

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Therapeutic Options for Eosinophilic Esophagitis

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G&H What is the current understanding of the potential causes of eosinophilic esophagitis?

IH It is important to first distinguish esophageal eosinophilia from eosinophilic esophagitis (EoE). Esophageal eosinophilia has been described in a variety of conditions, including gastroesophageal reflux disease (GERD), eosinophilic gastroenteritis, infectious esophagitis, drug hypersensitivity reactions, hypereosinophilic syndrome, and connective tissue disorders. EoE is a clinicopathologic disorder characterized by esophageal symptoms and dominated by dysphagia in adult patients, with esophageal eosinophilia that is not deemed to be secondary to these other disease states.

The majority of evidence to date suggests that EoE is an allergic disorder induced by antigen sensitization. Studies have clearly shown that there is a substantial role for dietary allergens in both the pathogenesis and treatment of EoE. Aeroallergens may also be involved, but there is much less evidence in this regard. Murine studies have identified the importance of Th2 cells and the expression of eotaxin-3, interleukin (IL)-5, and IL-13. Predisposing genetic factors, acid reflux, and other environmental cofactors are topics of active research.

G&H What are the usual presenting symptoms of EoE?

IH In adults, EoE typically presents with dysphagia and food impaction. Less common, but nevertheless impor-

tant, symptoms include atypical chest pain. In children, the symptoms also include abdominal pain, nausea/vomiting, and growth failure. EoE may present as proton pump inhibitor (PPI)-refractory reflux, though this possibility appears to be more of a concern in pediatric than adult patients.

G&H How is the diagnosis of EoE established, and why is it so difficult to establish?

IH EoE is diagnosed based upon the typical presenting symptoms discussed above, together with pathology demonstrating increased esophageal eosinophilia, generally greater than 15 or 20 EOS/HPF. Supportive features include endoscopic findings of concentric mucosal rings, longitudinal furrows, and white plaques or exudates.

In the recent past, the greatest difficulty in diagnosis was disease recognition. The diagnosis of EoE was missed for many years by radiologists, gastroenterologists, and pathologists, as the entity was not well described until the mid-1990s. In the past decade, there has been a dramatic increase in the number of diagnoses, which has been largely related to increased awareness of the condition. In fact, EoE has now become one of the leading causes of dysphagia and food impaction.

The recognition of suspected cases of EoE has become quite routine. However, differentiating EoE from GERD has become an increasingly difficult problem in clinical practice. At face value, the symptoms and endoscopic findings of EoE are distinct from those of GERD. However, a significant proportion of suspected EoE patients respond both symptomatically and histologically to proton pump inhibition, which blurs this distinction. Furthermore, because of the high prevalence of GERD, a significant proportion of EoE patients have abnormal esophageal acid exposure. Several pediatric and adult studies have demonstrated the effectiveness of PPI therapy in patients with esophageal eosinophilia. However, it remains unclear whether these patients have GERD, EoE, or both enti-

ties. The overlap and possible causative role for GERD in some patients with EoE is a source of controversy. More research is clearly needed.

In addition, there is currently confusion as to the role of allergy testing with radioallergosorbent tests, skin prick testing, and patch testing. Thus far, the accuracy of immunoglobulin (Ig)E-mediated tests to predict causation in EoE has been less than ideal.

G&H How effective are the medical treatment options, including acid suppressants, corticosteroids, and biologic agents, for EoE?

IH It is important to first identify a patient with EoE, as there are a number of very effective treatments available to patients.

The majority of therapeutic studies to date have focused on topical steroids in EoE. Randomized, placebo-controlled studies in both children and adults have demonstrated the efficacy of topical steroids in treating the symptoms and pathology of EoE. Systemic steroids are also effective, but their use as first-line agents is limited by side effects.

In terms of biologic agents, there are emerging data on the use of anti-IL-5, anti-IgE, and anti-tumor necrosis factor therapy for EoE. These agents hold promise as disease-modifying agents and for patients who do not respond well to steroids or dietary elimination. Other novel approaches are also under investigation.

In addition, montelukast and 6-mercaptopurine have been reported to show benefits in a small number of adult patients with EoE.

G&H Are there any other medical agents currently under investigation for treating EoE?

