Diagnosis and Treatment of Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a new disease. It is caused by a T-helper type 2 cell response to food antigens in contact with the esophageal mucosa. Although no single feature defines EoE, a constellation of compatible demographic, clinical, endoscopic, and histologic findings establish the diagnosis. Children present with symptoms and endoscopic patterns characteristic of inflammation, whereas adolescents and adults have manifestations of fibrosis and gross esophageal strictures. Clinical and endoscopic scoring systems have helped to standardize diagnosis. There is controversy in EoE research over the optimal endpoint for treatment. Although the most common endpoint is a reduced number of eosinophils in biopsies, changes in symptoms and endoscopic features are becoming important targets of therapy. We should improve our understanding of EoE progression and the need for maintenance therapy, and continue development of diagnostic tools that avoid endoscopy and biopsy analyses to more easily monitor disease activity.

Keywords: Eosinophilic Esophagitis; Esophagitis; Esophagus.

The first case of eosinophilic esophagitis (EoE) was described in 1978 and misinterpreted as achalasia.[1] In the early 1980s, the importance of esophageal eosinophilia was perceived, and esophageal eosinophilia was considered to be a diagnostic criterion for reflux disease.[2] It took more than a decade before EoE was described in 2 case series and recognized as a distinct disease entity characterized by symptoms of esophageal dysfunction and eosinophil infiltration.[3,4] Both studies found EoE to be prevalent in younger males with atopic conditions, and endoscopic findings to be discreet and differ from those of gastroesophageal reflux disease (GERD). Meanwhile, EoE has been observed in children and adults, in North and South America, Europe, Asia, and Australia.[5]

Initially, EoE was regarded as rare, but soon it became evident that its incidence and prevalence were rapidly increasing.[6] Several population-based studies from the United States[7,8] and Europe[9,10] have provided evidence that this is a true increase, rather than the effect of raised awareness. Based on a recently published meta-analysis, the prevalence of EoE in adults is 32.5 and in children 30.9 patients per 100,000 inhabitants. In other words, in Westernized areas, 1 patient with EoE lives in a community of approximately 3000 inhabitants.[11] Although EoE mainly affects persons 20–40 years old, it is seen in all age groups.[12] The incidence and prevalence of EoE are comparable with the values of Crohn's disease.

Diagnosis

An international panel of experts in pediatric and adult gastroenterology, allergy, immunology, and pathology defined EoE as "an esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation."[6] Other causes of esophageal eosinophilia must be ruled out—particularly GERD. Experts had therefore recommended that patients be treated with a double dose of proton pump inhibitors (PPIs) for 2 months; the effects are used to differentiate between EoE and GERD.[13] Unexpectedly, in a subset of patients with EoE, symptoms and histologic abnormalities resolved following PPI treatment, even in the documented absence of GERD.[14] This PPI trial brought more confusion than clarification, so a panel of experts recently recommended that PPI response not be used in diagnosis.[15] However, it is not clear how to differentiate reliably between EoE and GERD. Additional disorders leading to infiltration of the esophagus by eosinophils include eosinophilic gastroenteritis, celiac disease, Crohn's disease, achalasia, and drug hypersensitivity. The diagnosis of EoE is complex; therefore, clinicians should diagnose EoE based on a combination of symptoms and histologic and endoscopic

Abbreviations used in this paper: **DIS, dilation of intercellular space; EoE, eosinophilic esophagitis; EREFS, edema, rings, exudates, furrows, and strictures; GERD, gastroesophageal reflux disease; HPF, high power field; IL, interleukin; PPI, proton pump inhibitor; Th, T-helper.**

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findings—no single feature is sufficient to establish a definitive diagnosis.[16]

Symptoms in Children Vs Adults

The symptoms of EoE follow a hierarchal and pyramidal pattern from early childhood to adulthood (Table 1).[7,17,18] This presumably follows decades of diffuse inflammation leading to esophageal fibrosis. Specifically, the symptoms of EoE in early childhood are protean and include failure to thrive, feeding difficulties, nausea, vomiting, and abdominal pain. In older children, symptoms become more esophageal, with heartburn, chest pain, and early manifestations of dysphagia (such as slow and picky eating). In adolescents and adults, symptoms become specific to esophageal narrowing, with solid food dysphagia and food impaction. On rare occasions, impaction can lead to esophageal perforation (Boerhaave's syndrome).[19–21]

