced in the thymus and peripheral tissues, and acts to regulate Th2 responses [24]. A more recent study showed that polymorphisms in TSLP are risk factors for the development of EoE, independent of allergy status and phenotypes [25]. The same study found an association between polymorphisms in the thymic stromal Lymphopoietin receptor (TSLPR) gene on Xp22.3/Yp11.3 and EoE in male participants, suggesting a mechanism for the male predominance of EoE.

Despite this strong evidence supporting the genetic basis of EoE pathogenesis, studies have shown that the familial pattern of inheritance of EoE shares an underlying pathogenesis with sporadic cases of EoE [26].

Diagnosis

Clinical Manifestations: Emerging data and clinical experience are describing a variety of phenotypes associated with esophageal eosinophilia. The "classic" EoE patient is a highly atopic toddler who presents with vomiting and feeding dysfunction, who responds to an elemental diet or a young man with recurrent food impaction and dysphagia, and who improved with topical steroids [10]. But other patients may present with nonclassical symptoms, are not atopic, do not respond to dietary exclusions, or may only have an isolated esophageal food impaction. Taken together, current literature and expert opinion suggests that no two patients with EoE are alike and clinicians are expected to come across a phenotypic diversity.

Infants and toddlers often present with feeding difficulties, whereas school-aged children are more likely to present with vomiting or abdominal pain [27,28]. Dysphagia is the predominant symptom in adolescents. EoE in children is most often present in association with other manifestations of atopic diathesis (food allergy, asthma, eczema, chronic rhinitis, and environmental allergies) and is responsive to elimination of specific dietary antigens in that population [7].

The typical patient with EoE is an atopic male (male/female

ratio, 3:1) who presents in childhood or during the third or fourth decades of life; however EoE can occur at any age [28,29].

Physical examination is useful in children to identify normal growth patterns and in both children and adults to identify comorbid allergic diseases; however, no features on physical examination are specific in making the diagnosis of EoE [7]. In addition, no oral or pharyngeal manifestations of EoE have been identified, although some children who have EoE might present with laryngeal symptoms [30].

A subgroup of patients has been increasingly recognized who have: a) a typical EoE symptom presentation, b) have had GERD diagnostically excluded, and c) demonstrate a clinicopathologic response to proton pump inhibitors (PPIs) [31-34]. Terms used to describe these patients include *PPI-responsive eosinophilia* and *PPI-responsive EoE* [35-38].

Diagnostic Guideline: Clinically, EoE is characterized by symptoms related to esophageal dysfunction. Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically *PPI-responsive esophageal eosinophilia* [7].

Disorders associated with esophageal eosinophilia in addition to EoE, include GERD, eosinophilic gastrointestinal diseases, celiac disease, Crohn's disease, infection, hyper eosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, connective tissue disease and graft-versus-host disease [39].

Endoscopy: Endoscopy with esophageal biopsy remains the only reliable diagnostic test for EoE. Several studies have confirmed the presence of esophageal abnormalities identifiable by means of endoscopy in patients with EoE, including fixed esophageal rings (*trachealization*), transient esophageal rings (*felinization*), whitish exudates, longitudinal furrows, edema, diffuse esophageal narrowing, narrow-caliber esophagus, and esophageal lacerations induced by passage of the endoscope (a manifestation of mucosal fragility, gives the esophagus the appearance of crepe paper) [7,40]. However, because all of these endoscopic features have been described in other esophageal disorders, none can be considered pathognomonic for EoE.

The optimal number of mucosal biopsy specimens that should be obtained to maximize the diagnostic yield of EoE has begun to be addressed [41,42]. Using the threshold for diagnosis to be 15 eosinophils/hpf, one study identified a diagnostic sensitivity of 84%, 97% and 100% for obtaining 2, 3, and 6 biopsy specimens, respectively [41]. Two to 4 mucosal biopsy specimens of the proximal and distal esophagus should be obtained [7]. One study reported that at least 4 biopsy specimens should be submitted from the mid and/or proximal esophagus to optimize the chances of a positive diagnosis of EoE in populations not known to have undergone previous PPI therapy [42]. Most studies report the distal specimens to be taken within 5 cm from the squamocolumnar junction and proximal specimens taken 10cm proximal to the distal site. However, the yield is not increased beyond six biopsy fragments.

