Clinical Management Review

Eosinophilic Esophagitis and the Eosinophilic Gastrointestinal Diseases: Approach to Diagnosis and Management

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The eosinophilic gastrointestinal diseases (EGIDs) represent disorders of the gastrointestinal (GI) tract that result from the local infiltration and aberrant activity of eosinophils and other immune cells. Eosinophilic esophagitis (EoE) is the most well-characterized EGID and is defined by the presence of intraepithelial eosinophils in the esophagus (≥15 eosinophils per high-powered field) and clinical symptoms associated with esophageal dysfunction. The other EGIDs are rare and lack strong data regarding pathogenesis and management. The incidence and prevalence of EoE are increasing, and EoE is now a major cause of upper GI morbidity. Management is multidisciplinary, with collaboration between gastroenterologists, allergists, pathologists, and dieticians, and is aimed at amelioration of symptoms and prevention of long-term complications such as esophageal stricture. Treatment options for EoE include proton pump inhibitors, swallowed topical corticosteroids, and elimination diets. Esophageal dilation is used when esophageal strictures or fibrostenotic changes are present. Additional therapies targeting eosinophils and other mediators of Th2 inflammation are under development and are promising. Treatment options for other EGIDs typically involve corticosteroids or dietary elimination. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

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Eosinophilic gastrointestinal diseases (EGIDs), including eosinophilic esophagitis (EoE), gastritis (EG), gastroenteritis (EGE), and colitis (EC), are characterized by gastrointestinal (GI) tract eosinophilia and symptoms that cause significant morbidity in children and adults. EGID definitions and management are evolving as more is learned about the etiology and natural history of these disorders. EGIDs are chronic disorders that are thought to develop in response to an immunogenic trigger. The diagnosis of EGID is contingent on exclusion of other disorders associated with eosinophilia. This review focuses on the current clinical guidelines, controversial topics, and emerging therapies for the best characterized and most common EGID, EoE. In addition, a brief discussion of what is known, and unknown, about EG, EGE, and EC is presented.

WHAT IS KNOWN ABOUT EGID: EoE

EoE diagnosis

EoE was recognized as a distinct clinical entity in the early 1990s,[1,2] and since then incidence and prevalence have markedly increased.[3] Initial diagnosis and management guidelines were released in 2007[4] and updated in 2011,[5] 2013,[6] and 2017.[7] Early definitions of EoE required that symptoms of esophageal dysfunction and esophageal eosinophilia on biopsy (at least 15 eosinophils per high-powered field [eos/hpf]), not otherwise explained by a potential competing cause of eosinophilia, be present after a high-dose proton pump inhibitor (PPI) trial. Significant research advances over the past 5 years, especially those related to the understanding of the role of PPIs,[8] led a European task force to eliminate the requirement for a PPI trial. Therefore, those with esophageal eosinophilia who respond to PPI therapy (PPI-responsive esophageal eosinophilia [PPI-REE]) exist on the continuum of EoE. This decision was re-emphasized during a recent international consensus conference[9] based on substantial evidence of overlap between PPI-REE and EoE in terms of clinical symptoms, endoscopic findings, pathophysiology, and molecular profiles; updated and operationalized diagnostic guidelines will be released this year.

EoE pathophysiology

EoE is a non−IgE-mediated allergic immune response. It occurs more often in male patients (3:1 male:female), and its highest prevalence is currently in the third to fifth decades of

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Abbreviations used
APT- Atopy patch test
BET- Budesonide effervescent tablet
EC- eosinophilic colitis
EG- Eosinophilic gastritis
EGE- Eosinophilic gastroenteritis
EGID- Eosinophilic gastrointestinal disease
EoE- Eosinophilic esophagitis
eos/hpf- Eosinophils per high-powered field
FDA- Food and Drug Administration
FFED- Four-food elimination diet
FP- Fluticasone propionate
GI- Gastrointestinal
MDI- metered-dose inhaler
PPI- Proton pump inhibitor
PPI-REE- Proton pump inhibitor-responsive esophageal eosinophilia
RCT- Randomized controlled trial
SFED- Six-food elimination diet
SPT- Skin prick test
tCS- Topical corticosteroids
TFED- Two-food elimination diet

life.[3] Clinical symptoms differ in young children compared with older children and adults, partially due to the progression of EoE from an inflammatory to fibrostenotic phenotype over time.[10-12] Young children have feeding difficulties, reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive[13,14]; older children and adults experience dysphagia, heartburn, chest discomfort, exercise-induced chest pain, and food impaction.[15-20]

