



Editorial

Eosinophilic esophagitis 25 years after its recognition Where do we stand?



It has been truly amazing to witness the progress made in understanding and managing eosinophilic esophagitis (EoE) since its recognition 25 years ago. If we examine EoE through history, we notice sporadic reports starting in 1978 of patients with presentations consistent with EoE. Not until 1993 did Attwood et al describe their adult case series, raising awareness about this disease.¹ Two years later, Kelly et al discovered that EoE was triggered by food antigens rather than caused by acid-induced gastroesophageal reflux disease, through demonstration of disease remission with exclusive feeding with an amino acid-based formula.² The year 2003 was the start of an explosion of research studies exploring the causes, pathophysiology, and therapy for EoE. Three important historical milestones helped speed these research efforts. The first was the publication of consensus recommendations for diagnosis and treatment of EoE in 2007, which helped define EoE and described various therapies for the disease, followed by an update in 2011, which additionally highlighted research needs in EoE. A third important milestone was assigning EoE its first code (530.13) in the International Classification of Diseases, Ninth revision (ICD9), which allowed more accurate epidemiological assessment of EoE. In fact, the incidence and prevalence of EoE have been increasing worldwide. Therefore, the possibility of EoE can no longer be ignored in a patient with a history of esophageal food impaction or persistent heartburn, or in a child with upper gastrointestinal symptoms and growth failure, among other possible clinical presentations. In this issue, a series of articles cover various aspects of EoE and eosinophilic gastrointestinal disorders and are definitely worth reading in depth.^{3–5}

Clinical progress in EoE has occurred on 3 fronts: pathophysiology, diagnosis, and short-term therapy options. On the pathophysiology front, we now know that EoE is triggered by food antigens, and the cytokine profile of the esophageal tissue is consistent with an allergic T-helper type 2 disease. A unique esophageal transcriptome with distinct genetic susceptibility elements at 5q22 (TSLP) and 2p23 (CAPN14) has been established.⁶ In addition, we now know about the involvement of other immune cells besides eosinophils, such as mast cells, basophils, and T-lymphocytes, in the pathophysiology of EoE, in addition to a disruption of the esophageal epithelial barrier,⁶ suggestive of possible food antigen uptake at the esophageal level. The article by Samadi et al⁷ in this issue elegantly summarizes the effect of a disrupted intestinal barrier on

immunoglobulin E (IgE)–mediated food allergic immune responses. One wonders about the potential parallels in this regard between the intestine and the esophagus in IgE-mediated food allergy and EoE, respectively.

On the diagnostic front, we recently witnessed a paradigm shift in defining EoE, in which a trial with a high dose of a proton pump inhibitor (PPI) to rule out PPI-responsive esophageal eosinophilia may no longer be needed to confirm the diagnosis of EoE, when symptoms and esophageal histology are suggestive of EoE and other diseases have been ruled out.⁸

As for therapies for EoE, although we do not have yet a US Food and Drug Administration–approved drug for EoE, major advances have been made as we move from single-center to multicenter clinical trials, to test various formulations of fluticasone and budesonide for EoE (www.clinicaltrials.gov, NCT02605837, NCT02736409, NCT03191864, NCT02493335). Biologics are also being pursued, with the ongoing anti-interleukin (IL)-13 and anti-IL-4R trials (www.clinicaltrials.gov, NCT02098473, NCT02379052) demonstrating promising preliminary results. The success of these biologics highlights the importance of the cooperative role of various immune cells along with the eosinophils in diseases such as EoE, as highlighted in the article by Bochner⁹ in this issue. Dietary therapies also have been evolving, from 3 types initially described (elemental diet, test-directed elimination diet, and empiric 6-food elimination diet), to less restrictive empiric elimination diets such as the 4-food and 2-food elimination diets,^{10,11} and simple milk avoidance, the latter currently under study (www.clinicaltrials.gov, NCT02778867, NCT02610816). The article by Nhu and Aceves³ provides a comprehensive summary of these therapies for EoE.

As therapies for EoE get better established, 2 important management questions will be important to answer through future research studies. First, can we tailor therapies to specific patient populations for better success? The article by Lieberman⁴ in this issue discusses this in detail, because the need for a definition of EoE phenotypes is highlighted, similar to the approach currently being taken for asthma.

The second question stems from the fact that EoE is a chronic disease, and long-term therapy is important for continued disease remission and for reversal of potential esophageal fibrostenotic complications. Therefore, which therapies are effective, safe, and well tolerated by patients with EoE on a long-term basis? So far, we have very few studies addressing therapies for longer than a year. Fortunately, almost all multicenter clinical trials currently testing medications for EoE have extension trials built in. As for dietary therapies, the quest for balancing efficacy of the diet with preserving quality of life on the long run has been a challenge. Current efforts at testing and validating procedures that are less invasive than an endoscopy with esophageal biopsies are underway. If successful,

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these procedures may be used for faster and easier identification of food triggers in patients with EoE following successful restrictive diets, through quick testing for disease activity after sequential food challenges.

To conclude, practicing allergists are encountering patients with EoE on a regular basis, as the prevalence continues to increase, and a large subset suffer from atopic co-morbidities. Furthermore, allergists may start encountering EoE in some patients undergoing oral immunotherapy to foods, as more cutting edge immunotherapies for IgE-mediated food allergies are developed.¹² However, the future for EoE management is promising, as the pathophysiology and genetic aspects of EoE are more understood and the disease is better characterized in terms of its progression and response to treatment. In the next few years, we will likely be able to describe various EoE patient subtypes and their individual response to therapies, therefore entering the era of personalized medicine. This will help us achieve the goal of tailoring the best therapy for each patient that will ensure long-term disease remission.

Mirna Chehade, MD, MPH
Mount Sinai Center for Eosinophilic Disorders
Icahn School of Medicine at Mount Sinai
New York, New York
mirna.chehade@mssm.edu

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