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## Narrow-caliber esophagus of eosinophilic esophagitis: difficult to define, resistant to remedy

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The narrow- or small-caliber esophagus was one of the earliest recognized manifestations of eosinophilic esophagitis (EoE) in adults.<sup>1–3</sup> Narrow-caliber esophagus is not a specific indicator of EoE and can arise secondarily to radiation injury, long-segment Barrett's esophagus, caustic injury, lichen planus, and prolonged nasogastric-tube placement. Although a standardized definition does not exist, the entity of the narrow-caliber esophagus involves 2 components: radial narrowing and longitudinal extent. The requisite degree of narrowing provides the first point of discussion. The inability to pass an upper endoscope (thus, an esophageal diameter < 8–10 mm for an adult endoscope or <5–6 mm for a pediatric endoscope) provides an objective and readily generalizable measure; however, the inability to pass an endoscope excludes patients with less-severe esophageal stenosis that remains clinically significant. Thus, a gradation associated with the dysphagia (13 mm, as suggested by studies of Schatzki rings) and/or the risk of food impactions (17 mm) may represent a more clinically relevant threshold.<sup>4,5</sup> The second point of discussion remains the longitudinal extent of narrowing required. The length of reduced aperture required for a definition of narrow-caliber esophagus is more difficult to ascertain, given a lack of clinical data from which to draw and the need to differentiate from focal strictures.<sup>6</sup> An arbitrary definition is to require narrow-caliber esophagus to span the majority of the length of the esophageal body. Combining the 2 parameters, narrow-caliber esophagus might be defined by a reduction in esophageal diameter of less than 18 mm for greater than 50% of the length of the esophagus.

With this operational definition in mind, the method used to objectively identify the narrow-caliber esophagus becomes relevant. Although upper endoscopy is a widely used, first-line evaluation for esophageal dysphagia, endoscopy is limited in its ability to accurately define esophageal diameter.<sup>7</sup> On a practical level, endoscopy cannot estimate the length of narrowing when passage of the endoscope is prohibited by the degree of stenosis. The length of trauma observed with endoscopy after bougie dilation may provide a more objective finding of both the length and diameter, although it is limited by the obvious requirement to perform dilation.<sup>2</sup> The barium esophagram can objectively identify both stenosis diameter and extent, whereas the addition of a barium tablet of a known diameter can improve quantitative accuracy. However, the barium esophagram is limited by the inability to control for intraluminal distension pressure, variability because of extrinsic compression by mediastinal structures, and infrequent utilization given the widespread adoption of endoscopy. Another more recently available option is the functional lumen-imaging probe (FLIP), which uses a distensible, fluid-filled bag to simultaneously measure luminal

diameter with pressure related to esophageal distension. Use of the FLIP in EoE has demonstrated utility in identifying patients at risk for adverse outcomes of food impaction and thus may offer an improved, objective method to identify and define narrow-caliber esophagus at the time of upper endoscopy.<sup>5,8</sup> Local availability and familiarity limit the current adoption of the FLIP to general clinical practice. At present, we advocate a multifaceted approach to identify and classify EoE patients with narrow-caliber esophagus that acknowledges limitations to currently available diagnostic modalities.

Although a reduced symptom response is intuitive, the histologic response to steroids in patients with extreme narrow-caliber esophagus was approximately half that found in patients with regular-caliber esophagus.

In the present issue, Eluri et al<sup>9</sup> performed a retrospective, case-control study of patients with EoE and an “extreme narrow-caliber” esophagus defined by requiring a neonatal upper endoscope (outer diameter < 6 mm) to traverse the esophagus because of esophageal stenosis. As expected, patients with an extreme narrow-caliber esophagus more commonly had dysphagia, food impaction, and required dilations compared with EoE patients with “regular-caliber” esophagus (defined by allowing passage of an adult upper endoscope). Supporting previously published studies, greater symptom duration was observed in the extreme narrow-caliber cohort than the regular-caliber comparator group.<sup>9-11</sup> Interestingly, there was no difference in symptom duration between patients with extreme stenosis and those with regular-caliber strictures. A significant limitation of the Eluri study is in the definition of “narrow caliber” required for inclusion. Specifically, a threshold length of extreme narrowing was not defined; therefore, patients solely with high-grade focal stricture may have been included as “narrow-caliber esophagus.” Thus, although it may be imprecise to apply the findings of this study to the typical concept of the narrow-caliber esophagus of EoE, the study does highlight limitations in the definition of the narrow-caliber esophagus.

A central and novel observation in the Eluri study was that the EoE patients with extreme narrow-caliber esophagus were less likely to demonstrate symptomatic, endoscopic, and histologic response after topical steroid treatment when compared with patients with regular-caliber esophagus.<sup>9</sup> Although a reduced symptom response is intuitive, the histologic response to steroids in patients with extreme narrow-caliber esophagus was approximately half that found in patients with regular-caliber esophagus. The same results were found comparing the extreme stenosis group with EoE subjects with regular-caliber strictures. This important finding suggests that patients with an extreme narrow-caliber esophagus may represent a distinct clinical phenotype of EoE that is less amenable to standard therapy with topical steroids. Reasons for this apparent treatment resistance are unclear. The restricted caliber with associated subepithelial fibrosis could limit topical steroid delivery. The longer duration of disease may transition patients from an inflammatory to a “burned out” fibrotic form of disease that is less amenable to anti-inflammatory therapies. Finally, the extreme narrow-caliber group may represent a more aggressive subtype of EoE that is intrinsically less responsive to standard therapies.

Identification of this potentially steroid-resistant clinical subset of EoE carries several clinical and research implications. Patients with extreme esophageal stenosis may require higher doses or longer duration of topical steroids or perhaps steroid alternatives such as

biologic, elimination diet, or combination therapeutics. Furthermore, the extreme esophageal stenosis phenotype may need to be factored into inclusion criteria or stratification for enrollment in future clinical trials of topical corticosteroids because these patients appear to be less responsive to therapy. Similarly, the comparison of published therapeutic trials should consider whether patients with severe narrow-caliber esophagus were excluded. Finally, because the fibrostenosis likely results from chronic inflammation, one might speculate whether earlier initiation of anti-inflammatory therapies may alter the disease's natural history of EoE, thereby preventing development of treatment-resistant, narrow-caliber esophagus.<sup>12</sup> These substantial implications emphasize the need for future, prospective studies using objective metrics to define the clinical characteristics and therapeutic response in EoE patients with extensive esophageal stenosis.

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### DISCLOSURE

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## Abbreviations

<b>EoE</b>	eosinophilic esophagitis
<b>FLIP</b>	functional lumen-imaging probe

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