

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Clinical Presentation and Treatment of Pediatric Patients with Eosinophilic Esophagitis

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G&H What is the incidence of eosinophilic esophagitis in children?

CL Eosinophilic esophagitis is a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. The exact incidence of this disease is still unknown. Initial studies in the early 2000s reported incidence rates of approximately 1 in 10,000 individuals. The current incidence rate is likely higher—closer to 1 in 2,500 individuals. Pediatric gastroenterologists usually see more new patients with eosinophilic esophagitis than new patients with Crohn's disease. Eosinophilic esophagitis appears to be more prevalent in whites, but it is currently being diagnosed more often in nearly all races. The disease is more commonly seen in males than females.

Several years ago, we adopted an ICD-9 code for reporting this disease; we hope to have collected enough data in the near future to learn more about its incidence and epidemiology.

G&H Is eosinophilic esophagitis being recognized more frequently in children?

CL The increase in incidence is likely due to a combination of the disease being recognized more frequently in patients as well as the disease occurring more often. By

now, nearly all pediatric gastroenterologists know about this disease, and we rarely miss its diagnosis. When performing endoscopy in the 1980s and 1990s, we biopsied every patient and rarely saw patients with eosinophilic esophagitis, so the disease is actually occurring more frequently as well.

G&H What are the most common presenting symptoms in pediatric patients with eosinophilic esophagitis?

CL Pediatric patients with eosinophilic esophagitis present not only with dysphagia and swallowing difficulties—as do adults with the disease—but also with abdominal pain, reflux-like symptoms, and heartburn. For approximately every 10 children who go to a gastroenterologist for treatment of reflux, 1 child actually has eosinophilic esophagitis. I believe that a significant proportion of adults with reflux have a similar presentation, but this finding has not been reported to date.

G&H Since the presenting symptoms are often similar, how is eosinophilic esophagitis differentiated from gastroesophageal reflux disease?

CL When pediatric patients present with reflux, they are usually treated with a proton pump inhibitor. If their symptoms do not improve or completely resolve—or if they resolve but then recur when the medication is discontinued—an endoscopy with a biopsy should be performed to determine whether the patient has eosinophilic esophagitis. Because the symptoms of eosinophilic esophagitis and gastroesophageal reflux disease are similar, the only way to differentiate the 2 conditions is to treat the patient with a proton pump inhibitor to see

if the eosinophilia resolves. Without performing both an endoscopy and a biopsy, gastroenterologists cannot definitively determine the cause of the patient's symptoms. Eosinophilic esophagitis can only be diagnosed by the degree of esophageal eosinophilia in the biopsy. Blood tests do not have a role in diagnosis; to date, the only true diagnostic tool is endoscopy with biopsy.

It is important to stress that the mere presence of eosinophils in the esophagus is not enough to establish a diagnosis of eosinophilic esophagitis. When eosinophils are identified in the esophagus, the gastroenterologist must determine whether they are unresponsive to proton pump inhibitors (in order to exclude other diseases, particularly gastroesophageal reflux disease). The gastroenterologist should also look for the classic symptoms of eosinophilic esophagitis.

G&H Do most pediatric patients with eosinophilic esophagitis also have gastroesophageal reflux disease?

CL As previously mentioned, patients with eosinophilic esophagitis often present as though they have reflux; 1 in 10 patients who appear to have gastroesophageal reflux disease actually have eosinophilic esophagitis instead. However, there are patients who have eosinophilic esophagitis but also have reflux symptoms and need proton pump inhibitors. Some of these patients with eosinophilic esophagitis may have a secondary reflux that responds clinically, but not histologically, to acid suppression; once the patient's eosinophilic esophagitis is treated properly, the proton pump inhibitor can be withdrawn if the reflux symptom is secondary to eosinophilic esophagitis, as the primary disease has been treated and there are no further reflux symptoms. Rarely, the 2 diseases may coexist independent of each other.

G&H Are eosinophilic esophagitis patients genetically predisposed to the disease?

CL A genetic predisposition is often seen in patients with eosinophilic esophagitis. Last year, *Nature and Genetics* published research conducted by The Children's Hospital of Philadelphia and Cincinnati Children's Hospital Medical Center examining various genetic markers. The study found a general genetic predisposition in eosinophilic esophagitis patients. A gene locus was identified at chromosome 5q22 with the identification of the gene *TSLP* (thymic stromal lymphopoietin protein). Patients who are genetically predisposed likely have a trigger that sets off the disease. Children whose parents or siblings have eosinophilic esophagitis and who have clinical symptoms of the disease themselves should undergo testing.

