ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

Gastroesophageal Reflux Disease and Eosinophilic Esophagitis

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G&H Can you summarize the evolution of gastroesophageal reflux disease and eosinophilic esophagitis as 2 distinct disorders?

SS Since the 1980s, it has been well established that gastroesophageal reflux disease (GERD) can be associated with low-level eosinophilia of the esophagus, typically fewer than 7 eosinophils per high-power field on esophageal biopsy. In 1993, the first article to describe the syndrome that is now recognized as eosinophilic esophagitis (EoE) was published. EoE is characterized by a dense esophageal eosinophilia, usually more than 15 eosinophils per high-power field, although GERD also can be associated occasionally with dense esophageal eosinophilia. Generally, GERD presents with heartburn and regurgitation, whereas EoE presents with episodes of dysphagia and food impaction. However, GERD can also cause dysphagia, and EoE can also cause heartburn. Early on, this symptom overlap made it difficult for clinicians to recognize EoE as a distinct disorder, and the general tendency was to attribute eosinophils in the esophagus to GERD.

A consensus conference was held in 2007, during which the American Gastroenterological Association released an article on EoE stating that a nonresponse to proton pump inhibitors (PPIs) was a diagnostic criterion. At the time, it was thought that the major effect of PPIs was to prevent the stomach from making acid. Because GERD is the only acid-peptic disorder of the esophagus, it followed that, for patients with esophageal symptoms, a response to PPIs established a diagnosis of GERD. This distinction, which implied that GERD and EoE were mutually exclusive disorders, was unrealistic. Another conference was held in 2011 that tried to resolve some of the contentious issues of the earlier conference. The 2011 conference concluded that EoE is an immune/antigen-mediated disease, meaning it is actually an allergic disorder that manifests through eosinophils in the esophagus. However, the conference still concluded that a response to PPIs excluded a diagnosis of EoE. This was increasingly problematic, as studies had found that PPIs had various anti-inflammatory properties that had nothing to do with their effects on acid secretion. For example, some allergic cytokines stimulate esophageal cells to make eotaxin-3, a molecule that attracts eosinophils to the esophagus, and it was discovered that PPIs can block the production of eotaxin-3. This mechanism could explain why some patients presenting with symptoms typical of EoE and little evidence of GERD showed response to PPIs. The term PPI-responsive esophageal eosinophilia (PPI-REE) was created to describe this patient population.

Over the next few years, we learned that patients with PPI-REE had virtually every feature of EoE, the only difference being that, by definition, they responded to a PPI. In 2018, the AGREE (A Working Group on PPI-REE) Conference published consensus guidelines that removed PPIs as a diagnostic test for EoE, and instead considered PPIs a treatment for EoE. The

conference also concluded that PPI-REE is essentially indistinguishable from EoE. A patient with esophageal symptoms typical of EoE and an esophageal biopsy showing eosinophilia can be diagnosed with EoE once other eosinophilia-causing disorders are ruled out. Rather than excluding the diagnosis of EoE for such a patient, a response to PPIs is considered a treatment success.

The notion that PPIs might contribute to the development of EoE is seemingly paradoxical, as PPIs are used to treat the disease.

G&H What evidence was used to support the updates that were made to the EoE diagnostic criteria?

SS By 2018, enough research had accumulated demonstrating that every clinical, histologic, and gene expression feature of EoE and PPI-REE was identical. Additionally, reports appeared of patients with typical clinical and histologic features of EoE who initially responded to PPIs, but who also responded to diet therapy or topical corticosteroids when PPIs were stopped. For such patients, a diagnosis of GERD alone was simply untenable.

G&H How might GERD contribute to the development of EoE, and vice versa?

SS GERD increases the permeability of the esophageal mucosa. Food antigens that might have just passed through the esophagus to be digested in the stomach now might penetrate into the wall of the esophagus and incite an allergic response, conceivably contributing to the development of EoE. Conversely, EoE may contribute to the development of GERD. There are a number of eosinophil products that can relax the muscle of the lower esophageal sphincter that prevents reflux and can alter esophageal motility to delay the clearance of refluxed acid.

G&H What is the role of PPIs in patients with EoE?

SS PPIs are 1 of 3 established treatment options available for patients with EoE, with the other 2 being topical corticosteroids and diet. PPIs are generally the simplest choice. However, because EoE is a food allergy, PPIs, along with corticosteroids, do not get rid of the allergy but simply cover it up. A diet that eliminates the offending food allergen(s) conceptually is the best option to treat EoE, but is limited by several issues. The diet is restrictive and, therefore, difficult to follow and maintain. Additionally, it is expensive to implement because it requires multiple endoscopies to determine which food is triggering the problem. Typically, most patients prefer the PPI route if they have a response to the treatment.

G&H What are the possible connections between PPI use and the development of EoE?

SS The notion that PPIs might contribute to the development of EoE is seemingly paradoxical, as PPIs are used to treat the disease. Several years ago, I proposed the hypothesis that the mechanism by which PPIs might cause EoE is entirely different than the mechanism by which they might treat EoE. Ordinarily, the stomach makes acid as well as the digestive enzyme pepsin, which attacks proteins and peptide antigens in food. Pepsin requires stomach acid in order to be active, and PPIs prevent the production of stomach acid. Thus, pepsin often is not active in patients who take PPIs, and peptide antigens cannot be broken down in the stomach. As a result, the undigested antigens reach the small intestine intact, potentially stimulating an allergic response, leading to EoE. PPIs also increase the permeability of the stomach and have an effect on the gut microbiome, both of which also might contribute to allergy development. In support of this hypothesis, Dr Evan Dellon and colleagues recently reported that PPI use in infancy was the strongest risk factor for later development of EoE.

G&H What management options are available for patients diagnosed with GERD?

SS That could be a very long discussion. Briefly, various management options are available for patients with GERD, but the most commonly used treatment is PPIs, especially for patients with severe reflux. PPIs, histamine H2 blockers, and other medical treatments focus on decreasing acid production in the stomach. Surgical and endoscopic procedures are also available and are designed to prevent reflux by improving the antireflux mechanism.

G&H How should pediatric patients with GERD or EoE be treated?

SS Pediatric patients with EoE are treated much the same as adult patients with EoE, with PPIs, corticosteroids, or diet. GERD in the pediatric population is an especially controversial topic. It is very common for infants to have a lot of reflux—they spit up all the time—and authorities argue over precisely when, or if, clinicians should intervene medically or surgically in an infant with symptoms thought to be due to GERD.

G&H What are the priorities of research?

SS The highest priority is to learn why EoE has become such a common disorder since its discovery over 20 years ago. It is not really understood why some people develop this food allergy that manifests in the esophagus. If we could figure out the basic pathophysiology of the disease, perhaps we would have some better treatment options than we do presently.

Dr Spechler serves as a consultant for Ironwood Pharmaceuticals and Frazier Management LLC.

Suggested Reading

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