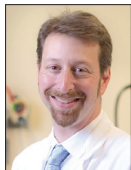


# ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: John Baillie, MB ChB, FRCP

## Treating Eosinophilic Esophagitis in Patients With a Narrow-Caliber Esophagus



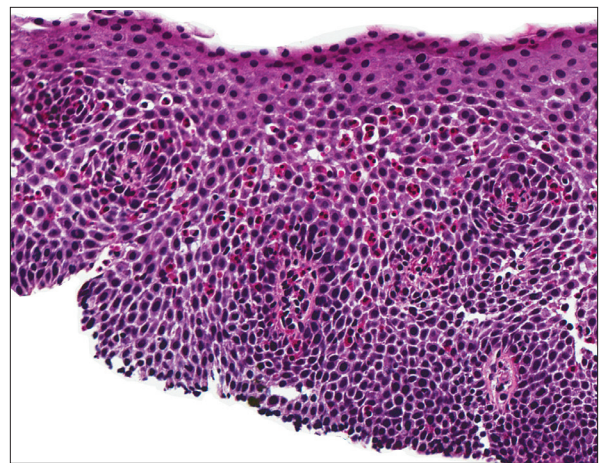
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**G&H** How do the signs and symptoms of eosinophilic esophagitis differ between a patient with a regular-caliber esophagus compared with a narrow-caliber esophagus?

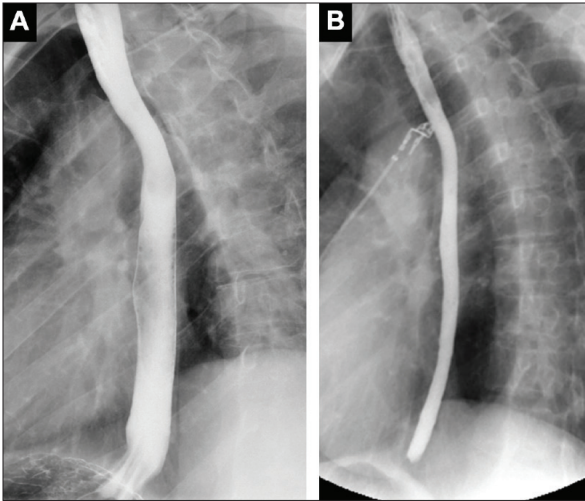
**ED** The signs and symptoms of eosinophilic esophagitis (EoE) can differ according to the age of the patient. The hallmark symptoms for adults and adolescents are dysphagia and food impaction. In younger children, dysphagia is much less common and the symptoms are nonspecific; children may present with heartburn, vomiting, regurgitation, and abdominal pain, and younger children may have failure to thrive or feeding intolerance.

Endoscopically, EoE presents with multiple signs that differ between adults and children. Esophageal rings, strictures, and mucosal fragility, which tend to be signs of esophageal remodeling and fibrosis, are more common in adolescents and adults and, more specifically, in patients who have had longstanding symptoms of EoE before being diagnosed. Children typically have more inflammatory findings, such as edema, linear furrows, and white plaques or exudates, which are thought to indicate eosinophilic microabscesses. A small proportion of patients, especially children, may have an endoscopically normal esophagus and require findings of eosinophils on biopsy to diagnose EoE. It is important to note that these signs are not fully specific, but are more common in EoE than in other conditions.

Histologically, adults and children present fairly similarly. Patients have a marked eosinophilic infiltrate, which for diagnosis of EoE has to be at least 15 eosinophils per high-power field (Figure 1). Additionally, there are associated histologic findings, such as eosinophil microabscesses, surface layering, basal-zone hyperplasia, spongiosis or dilated intercellular spaces, and lamina propria fibrosis. All of these findings can be seen in any patient with EoE.



**Figure 1.** An esophageal biopsy (40× magnification, hematoxylin and eosin stain) in a patient with eosinophilic esophagitis showing diffuse infiltration of the epithelium by eosinophils, prominent basal-zone hyperplasia, and spongiosis.



**Figure 2.** Radiographic images of a regular-caliber esophagus in a patient with gastroesophageal reflux disease (A) and a narrow-caliber esophagus in a patient with eosinophilic esophagitis (B).

Reproduced from Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. *Gastroenterol Clin North Am.* 2014;43(2):297-316.

Narrow-caliber esophagus (Figure 2), which has actually been noted to be an endoscopic finding of EoE for quite some time, tends to be more common in adults. These patients have a diffusely narrowed esophagus or a very tight series of strictures and, therefore, often present with much more prominent dysphagia and food impaction-type symptoms clinically. Strictures and narrowing will appear endoscopically (Figure 3), and the histologic features remain similar between this subgroup and the more standard phenotype of EoE.