G&H Have there been any updates to the consensus recommendations published in 2007?

CL An updated consensus report will be released in July 2011 in *The Journal of Allergy and Clinical Immunology*. There were several changes to the basic definition of eosinophilic esophagitis. We noted the importance of treatment with a proton pump inhibitor. Another addition was the mention of patients who appear to have large numbers of eosinophils that respond to proton pump inhibitors; this group may represent a type of acid reflux disease or perhaps another subset of patients. We are not yet sure how to define these patients; they are not eosinophilic esophagitis patients by definition because they respond to proton pump inhibitors. The final change was the addition of a conceptual definition; we wanted to make sure that patients understand that this disease is caused by the ingestion of antigens and/or an underlying immunologic process.

G&H What is the ultimate goal of therapy in these patients?

CL Most eosinophilic esophagitis patients visit a gastroenterologist because of their symptoms; thus, the first goal of treatment, as with any therapy, is to treat these symptoms. The second goal is to improve tissue histology and chronic inflammation in order to prevent complications such as fibrosis and other chronic problems. How aggressive treatment should be is a tricky question; it is unclear whether a patient should be treated until inflammation completely resolves or whether partial improvement of inflammation (eg, 50% or 75%) is sufficient.

G&H What are the most common first-line treatment options in pediatric patients?

CL Currently, the most common treatments are dietary therapy and topical steroids, which are equally effective. There are 3 types of dietary therapy. One type is to empirically guess which foods cause inflammation; gastroenterologists usually start by removing foods that typically cause eosinophilic esophagitis, such as milk, soy, wheat, eggs, nuts, and fish. In approximately 65–75% of patients, an empiric diet is effective and patients improve with the elimination of these foods. The second type of dietary therapy uses allergy testing (skin prick or patch testing) to determine which foods should be eliminated. The third type uses a strict elemental diet, in which all foods are eliminated and patients are given a formula. Although each of these options has shown efficacy for treating eosinophilic esophagitis, the most effective option is removal of all foods because it ensures the elimination of

the causative foods. If an empiric diet is utilized or if foods are removed based on allergy testing, all of the causative foods may not be removed and the patients' symptoms will not completely resolve.

The most common topical steroids for treating these patients are swallowed fluticasone and budesonide. Both steroids can be as effective as dietary therapy. Whenever steroids are discontinued, symptoms recur in the vast majority of patients because the food antigens causing these symptoms have not been eliminated.

G&H Do pediatric patients have difficulty following dietary therapy?

CL The amount of difficulty depends on how many foods are restricted. When only 2 or 3 foods are restricted, dietary therapy can be easy; when 5 or more foods have to be removed from a patient's diet, following the diet is much harder, and the patient's quality of life decreases. It may be easier to institute aggressive dietary therapy in younger children; as children grow, especially by the time they reach high school and college, they usually want to eat more, and it is more difficult to control their diet.

G&H Since steroids and dietary treatments are approximately equal in efficacy, how is the treatment option selected in each patient?

CL Treatment selection is a group decision; it depends on the experience of the physician and the acceptance of the parents and patient. Over the past 10–15 years, gastroenterologists have treated a large number of pediatric patients with eosinophilic esophagitis. Nowadays, many pediatric patients and their parents read about the disease on the Internet, so they know, for example, that if they choose topical steroids, the treatment may be easy, but it will be lifelong and may involve potential side effects and complications that are still unknown. In contrast, patients and parents know that dietary therapy will be effective and will decrease the need for medication; however, the patient's quality of life may suffer, depending on the type of dietary restrictions.

Often, diet is accepted more often by the parents of younger children in order to avoid the use of medication in these patients. Eosinophilic esophagitis does not spontaneously resolve—it is a lifelong process—so as young patients get older, they may choose to discontinue their restricted diet and try steroid treatment. On the other hand, patients who have been on a long-term treatment regimen of steroids may realize that they will be on chronic medication for the rest of their lives, and they may thus ask to try dietary treatment instead.

