



Optimizing Treatment in the Underdiagnosed Eosinophilic Esophagitis: An Interactive Guide

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Clinical Presentation

When looking at the clinical presentation of eosinophilic esophagitis (EoE), I think it's important to recognize that there are phenotypic differences between children and adults. For toddlers and young children, symptoms are dominated by feeding difficulty, vomiting and regurgitation, failure to thrive, coughing after eating and abdominal pain. These symptoms can be fairly nonspecific. For older children, symptoms are dominated by abdominal pain, chest pain and epigastric pain, reflux-like presentations, vomiting and also symptoms of dysphagia and food impaction. And then, going on through adolescents and adults, the symptoms become quite characteristically dominated by dysphagia, food impaction and, less commonly, heartburn or chest pain.

Looking at the histopathology, we all focus on the eosinophil density or the number of eosinophils per high-power field with the diagnostic threshold set at 15 or greater eosinophils per high-power field. However, it is important to recognize there's a lot more going on than simply the eosinophil density. Some of the other important histologic features are listed here, and these include basal zone hyperplasia, dilation of intercellular spaces, elongation of vascular papillae, eosinophilic microabscess formation and lamina propria fibrosis. These additional characteristics have been put into a scoring system called the EoEHSS, which has been developed by Margaret Collins at Cincinnati Children's Hospital. You'll see the EoEHSS being used in a number of clinical trials, going forward, and be listed as a secondary or exploration endpoint.

Endoscopically, there are several endoscopic characteristics that have been well-described in eosinophilic esophagitis. The vast majority of children and adults with EoE have endoscopic features that include edema, rings, exudate, furrows and stricture formation.

A number of studies have shown us about the natural history of eosinophilic esophagitis. We know eosinophilic esophagitis is not only a chronic condition, but a chronic and progressive disease that

leads, over time, to remodeling and fibrosis of the esophagus. If we look at the normal esophagus, we can interrogate this both endoscopically and histologically.

Endoscopically, the esophageal mucosa is bland, with bright vascular markings, and histologically, in the normal setting, there are no eosinophils in the squamous epithelium.

In early stages of eosinophilic esophagitis, inflammation is the hallmark. We can detect this endoscopically by the presence of edema, furrows and exudate and histologically, by dense esophageal eosinophilia.

Over time, there's progressive fibrosis of the lamina propria that leads, over time, to stricture formation and the narrow caliber esophagus.

This type of natural history presentation helps us to understand many of the phenotypic differences between children and adults, where children are presenting with an inflammatory phenotype and adults with a mixed inflammatory and fibrostenotic phenotype.

This type of model also helps us understand the role of therapeutic intervention where, early on, we're using anti-inflammatory-based therapies and dietary therapies and, with later stages of disease, treatment includes not just the medical therapy and dietary therapies, but also esophageal dilation to address the strictures of the esophagus.

Under- and Misdiagnoses

Underdiagnoses, misdiagnoses and delayed diagnoses are common in the eosinophilic esophagitis and there are several reasons for this. First of all, the symptoms, particularly in children, can be nonspecific and often occur with extraesophageal manifestations. In addition, patients often develop adaptive behaviors that obscure their symptoms of EoE.

These adaptive behaviors can be summarized by the acronym IMPACT, with I standing for imbibing fluids

with every meal, particularly solid food; M modifying food by cutting it up into small pieces or pureeing the foods; P for prolonging mealtimes; A for avoiding harder texture foods; C for chewing excessively; and T for turning away tablets or pills.

Performing mucosal biopsies in patients with food impaction or other foreign bodies is an important missed opportunity for the diagnosis of EoE by many clinicians. Several studies have now shown that it's the minority of patients who have food impactions or foreign body impactions where esophageal biopsies are obtained. By not obtaining a biopsy at the time of a food impaction, we're having, we're missing an important opportunity to establish a diagnosis of eosinophilic esophagitis.

Making an early diagnosis of EoE is extremely important. EoE, again, is a chronic disease with chronic inflammation leading over time to progressive fibrosis, remodeling and stricture formation. These strictures are then what drives the important complications of EoE that include food impaction, the need for esophageal dilation and put patients at risk for esophageal perforation risk.