### G&H What is the diameter of a pediatric endoscope used to move within a narrow esophagus?

**ED** The exact diameter of a pediatric endoscope varies by manufacturer; however, in general, the diameter is approximately 5 to 6 mms, if not slightly smaller. In comparison, the diameter of adult endoscopes is 8 to 10 mms, depending on the manufacturer and the model.

### G&H Could you please describe the design and key findings of your study on this issue?

**ED** My colleagues and I conducted a retrospective cohort study, led by Dr Swathi Eluri, of 513 pediatric and adult EoE patients at the University of North Carolina. We divided the patients into 2 groups, defined endoscopically. One group had a regular-caliber esophagus (in whom an



**Figure 3.** An endoscopic image of a narrow-caliber esophagus showing prominent rings, edema, subtle furrows, and diffuse narrowing, requiring the use of a neonatal endoscope.

adult endoscope could pass without any difficulty or tissue injury), and the other had a narrow-caliber esophagus. Patients in the narrow-caliber group required the use of a smaller, pediatric endoscope, either due to a very tight but focal stricture or because of a diffusely narrowed esophagus. In general, the narrow-caliber phenotype was comprised more of patients with a diffusely narrowed esophagus rather than a focal, tight stricture. In our study, we found that 46 of the 513 patients (9%) had a narrow-caliber esophagus. Interestingly, patients with a narrow-caliber esophagus tended to be more than 10 years older than those with a regular-caliber esophagus. Accordingly, there were fewer children in this group; only 6 of the 46 patients were under the age of 18 years.

Clinically, dysphagia was essentially universal in the narrow-caliber group, and more than half of these patients presented with food impaction, compared with approximately 30% of the regular-caliber patients. We found that the symptom length before diagnosis of EoE was much longer in the narrow-caliber group than in the regular-caliber group (11 years vs just under 3.5 years, respectively), which indicates that this phenotype has longstanding symptoms and likely enough time for the esophagus to be remodeled and develop scarring and diffuse fibrosis. Atopic diseases, sex, and race were similar between the 2 groups.

Endoscopically, the narrow-caliber group was much more likely to have esophageal rings and strictures, and 100% of the patients in this group underwent dilation, compared with 26% of patients in the regular-caliber group. This makes sense, as the former is a group of patients who have a high degree of strictures, narrowing, and esophageal remodeling. Interestingly, when we looked at

biopsies, there was no difference in the histologic features and eosinophil counts. Thus, the distinguishing features are in the patient's history and endoscopy.

### **G&H** How do treatment responses differ between the 2 subgroups of EoE?

**ED** The treatment responses between the 2 subgroups were actually quite different. We assessed the patients' data at baseline, noted the treatment they received, and then followed up by evaluating their posttreatment data, primarily looking at topical corticosteroids. In general, the treatment approach for the 2 subgroups was the same (ie, some type of anti-inflammatory treatment, either topical corticosteroids or dietary elimination, and then esophageal dilation if strictures were present). However, the treatment response, measured in a number of ways, was worse in the narrow-caliber group than in the regular-caliber group. Treatment outcomes included whether patients felt better (their global symptom response), whether they had an improvement in endoscopic findings, and whether their eosinophil counts dropped below 15 per high-power field (histologic response). For all of these outcomes, the response was much lower in the narrow-caliber group, and this low response persisted even after we conducted a multivariate analysis accounting for other possible confounding factors. Specifically, the odds of either symptomatic, endoscopic, or histologic response in the narrow-caliber group were less than a third compared with the regular-caliber group. That this narrow-caliber phenotype appears to be treatment-resistant was one of the really interesting findings of this study, and this was not necessarily known before.

### **G&H** What are the challenges of managing narrow-caliber EoE?

**ED** There are a couple of challenges to managing this phenotype. One is trying to identify a therapy that helps reduce eosinophil count and normalizes the appearance of the esophageal mucosa. There are not many treatment options for patients who do not respond to topical corticosteroids or dietary elimination. Several treatments have been studied, such as montelukast (a leukotriene receptor antagonist), cromolyn (a mast cell stabilizing agent), 6-mercaptopurine, infliximab (Remicade, Janssen), and omalizumab (Xolair, Genentech); however, none of these are particularly effective. The University of North Carolina previously published results of a study showing that only approximately half of all patients who fail to respond to first-line treatment will respond to one of these second-line agents. Thus, there is a significant difficulty in finding a therapy that will work.