G&H Are the same medications being used in adults and children? Are pediatric and adult eosinophilic esophagitis similar?

CL Initially, adult gastroenterologists did not think that adult eosinophilic esophagitis was the same as pediatric eosinophilic esophagitis. However, as more patients are being seen and more studies are being conducted, we are starting to realize that the adult disease is very similar to the pediatric disease. Over time, we have started incorporating the same therapies.

G&H Are there any other options for medical therapy?

CL Other medications, such as montelukast sodium (Singulair, Merck) and cromolyn, have been tried in patients with eosinophilic esophagitis. Although these agents are occasionally effective at producing symptomatic relief, they do not aid in tissue improvement; even with these treatments, eosinophils are still present, and there is still concern regarding ongoing fibrosis and tissue involvement. Therefore, we do not recommend these medications.

G&H Are there any emerging pharmacologic agents currently under investigation?

CL Biologic agents (antibodies that affect different interleukins and chemokines) may help prevent the recruitment or activation of esophageal eosinophils. Anti-IL5 is 1 of the biologic agents being studied; there are currently several ongoing studies examining different agents. Although these agents appear promising, I do not foresee them being used in all patients. Similar to how infliximab (Remicade, Centocor) is used in the treatment of Crohn's disease, these biologic agents will likely be used in a subset of eosinophilic esophagitis patients.

G&H Is esophageal dilation a therapeutic option in pediatric patients?

CL Most children with eosinophilic esophagitis do not usually have narrowed esophageal anatomy or strictures. This is likely because gastroenterologists have done a good job of treating these patients early on—by establishing a diagnosis when the patients had other symptoms, such as reflux—instead of waiting for fibrosis and a food impaction to develop, as may be happening in adult patients with eosinophilic esophagitis. In addition, there is evidence that the use of topical steroids and elemental dietary therapy may be able to reverse esophageal fibrosis

that is already present. Therefore, I always attempt to use either dietary or medical therapy before dilation.

Although dilation improves symptoms, it does not achieve the secondary goal of improving histology and possible tissue fibrosis. With dilation, gastroenterologists have to worry about whether tissue fibrosis will continue to be a concern and cause additional problems. Children rarely require dilation.

In contrast, it is more common for adult gastroenterologists to perform dilations in adult patients with eosinophilic esophagitis because the majority of adults with the disease are not diagnosed until they have esophageal narrowing. Hopefully, as adult gastroenterologists begin to recognize that patients with eosinophilic esophagitis may present with reflux-like symptoms, they will begin to treat them earlier with diet or steroids, which may reduce the development of fibrosis, thereby reducing the need for dilation.

G&H Do all children with this disease require lifelong treatment?

CL Yes, eosinophilic esophagitis is a lifelong disease in the overwhelming majority of patients; to date, very few children and adults (under 5%) have outgrown this disease. Over time, many patients may even develop deeper levels of fibrosis and inflammation, leading to esophageal narrowing and an increase in chronic quality-of-life issues due to the difficulty of ingesting certain solid foods.

G&H How are pediatric patients monitored over the course of this lifelong disease?

CL In general, routine office follow-up visits are required to monitor the symptoms of most patients. An endoscopy and biopsy should also be performed when medication or diet is instituted or changed in order to determine its efficacy. If the patient appears to be doing well and there is no change in the course of treatment, diagnostic testing is not routinely required; however, if symptoms worsen or if patients are not on any therapy, an endoscopy with biopsy should be performed every few years.

G&H What are the next steps for research in pediatric eosinophilic esophagitis?

CL There are currently many ongoing studies in this area being conducted by different specialists (including adult and pediatric gastroenterologists, allergists, and pathologists). One topic of interest is the development of easier, noninvasive diagnostic methods to replace endoscopy and biopsy; genetic testing and different types of markers are being examined for diagnosis and surveillance of eosinophilic esophagitis. Another area of interest involves the evaluation of other medications, such as biologic agents and different preparations of topical steroids. Allergists are conducting various allergy tests to determine whether they can find noninvasive ways of identifying which foods are causing inflammation, as well as whether topical steroids or dietary therapies are more effective for treating chronic fibrosis and long-term effects of the disease. As mentioned previously, these 2 treatments appear to be equal in efficacy; future investigation may finally reveal which treatment is the best.

Suggested Reading

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