# The extremely narrow-caliber esophagus is a treatment-resistant subphenotype of eosinophilic esophagitis

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**Background and Aims:** Some patients with eosinophilic esophagitis (EoE) have an extremely narrow esophagus, but the characteristics of this group have not been extensively described. We aimed to characterize the narrow-caliber phenotype of EoE, determine associated risk factors, and identify differences in treatment response in this subgroup of patients.

**Methods:** This retrospective cohort study from 2001 to 2014 included subjects with a new diagnosis of EoE per consensus guidelines. Demographic, endoscopic, histologic, and treatment response data were extracted from medical records. An extremely narrow-caliber esophagus was defined when a neonatal endoscope was required to traverse the esophagus due to the inability to pass an adult endoscope. Patients with and without an extremely narrow-caliber esophagus were compared. Multivariable logistical regression was performed to assess treatment outcomes.

**Results:** Of 513 patients with EoE, 46 (9%) had an extremely narrow-caliber esophagus. These patients were older (33 vs 22 years; $P < .01$), had longer symptom duration (11 vs 3 years; $P < .01$), more dysphagia (98% vs 66%; $P < .01$), and food impactions (53% vs 31%; $P < .01$). Dilation was more common with extreme narrowing (69% vs 17%; $P < .01$). Patients with a narrow-caliber esophagus were more refractory to steroid treatment, with lower symptom (56% vs 85%), endoscopic (52% vs 76%), and histologic (33% vs 63%) responses ($P < .01$ for all), and these differences persisted after multivariate analysis.

**Conclusion:** The extremely narrow-caliber esophagus is a more treatment-resistant subphenotype of EoE and is characterized by longer symptom duration and the need for multiple dilations. Recognition of an extremely narrow-caliber esophagus at diagnosis of EoE can provide important prognostic information. (Gastrointest Endosc 2016;83:1142-8.)

Eosinophilic esophagitis (EoE) is a chronic antigen-mediated disease characterized by a dense eosinophilic infiltrate and esophageal dysfunction.[1] With the increasing prevalence of EoE over the past decade, there has been a greater understanding of the variability in disease manifestation.[2-6] It is well established that adults and children have

*Abbreviations: CI, confidence interval; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; OR, odds ratio; UNC, University of North Carolina.*

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different clinical presentations.[7-9] Children commonly present with difficulty feeding, vomiting, heartburn, and abdominal pain, whereas adults typically have symptoms of dysphagia, strictures, and food impactions.[10-13] It is unknown whether these symptomatic differences represent distinct phenotypes of EoE or a progressive disease course that evolves from an inflammatory to a fibrostenotic stage in a time-dependent manner.[14]

Distinct clinical and endoscopic features differentiate inflammatory and fibrostenotic EoE phenotypes.[15] Inflammatory changes on endoscopy manifest as white exudates, linear furrows, and edema, and patients typically present with symptoms such as nausea and abdominal pain.[15,16] Patients with fibrotic features experience dysphagia and tend to have rings, strictures, and crepe paper mucosa on examination.[10] In addition, approximately 10% of EoE patients have a diffusely stenotic esophagus described as a narrow-caliber or small-caliber esophagus.[1] This can be characterized as a narrowed esophagus with a fixed internal diameter that can either extend the entire length of the esophagus or skip segments,[13,17] which differs from a stricture that is focal.[17] Although the narrow-caliber esophagus has been recognized as a distinct manifestation of EoE previously, the features of this group of patients has not been described in detail. Currently, there is no standardized definition of a narrow-caliber esophagus, and it is unknown whether it represents a new subphenotype of EoE.

The primary aim of this study was to characterize EoE patients with a narrow-caliber esophagus, determine associated risk factors, and identify differences in treatment response to topical steroids for this subgroup. Based on clinical experience, we hypothesize that the extremely narrow-caliber esophagus is a distinct EoE subphenotype and is associated with older age, longer disease duration, and treatment-resistant disease compared with patients with a regular-caliber esophagus.

## METHODS

### Study design, study population, and data source

This was a retrospective cohort study conducted at the University of North Carolina (UNC) by using the UNC EoE clinicopathology database from 2001 to 2014. The development and characteristics of the database were previously reported.[15,18,19] All subjects included in the study were patients at UNC with an incident diagnosis of EoE who met consensus diagnostic guidelines,[1,20,21] including symptoms of esophageal dysfunction, ≥15 eosinophils per high-power field (eos/hpf) (hpf area = 0.24 $mm^2$), nonresponse to a proton pump inhibitor trial, and exclusion of competing causes. EoE patients were categorized as having an extremely narrow-caliber esophagus if the endoscopy report documented a requirement to use a neonatal endoscope (<6 mm diameter) to traverse the esophagus due to the inability to pass an adult upper endoscope secondary to narrowing (Fig. 1). Cases of EoE that allowed passage of an adult upper endoscope despite a decrease in esophageal luminal diameter are referred to as regular caliber for the purposes of this study. Of note, focal esophageal strictures could be present in either group. The study was approved by the UNC Institutional Review Board.

Data were abstracted from the UNC electronic medical records, endoscopy reports, and pathology reports. Patient demographic characteristics, symptom characteristics and duration before diagnosis, history of atopic disease, and food allergy (documented by presence of allergic symptoms with reintroduction of a food or by testing directed by an allergist) were collected. Endoscopic findings included the presence of rings, linear furrows, white plaques or exudates, decreased vascularity, crêpe-paper mucosa, strictures, and therapeutic interventions such as dilations. For histologic data, the maximum eos/hpf (hpf area = 0.24 $mm^2$)[22] was used, as determined by pathologist review of biopsy samples. Finally, data on topical corticosteroid treatment, prescribed at the discretion of the gastroenterologist, were recorded. Steroid treatment at our institution consisted of an 8-week course of budesonide (0.5-1 mg twice daily mixed into a slurry with 5 g sucralose)[23,24] or fluticasone (440-880 μg twice daily).[25] Subjects were treated exclusively with topical steroids and did not receive concomitant dietary therapy. All subjects who completed an 8-week course of topical steroid treatment with either budesonide or fluticasone were evaluated for treatment effect.

### Definition of measures

In addition to characterizing the features of the narrow-caliber esophagus, 3 outcomes were also extracted from medical records to assess the response to an 8-week course of topical corticosteroid treatment. Symptom response was defined as a subjective patient report of global improvement of previous symptoms (such as dysphagia, food impaction, abdominal pain, nausea, vomiting, heartburn, chest pain, failure to thrive) characterized as yes or no. Endoscopic response was defined as the resolution of previously present features such as rings, furrows, and plaques. Finally, histologic response was defined as achieving an eosinophil count of <15 eos/hpf after a completed course of steroid treatment.

### Statistical analysis

Descriptive statistics were used to examine subject characteristics, and bivariate analyses were performed to determine the relationship between each independent variable and the presence of an extremely narrow-caliber esophagus, by using the Student $t$ test and Wilcoxon rank sum for continuous variables and the Pearson $\chi^2$ tests for