Treatment Planning

Let's now turn to shared decision-making in eosinophilic esophagitis. Shared decision-making may be described as a process by which providers and patients work together to decide about interventions based on clinical evidence and the patients' informed preferences. Because the ideal management strategy in EoE is not established and each treatment approach confers both advantages and disadvantages, shared decision-making is recommended.

Factors that can affect treatment selection include the efficacy of the treatment, ease of administration, cost, patient preference, quality of life, long-term effects and disease severity.

Looking at medication options, and this would include both proton pump inhibition and swallowed topical corticosteroids, advantages include a relatively short response time and ease of administration. Disadvantages include scarce long-term data about the effectiveness and safety, the fact that these medications are currently being used off-label, particularly for swallowed topical corticosteroids. Off-label use can be expensive

when medications are not covered by insurance. There are also potential long-term adverse effects, particularly of swallowed topical corticosteroid use, that are being actively investigated in prospective studies.

Currently in the United States, we do not have a readily available esophageal formulation.

Moving on to dietary therapy, advantages include the ability to use medication-free disease control. Disadvantages include the adherence problems with a strict diet. Many patients do not want to avoid common table foods, like milk, wheat, soy or egg, on a long-term basis. With elimination diets, there's a need for repeated endoscopies during the food reintroduction process to identify a specific food trigger. The repeated endoscopies require both time and expense for our patients. Finally, these types of dietary approaches can be difficult to administer in children and adolescents.

What about esophageal dilation? Dilation is now being viewed as both safe and extremely effective. It alleviates symptoms of dysphagia in over 90% of patients, however there are important disadvantages to consider. There is post-procedural chest pain which can occur in over 70% of patients who undergo an esophageal dilation. There's a need for periodic re-treatment where dilations had to be repeated. Finally, although we, again, think dilation is quite safe in 2022, there is small, but finite, risk of complications that can include esophageal perforation and a need for hospitalization due to post-procedural pain. The other disadvantage of esophageal dilation as monotherapy is that dilation does not address the underlying inflammatory process that caused that stricture to form in the first place.

Now, looking at combination therapy, we have limited data on the role of combination therapy for eosinophilic esophagitis. We need more data! But there are examples of situations where combination therapy can be appropriate. For patients that have eosinophilic esophagitis, and have concomitant gastroesophageal reflux disease manifested by erosive esophagitis, Barrett's esophagus or significant heartburn, these patients typically benefit from combining antireflux therapy, a PPI or H2 blocker combined with medical therapy or dietary therapy directed against their eosinophilic esophagitis.



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In addition, in my own practice, I do combine the use of swallowed topical corticosteroids with PPI therapy in those patients who show me a partial, but incomplete response to PPI therapy alone. For example, patients may show you a reduction in their esophageal eosinophilic count from 75 Eos per high power field down to 20 or 25 Eos per high power field. So, it's an improvement but not normalization. In those situations, I will typically add the swallowed topical steroid on top of the PPI therapy.

Finally, for any type of medical or dietary therapy, dilation can be considered a type of combination therapy where we're adding dilation on top of an effective medical or dietary therapy, with dilation addressing the stricture or remodeling consequences of disease.

Additional special situations to consider include those that may require you to deviate from the standard treatment approaches for eosinophilic esophagitis. We've already talked about patients that have EoE with concomitant GERD, but there are also EoE patients who have concomitant eosinophil gastrointestinal disease below the diaphragm. That is, patients who have eosinophilic gastritis, enteritis or colitis. These patients may require more than therapies that are targeting the esophagus. They may require systemic therapies or dietary therapies to provide a more global relief of their allergic inflammation.

In addition, there are EoE patients that have IgE-mediated food allergy that is in addition to their eosinophilic esophagitis. They may have oral allergy syndrome or food-related anaphylaxis. These patients can require elimination of foods for different reasons, both for their EoE and for their IgE-mediated food allergy.

For patients that have multiple food allergies, that is IgE-mediated food allergies, I find that further elimination diets can be very cumbersome and difficult for these patients to adhere to because now you're asking this patient to eliminate more and more foods from their diet, making their lifestyle quite difficult.

I'm not going to go through all these different special situations, but one other circumstance to keep in mind are EoE patients that have concomitant inflammatory bowel disease. This is an increasingly recognized condition where patients have 2 of these GI disorders and we have to consider the use of medical therapeutics that might address both their IBD and their EoE.

