Future Directions in Eosinophilic Esophagitis

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KEYWORDS

• Eosinophilic esophagitis • Gastroesophageal reflux disease • Dysphagia
• Food allergy • Esophageal stricture • Esophagitis

KEY POINTS

- Advances in awareness, scientific understanding, and treatment options for eosinophilic esophagitis have paralleled the dramatic increase in the prevalence of this relatively newly identified esophageal disorder.
- Future directions include efforts to refine the diagnostic criteria, identify genetic and environmental risk factors, appreciate the contribution of inflammatory pathways and cellular elements beyond the eosinophil, recognize the importance of subepithelial remodeling, validate appropriate endpoints for therapeutic trials, define a role for targeted biologic therapies, and optimize approaches to dietary therapy.
- From the perspective of gastrointestinal endoscopy, endoscopic outcomes have emerged as an objective and reproducible endpoint in clinical trials of novel therapeutics in eosinophilic esophagitis that complement current activity measures of symptoms and histology.
- Ongoing efforts continue to develop novel, less invasive methods to assess the activity of eosinophic esophagitis to obviate the need for repeated endoscopy.
- Assessment of esophageal distensibility using the functional lumen imaging probe have demonstrated clinical relevance as an important determinant of disease complications and potential utility as a therapeutic endpoint in eosinophilic esophagitis.

Over the past 2 decades, tremendous progress has been made in understanding the diagnosis, epidemiology, pathogenesis, and treatment of eosinophilic esophagitis (EoE).[1] At the same time, major questions and controversies have arisen. The diagnostic criteria, reasons for the growing incidence, appropriate therapeutic endpoints, and efficacy of nonsteroid therapeutic options are among these. This article summarizes and speculates on future issues facing both clinicians and investigators entering the third decade of EoE.

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DIAGNOSIS: BEYOND THE EOSINOPHIL

The diagnosis of EoE combines clinical manifestations of esophageal dysfunction with esophageal histopathologic features of eosinophil predominant inflammation.[2] Before the recognition of EoE, eosinophil-predominant inflammation was considered a hallmark of gastroesophageal reflux disease (GERD). To distinguish EoE from GERD, a therapeutic trial of proton pump inhibitor (PPI) therapy was recommended as a means of excluding GERD based on the persistence of eosinophilia.[3] Recent studies have noted that patients with esophageal eosinophilia that resolves with PPI therapy, or PPI-responsive esophageal eosinophilia (PPIREE), are demographically, symptomatically, endoscopically, histologically, and genetically largely identical to EoE.[4,5] Thus, emerging consensus recommendations have advocated that the PPI trial be removed from the diagnostic criteria for EoE.[5] Instead, the contribution of disorders that may resemble, cause, or contribute to the clinical presentation of EoE (eg, GERD, lichen planus, radiation esophagitis, graft-versus-host disease) and histologic manifestations (eg, GERD, Crohn disease, drug hypersensitivity) are considered before a formal diagnosis of EoE, without mandating a formal PPI trial. As the operational definition of EoE evolves, challenges in the near-term include clarifying whether the similar baseline characteristics between EoE and PPIREE translate to equivalent response to specific therapeutic interventions (ie, do patients with EoE and PPIREE have similar response rates to either diet or steroids).[6,7] The significance of this distinction affects the generalizability of the existing literature on EoE therapy that has predominantly focused on the subset of patients who have not responded to PPI. The mechanisms responsible for the reported 25% to 50% histologic response to PPI therapy need elucidation regarding the relative importance of acid suppression and recently identified, anti-inflammatory properties of PPI therapy.[8–10] Future studies examining the complex interactions between acid reflux, PPI therapy, and antigen-triggered immune responses will improve understanding of both the pathogenesis and treatment of EoE.

Molecular and genetic characterization of EoE continues to advance the understanding of the pathogenesis and has identified novel biomarkers that characterize the disease.[11] Recently, a cohort of 5 adult subjects with dysphagia of unclear cause responsive to corticosteroids but without esophageal eosinophils was described.[12] These subjects had increased T-lymphocytes in the esophageal epithelium compared with controls. Messenger RNA tissue expression of certain genes (MUC4, CDH26) upregulated in EoE were observed but did not include eotaxin-3 expression. This novel observation suggests that EoE may represent a part of a larger, chronic, esophageal inflammatory disease involving T-lymphocytes. Although less common than EoE, increasing reports of patients with dysphagia and endoscopic features of EoE with numerous esophageal intraepithelial lymphocytes without eosinophilia have been characterized as lymphocytic esophagitis (**Fig. 1**). It remains unclear if these patients are a distinct entity or part of an evolving spectrum that includes EoE. Several studies have identified a distinct mast cell signature in the esophageal epithelium of both children and adults with EoE.[13–16] In another study, the role of basophils in the pathogenesis of EoE was demonstrated in a murine model.[17] Depletion of basophils in a novel, ovalbumin-sensitized murine model of EoE led to significant reduction in esophageal eosinophilia and expression of type 2 T helper cell cytokine response. These important studies open the door to the exploration of the role of inflammatory cells beyond the eosinophil in disease pathogenesis and utility of novel biomarkers in the definition of EoE. The importance of these elements is being explored with therapeutics that target specific cell types.