IH There are currently a number of novel medical therapies being investigated. This is an important issue, as there are currently no treatments approved by the US Food and Drug Administration for EoE. Biologic therapies target several of the key inflammatory mediators. EoE clearly carries a significant morbidity for many EoE patients who are on restricted diets due to dysphagia or who are experiencing repeated food impaction.

G&H Have elimination or modification diets shown any benefits for treating EoE?

IH Dietary therapy is an exciting and novel form of therapy for EoE. Three different dietary approaches have been examined, including the use of an elemental formula, an elimination diet based upon the results of allergy testing, and an empiric elimination diet with the removal of

common food allergens (milk protein, egg, nuts, seafood, wheat, and soy). The goal of all 3 dietary approaches is the identification of a limited number of specific causative foods that are acting as the antigenic trigger.

G&H Is endoscopic esophageal dilation a therapeutic option for patients with EoE?

IH This option has been a topic of controversy in the treatment of EoE. Concerns regarding the safety of dilation stem from several small case series of complications of esophageal perforation or severe chest pain that required hospitalization and narcotics. However, 2 studies published this year put these concerns into perspective by reporting the experiences of esophageal dilation in over 200 patients. These studies noted a low complication rate and no esophageal perforations. Furthermore, the relief of dysphagia lasted for over 1 year in many patients. Therefore, esophageal dilation is an effective means of alleviating dysphagia in EoE patients with strictures. Nevertheless, controversy remains as to whether dilation should be performed as primary therapy, in combination with medical therapy, or reserved for patients failing medical or dietary therapy.

G&H What is usually the first therapeutic step? How is treatment selected for a patient with EoE?

IH The recommendations for initial therapy are evolving. At our own center, initial therapy begins with a course of PPI therapy. Patients who are unresponsive to PPIs are offered dietary elimination or topical steroids. Dilation is used as an adjunctive therapy for severe strictures or patients who are not responding to medications or dietary changes. The treatment plan is individualized for patients. The dietary approach requires both a motivated patient and gastroenterologist, but it has the advantages of avoiding medications and removing the underlying environmental allergen.

G&H What is the goal of therapy?

IH The optimal goal of therapy is unclear at this time and, in my view, depends upon the severity of the patient's presentation. Although no one would argue that symptom relief is central, some patients become asymptomatic through avoidance of meat or solid foods and minimize eating at restaurants, which is not ideal. On the other hand, the importance of persistent tissue eosinophilia and esophageal mucosal changes on endoscopy in patients who are truly asymptomatic is uncertain. At our institution, patients with severe symptoms who have undergone repeated dilations or have suffered

from frequent food impactions have more strict treatment goals.

G&H How does treatment differ for children and adults?

IH Similar therapeutic options have been used for both children and adults. Certain agents such as montelukast, immunomodulators, and antihistamine therapy have only been reported in adult cohorts thus far. Uncontrolled studies of dietary therapy have described greater response rates in children than adults, though dietary therapy is effective in both populations. Esophageal dilation is used more frequently in adults, as strictures are less commonly seen in pediatric cases.

G&H Are there any specific concerns or adverse events associated with any of the treatments discussed above?

IH The major concerns have been the esophageal injury associated with esophageal dilation. Topical steroids have thus far been very safe, with a minority of patients developing esophageal candidiasis, which is usually asymptomatic. Systemic steroids are usually not necessary and clearly carry a greater side-effect profile. Elemental dietary therapy has often necessitated nasogastric or percutaneous gastrostomy tube administration. The adult patients at our center treated with the elemental diet have not required tube feeding. The expectations of the dietary approach include the eventual identification of specific food allergens and the resumption of a regular diet by mouth.

G&H What does long-term management usually consist of?

IH The importance and appropriate use of maintenance therapy in EoE are just beginning to be elucidated. The majority of patients have symptomatic recurrence after the withdrawal of therapy. In addition to monitoring symptoms, select patients may be monitored with repeat endoscopy and biopsy.

G&H What are the next steps for future research in this area?

IH As EoE is a new disease entity, there is a tremendous need for clinical, translational, and basic science research. Animal models that resemble the human disease state are being developed. Understanding what has changed in the environment to allow for the emergence of EoE over the past several decades is another fascinating topic. Noninvasive diagnostic modalities would offer the ability to follow patients without the need for costly endoscopy. Finally, novel therapies that target the antigenic stimulus or specific sites in the inflammatory cascade are being investigated.

Suggested Reading

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