

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

Tests for Evaluating Eosinophilic Esophagitis



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G&H How do patients with eosinophilic esophagitis typically present?

JC Eosinophilic esophagitis (EoE) presents differently in the adult population than it does in the pediatric population. In adults, the main symptom of EoE is dysphagia to solid foods. A smaller subgroup of the adult population—approximately 25%—will experience food impaction. In children, symptoms tend to be less specific and more inflammatory in nature, and consist of nausea, food aversion, acid reflux, and abdominal discomfort. Unlike in the adult population, dysphagia is not a key symptom in pediatric patients.

G&H What features differentiate EoE from gastroesophageal reflux disease?

JC EoE is a clinicohistopathologic disorder, which means that certain clinical and histologic criteria must be met in order to make a diagnosis. The main determination is an eosinophil count of 15 per high-power field in conjunction with appropriate clinical symptoms.

There are subsets of gastroesophageal reflux disease (GERD) that can have inflammatory components, in which case a rise in eosinophils will not diagnose EoE. More often than not, though, the number of eosinophils seen in GERD, if any, is typically less than 5 per high-power field. Other histologic features of GERD are changes within the basal membranes and alterations in mast cell expression.

G&H How is a diagnosis of EoE made?

JC A diagnosis of EoE is typically made with endoscopy and biopsy. However, one of the major issues with EoE is that there is no standard method of assessing disease

activity in routine clinical practice other than through biopsies. This means that patients may have to undergo several procedures to confirm the diagnosis, ensure lack of response to proton pump inhibitor (PPI) therapy, and monitor response to therapy. Due to high costs, anesthesia needs, and time off work, this approach is not practical for the majority of patients that are seen.

G&H What is the relationship between EoE and food allergies?

JC It is believed that EoE is a process that is mediated by allergy. In children, food allergy is the most common trigger, and there are several studies that show that pediatric patients on an elemental diet or a strict elimination diet experience decreased inflammation. Studies have not been as robust in adult patients, although it is likely that food allergies remain a common cause in that population as well.

The other question involves environmental allergies. There are several papers that have looked at seasonal variation, which may be environmental in origin. It seems clear that allergy is the main link by which EoE occurs, which is supported by animal models as well. However, the relative breakdown between diet and environment is not entirely clear.

G&H What are the common allergy tests that are performed to evaluate EoE?

JC There are a number of different tests performed for EoE, although there is no firm consensus across health care centers on which test should be performed and when. The most common methods include skin prick testing, blood allergy testing, and food patch testing.

G&H Are there other methods used to evaluate EoE besides allergy testing?

JC The mainstay is endoscopy with biopsy. Barium studies may be performed if there appears to be a complex stricture. pH testing is an option for determining acid reflux vs EoE, although in most cases this method is unnecessary given that PPI trials and biopsies are also involved. Only in limited circumstances should formal reflux testing be performed.

Dietary therapies include the elemental diet, 6-food elimination diet, and allergy-directed diet. These options should be discussed with an allergist.

There are several techniques currently being studied that may provide an alternative to biopsy and endoscopy. The University of Cambridge is developing the Cytosponge, which scrapes tissue from the esophagus and allows the specimen to be analyzed directly. A gene polymerase chain reaction (PCR) array is another method that may allow the clinician to separate disease subtypes and predict response toward therapy, although biopsy tissue is still required for this technique. A few groups have investigated confocal microscopy, which may allow a real-time diagnosis to be made; however, the challenge is that endoscopy is still required, as is a fair amount of training, and confocal microscopy is not readily available. EndoFLIP (Crospon) is a newer technology that measures distensibility and may provide information with regard to prognosis for food impaction but still, at this point, requires endoscopy.

G&H What are the advantages of these tests, as well as their limits?

JC The benefit with endoscopy is that the clinician is able to directly assess inflammation, obtain biopsies, and evaluate for changes within the esophagus. Endoscopy also provides the option of performing potential therapy via dilatation. The main limits with endoscopy are that the procedure requires anesthesia, there is a risk of perforation or discomfort, and it is reasonably expensive and time-consuming.

The Cytosponge may be able to access the same information as endoscopy with regard to inflammatory change without the risk or cost associated with anesthesia; however, it is still in its research phase.

The main benefit of the barium study is that it allows the clinician to stage complex strictures. The downside is that it is neither sensitive nor specific for EoE, and its use is limited to investigating a luminal diameter and evaluating a complex stricture; further, it is not useful in obtaining biopsies or pursuing therapy.