The natural history of EoE appears to progress from an inflammatory to fibrostenotic phenotype,[11,12,21-27] but subepithelial fibrosis is detected even in children, suggesting that esophageal remodeling occurs early in the disease process.[11,28] Esophageal remodeling may also contribute to esophageal dysmotility in EoE.[27,29-36] Patients with EoE demonstrate impaired esophageal epithelial barrier integrity[27,37-41] and increased esophageal sensitivity to acid[42] and local allergen exposure.[43] The treatment of esophageal inflammation, either with topical corticosteroids (tCS) or elimination diets, likely prevents long-term fibrostenotic changes and improves impaired barrier integrity in patients with EoE.[39,41,44-53] Evidence does not currently support EoE as a premalignant lesion,[54] although there are small case studies suggesting an association between esophageal eosinophilia and granular cell tumors.[55-59]

The prevalence of atopic disease such as allergic rhinitis, bronchial asthma, IgE-mediated food allergies, and eczema is far higher in patients with EoE than the general population,[60] suggesting a prominent role for the allergist in the treatment of these patients' allergic comorbidities.[61] However, the definition of "food allergy" varies widely across studies,[60,62] which highlights a fundamental misunderstanding of the nature and role of skin prick testing (SPT) and serum food-specific IgE testing in diagnosing IgE-mediated food allergies. Allergists are uniquely qualified to determine "probable," "possible," and "unlikely" culprit food allergens from the clinical history and epidemiology of food allergies, which then informs subsequent testing. The 2011 guidelines recommended that patients with EoE who previously demonstrated sensitization to a particular food based on allergy testing undergo office-based oral challenge before reintroduction of that food into their diet,[5] as there are case reports of patients with EoE who develop an IgE-mediated food allergy after avoiding their EoE trigger food.[63-67] On the other hand, there are case reports of patients with IgE-mediated food allergy on oral food immunotherapy who develop EoE, although the presence of EoE before starting this immunotherapy is not known.[68,69] A recent literature search estimated the prevalence of EoE in patients during oral immunotherapy for IgE-mediated food allergy to be approximately 5%.[70] EoE itself is understood as a non−IgE-mediated food allergy; therefore, allergy testing to guide treatment is controversial and discussed below under the "Elimination diets" section.

There is evidence suggesting that exposure to aeroallergens may contribute to the pathogenesis of EoE in some individuals, although it is unclear whether aeroallergens alone can cause EoE or if exposure can modify disease in certain patients with food-triggered EoE.[71] In a retrospective chart review, Ram et al[72] identified a subset of patients with EoE and aeroallergen sensitization whose EoE symptoms and histopathologic findings worsened during the season corresponding to their specific aeroallergen sensitization in the absence of dietary or treatment changes.[73] Interestingly, there are case reports of patients on oral or sublingual aeroallergen immunotherapy who develop EoE that subsequently resolves with the cessation of the immunotherapy.[74-76] It is not known whether EoE disease activity improves in these patients with the more aggressive treatment of allergic rhinitis and with counseling on allergen avoidance, but 1 intriguing case report showed resolution of EoE in 1 patient after 2 years of dust mite oral immunotherapy.[77] Therefore, the allergist's role in the management of EoE is multifaceted.

EoE monitoring

Several validated scoring systems measure symptoms and disease activity in EoE, although most are currently being used primarily for research purposes.[78-81] Scoring systems focused on tracking changes in endoscopy/histology findings are being increasingly used in clinical practice, including the EoE endoscopic reference score (Figure 1).[82,83] This classification is increasingly being used in endoscopic reports and represents an important way to monitor endoscopic severity over time.

There can be a disconnect between EoE symptoms and endoscopic or histologic measures of disease activity. For example, patients may be able to minimize symptoms with dietary avoidance or modification (careful chewing, slow eating, and avoiding hard or fibrous foods) despite ongoing inflammation, or conversely, if there is an esophageal stricture, symptoms may persist despite resolved inflammation. Therefore, a close clinical follow-up of patients is required, and histopathology remains necessary for monitoring EoE disease activity. However, studies have used varying thresholds of eos/hpf to determine treatment response.[84] Recent work supports histologic response as an eosinophil count of <15 eos/hpf, as it is modestly predictive of gross endoscopic or symptomatic improvement, but a more stringent level of <5 eos/hpf correlates with combined improvement in both of these parameters.[85,86] Although EoE is a chronic disease, the optimal intervals for endoscopic surveillance of patients who have achieved remission is not known and should be an area of future study. However, endoscopic assessments with esophageal biopsy should be made approximately 6 to 8 weeks after a treatment is initiated or changed to evaluate treatment efficacy as measured by endoscopy and histologic response. Once the disease is under control, less frequent