So, topics that we've summarized here, and key considerations for treatment planning, include the role for shared decision-making for the management of eosinophilic esophagitis, consideration of factors that affect treatment selection, both the pros and cons of each different treatment approach, scenarios that warrant the use of combination therapies, and these special situations that warrant modifications or deviations from our typical standard of care approach.

Case 1

So, our first case is a missed opportunity and a possible diagnosis. This is a 35-year-old woman who presents to the ER with a food impaction. Three hours earlier, she was eating dinner and noted suddenly that she could not swallow her food. She attempted to drink water to wash down the food, but only regurgitated the water and not the food. In the ER, she's noted to have difficulty handling her saliva and is drooling.

As we see on the endoscopic image, there is a food impaction with a food bolus stuck in the esophagus with endoscopic features of eosinophilic esophagitis. The food was successfully disimpacted in the emergency room and the patient was discharged to home.

Three years later, the patient presented to her primary care physician with complaints of difficulty swallowing. She noted, at that time, that she needed to cut up her food into very small pieces, to sip water after taking each 1 to 2 bites of food, and that it took her approximately 1 hour to complete a meal, all of which helped her to alleviate her symptoms. But in spite of these adaptive eating behaviors, she's now presenting with progressive dysphagia.

Her primary care physician ordered an upper endoscopy with biopsy, and the findings, as depicted here, are quite characteristic for eosinophilic esophagitis with the endoscopy demonstrating the endoscopic features of edema, rings, furrows and exudate of the esophagus and histopathology showing dense esophageal eosinophilic infiltration of the squamous epithelium.

Now, this case demonstrates very clearly a missed opportunity. When the patient presented 3 years earlier to the ER and had that upper endoscopy, she really should've had an endoscopic biopsy. That would've established at that time point the diagnosis of eosinophilic esophagitis. The patient had classic symptoms of EoE with dysphagia and food impaction. She had classic endoscopic features of EoE, but unfortunately the histopathology was not obtained so she did not have an established diagnosis of EoE without histopathologic confirmation.

This is something that we're seeing very commonly in clinical practice, where biopsies are not done at the time of the ER food impaction. The reasons for this are not entirely clear. It may be that these cases are being done late in the evening or in the middle of the night. It may be that the diagnosis was not entertained at the time, or sometimes there are concerns that the patient had had a complication of a food impaction and there are concerns that you don't want to prolong the procedure by getting biopsies. However, once you've alleviated the food obstruction by doing successful endoscopic disimpaction, there is very little risk to doing biopsies. Biopsies take only 2 to 3 minutes to obtain and, again, this would help to establish a diagnosis and not delay that patient's need for further testing.

Also in this particular case, you'll notice that the patient then presented 3 years later to her primary care doctor. In that 3-year interval, she's had progressive disease. She's developed worsening symptoms. She's required more adaptive behaviors, the impact behaviors that try to alleviate her symptoms. So, there was a missed opportunity that

led to progression of disease, progressive remodeling of the esophagus and stricture formation.

Case 2

Our second case represents a patient with EoE with refractory disease. This is a 45-year-old man with a past medical history significant for allergic rhinitis, atopic dermatitis and eosinophilic esophagitis who presents to his primary care physician with complaints of worsening dysphagia. Five years earlier, he presented to an ER with a food impaction. The food was disimpacted and biopsies were collected. Esophageal rings, furrows and narrow caliber esophagus were noted, and biopsies demonstrated 80 eosinophil per high-power field. So clearly in excess of the diagnostic threshold of 15 or greater eosinophils per high-power field.

Endoscopically, we see the characteristic features of edema, rings, furrows and a narrow caliber esophagus.

The patient, appropriately, was given swallowed topical corticosteroids. Again, this is an example where we're going to use shared decision-making. Discuss with the patient that different therapeutic options that include swallowed topical corticosteroids, proton pump inhibition and dietary elimination. In this particular scenario, the patient was given swallowed topical steroids with budesonide. However, in spite of the use of the medication, the patient had a follow-up upper endoscopy and the biopsies demonstrated persistent endoscopic features of eosinophilic esophagitis and biopsies show 70 eosinophils per high-power field.

The patient underwent an esophageal dilation at that follow-up upper endoscopy. So, in this particular scenario, minimal histologic improvement. The biopsies went from 80 Eos down to 70 Eos per high-power field and the patient demonstrated persistent endoscopic features and a stricture that required dilation.