As the population of patients with EoE increases and they are studied more carefully, it becomes clear that this timeline is not firm. For example, recent data show that chest pain may be a prominent symptom in adults, perhaps reflecting an inflammatory component.[22] Similarly, heartburn may occur in adults.[12] Conversely, school-age children may present with dysphagia.[18] It is not clear if these are different symptoms of a similar disease or that the degree of esophageal inflammation and fibrosis varies with age.

Symptom Scoring Systems

As for many chronic diseases, symptoms of EoE may be obvious or arise via compensatory maneuvers to cope with the disease. It is important to document the frequency and chronicity of symptoms, as well as the intensity. Several scoring systems have been developed for the comprehensive evaluation of EoE symptoms. These systems serve not only to achieve greater accuracy in grading a patient's symptoms, but also function as a standardized objective tool that can be used to assess the disease over time and evaluate the effects of treatments or agents in clinical trials.

The EoE activity index[16,23] is a patient-reported outcome instrument that was developed using symptoms of 183 patients in Switzerland with EoE. The system is based on a conceptual framework to assess symptoms, behavioral adaptations, and biologic activity of adult patients with EoE over periods of 1, 7, and 30 days. The score is an indicator of dysphagia. It is comprehensive, documenting the frequency, intensity, and duration of dysphagia; the duration of dysphagia episodes and occurrence of food impaction; time required to eat a regular meal; and frequency of pain with eating. This scoring system also detects accommodating symptoms of EoE, such as slow eating, careful chewing, and food avoidance. The score is validated in a 7-day recall period, which was deemed adequate. Scores have been shown to correlate with global assessment score endoscopic and histologic findings.

The Mayo dysphagia questionnaire is a validated symptom scoring system that has been used for EoE but was originally developed for peptic esophageal strictures or general use with dysphagia. It is a 28-item instrument that takes, on average, 10 minutes to complete.[24] It has been used in several trials of therapeutic agents in the treatment of EoE[25–27]; findings correlate variably with findings from histologic analysis. It is not clear if this variation is because of the inaccuracy of the scoring system for inflammation or differing presentations of peptic and EoE strictures.

Dysphagia scoring systems have also been used to evaluate pediatric patients with EoE. For example, the University of Cincinnati developed the Pediatric EoE Symptom Scoring System[28,29]; scores correlate with findings from histology. This scoring instrument also assesses quality of life, and can include parental interpretations of symptoms.

Nevertheless, many studies have used their own non-validated indices to evaluate EoE symptoms. One problem with the scoring systems is that, although they are well suited for clinical trials, they can be cumbersome in clinical care. Some investigators have developed more patient-friendly scoring systems. For example, the Dysphagia Symptom Questionnaire[30] is a 3-question instrument, administered daily for 30 consecutive days; it was developed and tested in a small group of patients with EoE. The questions are: Since you woke up this morning, did you eat solid food? Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest? And, for the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief? Patient compliance and acceptance was excellent. Even though many studies use non-validated scoring systems, more concerning is a general lack of scoring system use to accurately monitoring clinical disease.

Table 1. Symptoms of EoE in Children vs Adults

Children	Adults
Failure to thrive	Dysphagia
Feeding difficulties	Eating slowly
Nausea and vomiting	Solid food avoidance
Abdominal pain	Avoidance of social eating
Heartburn	Chest pain
Picky eating	Heartburn

Endoscopy

Patients with EoE undergo endoscopy for collection of epithelial biopsies and detection of gross abnormalities. With increasing physician recognition of the characteristic endoscopic findings, normal-appearing esophageal mucosa is found in less than 5% of patients with EoE.[31] Findings vary among children and adults. Like symptoms, in children, endoscopic findings change with level of inflammation. Exudates, linear furrows, and edema are the most common endoscopic features of EoE in children.[32,33] In adults, endoscopy often detects a combination of inflammation and