ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

Dietary Therapy for Eosinophilic Esophagitis

Nirmala Gonsalves, MD
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

G&H What is eosinophilic esophagitis?

NG Eosinophilic esophagitis (EoE) is a chronic immune- or antigen-mediated condition that causes eosinophil-predominant esophageal inflammation, which can lead to esophageal dysfunction. Typical symptoms in adults include difficulty swallowing, heartburn, and food impaction. Children typically present with abdominal pain, refractory reflux symptoms, and nausea/vomiting. Older children may present with the adult phenotype and have difficulty swallowing and food impaction.

G&H How is a diagnosis of EoE made?

NG A diagnosis of EoE is made based on not only symptoms but also histologic abnormalities. The current histologic guidelines suggest that biopsies should show more than 15 eosinophils per high-power field. Because gastroesophageal reflux disease also can lead to eosinophils in the esophagus, EoE is not diagnosed until after patients have taken appropriate acid suppression with a proton pump inhibitor for at least 6 to 8 weeks prior to an endoscopy showing persistent eosinophils. Other allergic and immune disorders can also lead to eosinophilia in the esophagus and need to be ruled out.

G&H When was EoE first recognized as a diagnosable condition?

NG Some of the first case reports of EoE were published in the late 1970s, but for many years patients had been misdiagnosed as having reflux or nonspecific esophageal strictures. In the past 15 years, EoE has been increasingly recognized by pediatric and adult gastroenterologists, pathologists, and allergists. Now that we know much more about the condition, patients are being diagnosed earlier in the disease process.

G&H Why did EoE become better recognized?

NG Diagnosing EoE requires an esophageal biopsy, and years ago patients were not receiving routine biopsies. Gastroenterologists would biopsy the esophagus of adult patients with swallowing difficulties only if other significant abnormalities were present. As the condition has become better recognized, more practitioners have put biopsy protocols into place for patients presenting with difficulty swallowing, allowing for greater recognition of this condition. In addition, EoE has become a focus of many major symposia at professional meetings.

G&H When did dietary therapy first enter the field as a treatment for EoE?

NG A landmark study by Kelly and colleagues that was published in *Gastroenterology* in 1995 showed that pediatric patients with high levels of eosinophils in their esophagus treated with what is called an elemental or amino acid–based formula diet—essentially a nonallergenic diet—for 6 to 8 weeks had a complete resolution of eosinophils in their esophagus. When foods were reintroduced, the eosinophils returned. This study, subsequently replicated by several groups, confirmed the link to food allergens in children.

At Lurie Children's Hospital in Chicago, Kagalwalla and colleagues investigated an empiric elimination diet that removed the 6 food groups that typically trigger EoE: milk, wheat, soy, eggs, nuts, and seafood. They found that pediatric EoE could be treated with this diet. As a result of these studies, dietary therapy has become a first-line therapy for EoE in children.

G&H Were these findings immediately translated to adult patients?

NG No. Although pediatric EoE was considered to be driven by food allergies, this mechanism was not universally accepted in adults. Further study was needed to see the effects of diet alterations on adult EoE. In 2012, Ikuo Hirano and I—together with our collaborators at the Feinberg School of Medicine—completed the first prospective food-elimination trial in adults with EoE. In this prospective study, 50 adult patients with EoE were offered a 6-food elimination diet as an alternative to topical corticosteroids. In this diet, patients eliminated milk, wheat, soy, egg, nuts, and seafood for 6 weeks. More than 70% of patients responded to this therapy with reduction of eosinophils to less than the threshold level for a diagnosis of EoE. The empiric elimination diet in adults has also been investigated by Molina-Infante and colleagues in Spain, with similar results. As a result of these studies, dietary therapy is being considered as a first-line treatment approach in both adults and children.

G&H Are medical interventions sometimes recommended?

NG Swallowed topical corticosteroids are considered the most common form of medical treatment in adults. Currently, there are no medications approved by the US Food and Drug Administration for EoE, so treatment has focused on the use of topical corticosteroids typically used to treat asthma. These may be in the form of an asthma inhaler or a nebulizer solution, but instead of inhaling the medication, patients are instructed to swallow it. Because eosinophils in the esophagus cause inflammation in EoE, using a swallowed topical corticosteroid helps to reduce and eliminate these eosinophils from the tissue. As a result, the inflammation is reduced. This treatment is given for varying lengths of time and is a very effective way to control symptoms and tissue inflammation.

One of the disadvantages of this approach is that when the medication is stopped, the eosinophils return because the underlying cause of the inflammation is not being controlled. Therefore, a topical corticosteroid is often used as maintenance therapy to control and prevent recurrence of the condition.

G&H What is currently understood about the connection between foods and EoE? Why do certain foods trigger this type of reaction?

NG No one knows exactly why certain foods trigger this reaction in some people. Patients who tend to develop EoE also have an increased risk of other allergic conditions such as asthma, allergic rhinitis, and eczema. Their immune system seems to be more primed to react to these foods when ingested.

Although EoE is thought to be a food allergy–driven disease, the reaction is different from what we typically think about with a food allergy. For instance, when we think of a reaction brought on by a food allergy, we think about anaphylactic symptoms such as hives, tongue swelling, and throat tightness. Patients with EoE do not experience this classic immunoglobulin E (IgE)- or histamine-mediated food-allergy response.