Formal reflux testing has the benefit of clarifying the relationship between acid reflux and EoE, although the challenge associated with this procedure is that there are

patients who do not have documented acid reflux who respond to PPI therapy. Conversely, there are patients who do have documented acid reflux but who do not respond to PPI therapy. Reflux testing is more of an adjunct test within select patients and is not beneficial for everyone.

The advantage of allergy testing is that the identification of a food or a group of foods allows the clinician to tailor a focused elimination diet specifically to the patient. The disadvantage is that the literature shows that food allergy testing does not necessarily correspond with a clinical response toward dietary elimination. Allergy testing is helpful if the result is positive, but if the result is negative, the test does not necessarily exclude a food culprit.

G&H Can these tests be used in both children and adults?

JC The testing described above can be used in both patient populations. Although endoscopy is the mainstay of testing within the adult population, it can be challenging in the pediatric population. At present, however, there is no other means of making this diagnosis or staging disease activity. In children, barium studies typically have limited utility because the main benefit with that technique is to stage complex strictures. The current thought process is that children tend to have more inflammatory symptoms such as nausea and food aversion, whereas adults tend to have more fibrostenotic symptoms such as strictures. Thus, a barium study in a child is a method that would not help much. Barium studies aside, it is possible to use any of the above tests in both populations.

G&H Have there been any long-term studies to examine the reliability of these tests?

JC There are no long-term studies to my knowledge. The upper endoscopy and biopsy methods have been around for a long time. There are studies showing that formal reflux testing is problematic in patients for a variety of reasons, although that may be an issue of the study itself being unreliable. It is more that the acid reflux/EoE relationship is gray. For allergy testing, there certainly is a discordance between which foods patients respond to in a food elimination diet and the results found from testing. I do not think it is an issue of unreliability, but that specific mechanisms, which are looked at via conventional food testing, may be different from the underlying mechanisms that present in EoE.

G&H How do these tests compare in cost and reimbursement?

JC Endoscopic biopsy is a reasonably expensive procedure; however, it is the only test currently available that evaluates

disease activity directly and is covered by most insurance plans. Allergy testing is recommended by the current consensus guidelines and, within Maryland, is covered by insurance plans. Barium studies and formal reflux testing are also covered within Maryland, although they are best used to test dysphagia and acid reflux, respectively. The Cytosponge is still, at this point, investigational; therefore, it is not commercially available or covered by insurance.

G&H Are there other emerging tests currently being studied?

JC The main procedures being studied right now are the Cytosponge and the 96-gene PCR array, in which the gene expression within the esophageal tissue is investigated. Studies of this latter method have shown that patients with EoE can be separated from patients with GERD and from patients who present without symptoms. This test may be able to predict who is likely to respond to one therapy vs another, as well as detect patients in remission from patients who are not. Although this test is not yet commercially available, there is a fair amount of interest within the medical community to develop it further.

Another test is transnasal endoscopy; instead of using anesthesia and entering the mouth, a thin endoscope is placed through the back of a numbed nose into the esophagus. The biopsy would provide the same information as a standard endoscopy, but without the risk of anesthesia and requiring the patient to take time off from work.

G&H What are the priorities for research in this field?

JC There are 4 main priorities for research. The first is to better define the underlying mechanism of EoE. The term *eosinophilic esophagitis* was derived from the fact that eosinophilic cells are ubiquitously present on pathology; however, it is unclear if eosinophils are the cause of the symptoms or if they are merely the marker and some other process is present. Without knowing the exact mechanism that is at play, prescribing a therapy is difficult.

The second priority is to investigate why this disorder appears to be increasing as quickly as it is. The first case of

EoE was reported in 1977, but it seems that its prevalence is currently skyrocketing, and the reasons are not entirely clear. More research might reveal if pollution, a change in the microbiome, dietary adjustment, or chemicals and pesticides play a role—or if it is something else entirely.

A third priority is the development of noninvasive biomarkers. Currently, the only way to assess disease activity is with an endoscopic biopsy. This poses problems in terms of the need for sedation, the cost of the procedure, the time off from work, and the risks and possibly the discomfort associated with the procedure. Ideally, a blood-based biomarker would be perfect—something to assess disease activity that would make approaches such as diet easier because there would be something to follow up on. If there was a way to look at a genetic code or expression and understand what the patient is most likely to respond to, it may allow the clinician to customize therapy accordingly instead of going down a pathway of diet or corticosteroids or some mixture of the above.

Finally, the fourth priority is to develop more customized therapy. The therapies that are currently available are very general. If we knew specifically which pathway was involved, it may allow us to tailor a therapy based on certain pathways or certain cellular mechanisms. It may be that EoE does not present in the same pathway in each patient, and knowing the mechanisms would allow for better treatment options.

Dr Clarke has no relevant conflicts of interest to disclose.

Suggested Reading

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