The biopsy protocol among gastroenterologists can vary by the location in the esophagus, the number of biopsies taken, and how the samples are submitted to the laboratory. It has been suggested that targeting esophageal biopsies to areas with the most involved-appearing mucosa (such as white plaques or exudates) may increase the diagnostic sensitivity of detecting EoE, compared with obtaining biopsies at predetermined distances regardless of the mucosal condition [40,43,44]; however, this has yet to be confirmed. It is also unclear whether or not there is a uniform distribution of eosinophils in the esophagus in EoE [40], or if there is a higher density in the distal esophagus [45].

Allergy Assessment: EoE is often one of the multiple concurrent allergic diatheses, with 42% to 93% of pediatric patients having another allergic disease [46,47]. Several studies have reported that 50% to 60% of patients with EoE have a prior history of atopy [47-49].

The testing method and definitions of food allergy vary among studies, but estimates of IgE-mediated immediate food hypersensitivity in patients with EoE range from 15% to 43% [47, 48]. Rates of allergic rhinitis, asthma, and eczema in children and adults with EoE range from 40% to 75%, 14% to 70%, and 4% to 60%, respectively [50-52]. Retrospective analyses show decreased EoE diagnosis in the winter and increased diagnosis in the spring, summer, and fall in a total of 583 pediatric and adult patients with EoE [11,47,48].

Skin prick testing and the measurement of food allergen-specific IgE levels are often useful in identifying potential culprit foods in IgE-medicated reactions [39]. However, atopy patch testing to foods has been proposed as a useful method to potentially identify foods causing symptoms through a non-IgE-mediated immune mechanism [21,53].

Per the updated Consensus Recommendations on EoE in children and adults, a thorough evaluation by an allergist or immunologist is recommended because of the high rates of concurrent asthma, allergic rhinitis, eczema, and food allergy/anaphylaxis; the potential seasonality of EoE diagnosis; and the complex interplay among multiple allergic diathesis [6,7].

Few studies have documented peripheral eosinophilia in pediatric patients, with 40% to 50% having increased numbers of circulating eosinophils (>300-350 per mm^3) [11,54]. Some studies suggest that the peripheral eosinophilia decreases after successful esophageal topical corticosteroid therapy and can correlate with tissue eosinophil number [54]. One additional pediatric study supports previous findings suggesting that total IgE levels are increased (>114kU/L) in 50% to 60% of patients with EoE [52,55]. Higher total IgE levels are reported in allergen-sensitized versus nonsensitized patients with EoE. There is currently insufficient information to support the clinical utility of any peripheral marker to function as a surrogate disease indicator of histologic inflammation in patients with EoE [6,7].

Treatment

Dietary Management: Three dietary approaches for the management of EoE have emerged over the past decade:

a) Elemental diet

b) Empiric Six- food elimination diet

Table 1: Clinical manifestations of EoE by age.

	Infants/ Toddlers	Children	Adults
Symptoms	Feeding aversion Vomiting Choking with meals Failure to thrive	Dysphagia Food impaction Abdominal/ chest pain Vomiting	Dysphagia (predominant) Food impaction Intractable heartburn Food avoidance

Table 2: Endoscopic features of EoE.