Another challenge relates to the dilation and treatment of the fibrotic component of EoE. When a patient has such a diffusely narrowed esophagus, numerous endoscopic dilations are required, which is burdensome for the patient. Undergoing dilations in the short term opens up the esophagus and aids with symptomatic response, but the procedure does not impact the underlying inflammation or pathophysiology. If the inflammation cannot be controlled, strictures are likely to recur, and more dilations will be needed in the future.

### **G&H** How are strictures dilated in a narrow-caliber esophagus?

**ED** Several approaches exist for dilating strictures in patients with a narrow-caliber esophagus. Because a narrow esophagus requires the use of a pediatric scope, the through-the-scope balloon system cannot be readily used. In my own practice, I typically use wire-guided bougie dilation to effectively dilate the entire esophagus for patients with this phenotype. If the neonatal endoscope passes with resistance, or if there is concern about the diameter, it is best to start with either a 5-mm or a 7-mm bougie and, after every bougie pass, to check for any tears or rents in the mucosa that indicate an effective dilation. If the bougie passes through and there is no disruption in the mucosa, then a dilation has not been performed and the next larger size bougie should be used.

There are also wire-guided balloons that can be used. In this procedure, a wire is passed through the endoscope and a balloon is then passed over the wire. The endoscope is placed and the balloon dilation can be performed under direct vision. Alternatively, fluoroscopy can be used for these procedures, but it is not always necessary.

### **G&H** Is there an increased risk of perforation or bleeding when dilating these strictures?

**ED** Perforation is a concern and possible risk; however, data have emerged over the last 5 to 6 years showing that, in general, dilation is fairly safe in EoE. The risk of perforation is likely around 3 per 1000, which is very close to the rates that are quoted for dilation in non-EoE-related strictures. With a careful approach, dilation can be performed quite safely without perforation. However, there are prospective studies that show that approximately three-quarters of patients with EoE who undergo dilation will experience some degree of chest discomfort after the procedure, and sometimes the discomfort can be quite severe. Therefore, it is best to discuss this procedure with patients and, in certain cases, to prescribe analgesics.

## G&H Should patients with narrow-caliber EoE be managed in a specialist center?

**ED** A specialist center is not necessary as long as an endoscopist is familiar with using a pediatric or neonatal endoscope and is comfortable performing endoscopic dilation in EoE patients. If the dilation cannot be performed and the esophagus cannot be fully assessed, if all treatment options have been exhausted, or if there is interest in a clinical trial, the patient should be referred to a specialist center.

## G&H What role do corticosteroids play in managing a narrow-caliber esophagus?

**ED** For EoE in general, corticosteroids are the first-line pharmacologic agent for treatment, and usually these are asthma medications that are adapted for EoE (eg, fluticasone, often in a multidose inhaler form, or the aqueous form of budesonide mixed into a slurry). Patients swallow these medications rather than inhale them in order to coat the esophagus. Overall, the majority of patients may respond to this medication class. However, our study found that only 52% of patients with a narrow-caliber esophagus had a histologic response to the topical corticosteroids vs approximately 76% of patients with a regular-caliber esophagus. This is important because patients with a narrow-caliber esophagus need to know that their particular phenotype may be more treatment-resistant compared to patients with a regular-caliber esophagus.

## G&H What are the next steps in research in this field?

**ED** One area of research is a more in-depth look at different treatment options to attempt to optimize response in EoE patients with this phenotype. The majority of patients in our study were treated with the standard dose of topical corticosteroids (approximately 1760 µg of fluticasone or 2 mg of budesonide/day), but it is unknown whether the response rates might have been better if those doses were higher. We had a small population with the narrow-caliber phenotype who underwent dietary elimination, and that is another treatment option that could be researched further. In addition, there are quite a number of novel treatments for EoE that are being developed and

that are in clinical trials. It would be useful to target this population of patients with these novel treatments, especially if they are antifibrogenic.

Another step is to look more in detail into the phenotype itself. The mechanisms of why some patients develop this phenotype and others do not—whether it is related to time before diagnosis or if different genes are expressed in the esophagus—are not understood. It is also unknown to what degree this is a transmural process; therefore, studying esophageal compliance, evaluating the contribution of dysmotility to symptoms in patients with a narrow-caliber esophagus, and utilizing endoscopic ultrasound to assess wall thickness could be very interesting.

Lastly, more research needs to be done on the long-term outcomes in this patient subgroup, particularly regarding dilations.

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## Suggested Reading

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