Rather, the allergic reaction that leads to EoE is the result of chronic exposure to these foods and is somewhat delayed. Researchers have shown that EoE is linked to a T helper 2 cell–mediated reaction. Here, certain lymphocytes trigger an immune reaction that leads to the recruitment of eosinophils into the tissue of the esophagus, where they break down in response to food allergies. That disintegration releases cytotoxic granules that cause inflammatory changes in the tissue. Over time, those changes can cause fibrosis or scarring, leading to changes in the lining of the esophagus as well as possible narrowing of the esophagus. However, we do not yet know the trigger for the body's initial reaction to the foods. Understanding why EoE develops and what triggers patients to start reacting is an important area of research.

G&H What different dietary therapy approaches are used to treat EoE?

NG There are 3 different dietary approaches to treating EoE. The first approach is called an elemental diet, in which all food allergens are removed, and patients ingest an amino acid–based formula for their nutrition. This approach commonly has been used in children. Patients take the formula for a period of approximately 6 weeks. If the follow-up endoscopy shows that all of the eosinophils have been eliminated and the inflammation has resolved, then foods are reintroduced slowly, one at a time, with the goal of identifying the patient's food triggers.

Although this is the most effective dietary approach to controlling inflammation, it has some limitations. First, it is costly and often is not covered by insurance. Second, the formula can be difficult for some patients to drink because of its taste. Pediatric patients often require a feeding tube to administer the formula. One of the

biggest challenges is that the food reintroduction process after being on an elemental diet can be lengthy. It also tends to involve numerous endoscopies.

The next type of dietary therapy is the empiric or 6-food elimination diet. If adults embark on dietary therapy, this is typically the approach used. After eliminating the 6 most common food allergens—milk, wheat, soy, egg, nuts, and fish—for 6 weeks, the patient undergoes an endoscopy. If the EoE has disappeared, then we know that the cause is 1 or more of these 6 foods. Each of these 6 foods is then added back one at a time with the goal of identifying the allergen.

In our study, the most common food to trigger EoE was wheat, which affected 60% of patients. This was followed by milk, which affected 50% of patients. The problem was soy or nuts, each in 10% of patients, and egg in 5% of patients. These common allergens are similar to those seen in children.

The third approach to dietary therapy is an allergy-directed diet based on skin-prick testing, patch testing, or blood testing for the food allergen. The clinical data on this approach are varied. A group at the Children's Hospital of Philadelphia found that a combination of skin-prick testing and patch testing was effective for identifying allergens and then eliminating those foods as a treatment for EoE. Unfortunately, this approach has not shown promising results in adults based on our study and 2 other adult studies from Spain, suggesting that adults and children may have a different type of immune reactivity. In our study, the correlation between skin-prick testing and EoE triggers was less than 13%. This low correlation is likely because current food allergy testing focuses on IgE-mediated reactions, and it is still unclear where on the spectrum EoE falls. Development of optimal allergy testing for food triggers in EoE is an area of active investigation within the allergy community.

G&H Could you discuss the data on the 6-food elimination diet as a treatment for EoE?

NG As discussed earlier, our study from 2012, published in *Gastroenterology,* showed that this approach led to the resolution of EoE in 70% of patients. The diet effectively controlled not only the histologic eosinophilia but also the symptoms and endoscopic changes. That response rate is fairly similar to what is seen with topical corticosteroids and what was experienced with the studies in children.

G&H Is it difficult for adult patients to follow an elimination diet?

NG Initially, I thought that this approach would be difficult for patients to follow. However, I have found that once patients understand the underlying rationale for the diet, they are highly motivated to follow it and learn what is causing the condition. The goal of dietary therapy is not to eliminate these foods forever. Rather, we want to slowly reintroduce foods and hopefully find the single trigger. In our experience, the allergen is usually 1 of the 6 eliminated groups, not multiple foods. Currently, more than 50% of our patients choose dietary therapy.

The major challenge with dietary therapy is that we do not have a noninvasive way to test for EoE. The only approach is repeated endoscopy to see if the patient is reacting to the food. Some patients do not experience symptoms, so we cannot rely on symptoms to confirm that the EoE has returned; studies have shown a poor correlation between symptoms and EoE. There are some noninvasive tests in development that may turn out to be useful and may be able to take the place of follow-up endoscopies in the future.

Also, in order for dietary therapy to be effective, practitioners need to partner with a dietitian who is familiar with eosinophilic gastrointestinal disease and can help educate patients on the logistics of dietary therapy. My colleagues and I recently published a paper in the journal *Diseases of the Esophagus* that summarizes our approach at the Feinberg School of Medicine. We take a very hands-on approach with our patients. All patients have a 1-hour education session with our dietitian and then contact us within 2 weeks of starting the diet to ensure that there is no contamination. Our patients are in contact with our dietitian periodically throughout the duration of the diet. Her expertise is critical to the success of the dietary program.

Many patients find the process challenging during the first 6 weeks because of the numerous limitations. However, after the diet and reintroduction process is complete, they usually are happy to know what is triggering their EoE and to be able to avoid those foods. All patients know that they can transition to medical therapy at any time if they find the diet too restrictive, but most patients who start dietary therapy tend to continue it.

G&H Do the allergies that cause EoE in adults ever go away spontaneously?

NG This immune-mediated condition does not appear to disappear over time. Studies have shown that pediatric patients with EoE rarely outgrow their allergic triggers, but longer natural history studies are needed to better address this issue. Because EoE is a chronic condition, successful treatment hinges on a good working relationship among all of the specialists involved, including the gastroenterologist, allergist, pathologist, and nutritionist.

Dr Gonsalves is on the speakers bureau for Nutricia.

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Suggested Reading

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