Endoscopic feature	Description
Linear furrows	Vertical esophageal ridges in the esophageal wall
Concentric rings	Multiple rings that may be fine, web- like (felinization) or thickened (trachealization)
White exudates	Patches of white papules (1-2 mm in diameter). Resembles esophageal candidiasis.
Linear mucosal tears	Mucosal abrasions that occur upon minimal contact (after passage of the endoscope)
Small caliber esophagus	Narrowed esophagus with fixed internal diameter. Featureless, poor expansion on air insufflation

c) Targeted dietary restriction

The elemental diet involves the removal of all sources of potentially allergic protein from the patient's diet through the use of an amino acid-based formula for nutritional support. Although the elemental diet is associated with high rates of clinical and histologic improvement in both adults and children with EoE, symptoms often recur after normalization of the patient's diet [18,56]. This approach can be particularly challenging in adolescents given the unpalatable taste of elemental formula and requirement of a nasogastric tube-feeding regimen.

Most practitioners would employ the empiric or targeted food elimination diet restriction before considering an elemental diet. Empiric six- food elimination diet involves elimination of the six most common allergic foods: dairy, eggs, wheat, soy, peanuts and fish/shellfish, irrespective of the results of the allergy testing.

Targeted dietary restrictions involve elimination of foods based on the results of allergy testing (skin prick and atopy patch testing). Although the response rates noted with this approach are lower than those noted with the elemental diet, targeted dietary restrictions have been shown to be effective in 70%-80% of patients [21].

With all dietary approaches, it remains unclear how long specific foods need to be avoided. There is a vast need to have studies dedicated to evaluate the role of the dietary approach in management of EoE, including an attempt to evaluate patient quality of life given the extensive dietary restrictions that are often required [1]. When deciding on the use of a specific dietary therapy, the patient's lifestyle, adherence to therapy, and family resources need to be considered. Consultation with a dietician is strongly encouraged [6].

Pharmacologic Management: Medical therapies for EoE include corticosteroids, leukotriene modifiers and biologic agents. Both clinical and histologic improvement have been noted in approximately 95% of EoE patients using systemic corticosteroids, however, upon discontinuation of therapy, 90% of patients experience a recurrence in symptoms [57]. Therapy with systemic steroids at this time is reserved for severe cases: Dysphagia requiring hospitalization or patients experiencing or dehydration due to swallowing [6]. The long-term use of corticosteroids is not recommended, given well-known and potential serious side effects.

Topical corticosteroids delivered to the esophagus have become the mainstay of pharmacotherapy for patients with EoE, given their substantially better safety profile. Randomized clinical trials of topical fluticasone propionate therapy have shown both histologic and symptomatic improvements in 50-80% of patients with EoE [58,59]. ln a randomized, placebo-controlled trial, Dohil et al (60) showed that oral viscous budesonide (budesonide respules mixed with sucralose) is an effective treatment of pan-esophageal disease in children with EoE and resulted in improved symptoms and endoscopic and histologic features.

A small study of 8 patients with EoE examined the efficacy of the leukotriene receptor antagonist, montelukast, and found a significant improvement in symptoms in the majority of subjects, but no improvement in histology [61].

Given that both IL-5 and IgE appear to play a role in the pathogenesis of EoE, humanized monoclonal antibodies against IL-5 (reslizumab, mepolizumab) and IgE (omalizumab) may also be potential therapeutic options for the disease. Results from small case series using the IL-5 antibodies in patients with EoE suggest that these biologics are well tolerated and may improve clinical symptoms, histology and quality of life [62].

Prognosis

The long-term prognosis for patients with EoE is unknown. Some patients may follow a course characterized by exacerbations followed by periods of remission. Reports of apparent spontaneous remission also exist in the current medical literature; however the risk of recurrence in these patients is unknown. At present, it is an apparent life-long disease in the over-whelming majority of patients. Currently, it is unclear if dietary or medical therapy modifies the natural history of the disease [2].

SUMMARY

- EoE is a clinicopathologic disease isolated to the esophagus.
- EoE represents a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.
- Endoscopy with esophageal biopsy currently remains the only reliable diagnostic test for EoE.
- An allergy evaluation should be considered in patients diagnosed with EoE.
- EoE is managed with treatments of dietary exclusions, topical corticosteroids, or both.

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