Accuracy, Safety, and Tolerability of Tissue Collection by Cytosponge vs Endoscopy for Evaluation of Eosinophilic Esophagitis

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BACKGROUND & AIMS: **Management of eosinophilic esophagitis (EoE) requires repeated endoscopic collection of mucosal samples to assess disease activity and response to therapy. An easier and less expensive means of monitoring of EoE is required. We compared the accuracy, safety, and tolerability of sample collection via Cytosponge (an ingestible gelatin capsule comprising compressed mesh attached to a string) with those of endoscopy for assessment of EoE.**

METHODS: **Esophageal tissues were collected from 20 patients with EoE (all with dysphagia, 15 with stricture, 13 with active EoE) via Cytosponge and then by endoscopy. Number of eosinophils/high-power field and levels of eosinophil-derived neurotoxin were determined; hematoxylin-eosin staining was performed. We compared the adequacy, diagnostic accuracy, safety, and patient preference for sample collection via Cytosponge vs endoscopy procedures.**

RESULTS: **All 20 samples collected by Cytosponge were adequate for analysis. By using a cutoff value of 15 eosinophils/high power field, analysis of samples collected by Cytosponge identified 11 of the 13 individuals with active EoE (83%); additional features such as abscesses were also identified. Numbers of eosinophils in samples collected by Cytosponge correlated with those in samples collected by endoscopy ($r = 0.50$, $P = .025$). Analysis of tissues collected by Cytosponge identified 4 of the 7 patients without active EoE (57% specificity), as well as 3 cases of active EoE not identified by analysis of endoscopy samples. Including information on level of eosinophil-derived neurotoxin did not increase the accuracy of diagnosis. No complications occurred during the Cytosponge procedure, which was preferred by all patients, compared with endoscopy.**

CONCLUSIONS: **In a feasibility study, the Cytosponge is a safe and well-tolerated method for collecting near mucosal specimens. Analysis of numbers of eosinophils/high-power field identified patients with active EoE with 83% sensitivity. Larger studies are needed to establish the efficacy and safety of this method of esophageal tissue collection. ClinicalTrials.gov number: NCT01585103.**

Keywords: Eosinophilia; Inflammation; Response to Treatment; Comparison.

Eosinophilic esophagitis (EoE) is a relatively new disease in which esophageal eosinophilia leading to inflammation and stricture formation is thought to result from exposure to food antigens.[1] It can be effectively treated with topical steroids and/or elimination diets. Because symptoms do not reliably reflect disease activity[1–3] and ongoing inflammation commonly leads to fibrosis and stricture formation,[2] consensus guidelines recommend assessing response to therapy by endoscopy and biopsy.[1,3] In 2 recent studies of elimination diet in patients with EoE, up to 10 endoscopies were required to accurately identify problem foods on withdrawal or reintroduction.[4,5] The risk, expense, and time required

Abbreviations used in this paper: **EDN, eosinophil-derived neurotoxin; EoE, eosinophilic esophagitis; eos/HPF, eosinophils per high-power field; SC, small-caliber esophagus.**

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for these strategies are self-evident. An alternative form of monitoring therapeutic response in EoE is to be highly desired.

The esophageal string test is minimally invasive and accurate in the assessment of EoE.[6] After the patient swallows the string, it is kept in overnight, after which secretions adherent to the string are analyzed for markers of eosinophil degranulation. On the other hand, overnight tolerance of the string can be difficult in some patients, and esophageal eosinophilia is not directly measured.

The Cytosponge is a device recently developed as a potential, less invasive means of screening for Barrett's esophagus and esophageal cancer.[7] The device consists of an ingestible gelatin capsule containing a compressed mesh attached to a string. The capsule is swallowed, and once in the stomach, the gelatin dissolves, and a spherical mesh of 3-cm diameter is released. The mesh is withdrawn through the mouth by traction on the attached string, and a tissue specimen is collected. In a recent study evaluating the Cytosponge in patients with Barrett's esophagus,[8] the sensitivity and specificity of the test were 73.3% and 93.8%, respectively, for 1-cm Barrett's esophagus and 90.0% and 93.5%, respectively, for segments of 2 cm or more. There was also overall excellent tolerance by patients who were using the Cytosponge. In the latter study, 1.4% of specimens analyzed (7 of 504) showed a marked eosinophilic infiltrate, suggesting that the Cytosponge test would be a reliable noninvasive tool for evaluating EoE.

The aim of this study was to determine the accuracy, safety, and tolerability of the Cytosponge compared with standard endoscopy and esophageal biopsy in the assessment of EoE.

Methods

Patients

Twenty adult patients with known EoE diagnosed in accordance with consensus guidelines[1] including a lack of histologic response to proton pump inhibitors were included. Patients with active disease ($\geq$15 eosinophils per high-power field [eos/HPF]) or in remission ($<$15 eos/HPF) who were undergoing clinically indicated upper gastrointestinal endoscopy and esophageal biopsies were included. This endoscopy could be performed at initial diagnosis or after a standard 8-week course of treatment with topical steroids or elimination diet to confirm histologic improvement. Endoscopy was performed after the Cytosponge procedure to assess the degree of mucosal injury resulting from the sponge procedure. All patients also underwent barium esophagogram, which is part of the routine evaluation for EoE patients in our clinic. Minimal diameters of the esophageal lumen were recorded.

Demographic and clinical information and endoscopic and histologic findings were collected on each patient. Patients also filled out a questionnaire (Supplementary Figure 1) that assessed the Cytosponge and endoscopy experiences with a 10-cm numeric visual analogue scale (10 being the most favorable). Comments were requested, and patients were asked which procedure was preferable.

Because the main objective was the assessment of sensitivity of the technique that required presence of eosinophils in samples assessed, control patients were not recruited because this has been accomplished in prior studies that documented rare yield of esophageal eosinophils with the Cytosponge.[9]

Upper Gastrointestinal Endoscopy

Endoscopy was performed in standard fashion in an outpatient setting by using administration of midazolam and fentanyl for conscious sedation. Esophageal endoscopic appearance was assessed and scored (EREFS[10]). A total of at least 6 biopsies were obtained from the distal and proximal esophagus. At the time of endoscopy, an endoscopic graded assessment of Cytosponge mucosal injury was made (Supplementary Table 1).

Cytosponge Sampling

Sample collection procedure. The procedure was performed 2 hours before endoscopy was scheduled. Briefly, the capsule and bunched up string were placed by the investigator on the back of the patient's tongue and swallowed with water. The string was held without any tension to allow the capsule to move into the stomach. The patient was instructed to hold onto the string for 5 minutes after ingestion to allow the gelatin capsule to dissolve in the proximal stomach with release of the 3-cm spherical mesh. The back of the throat was sprayed with 1% lidocaine, and the expanded mesh was quickly withdrawn by the investigator during a 5-second period by pulling on the string with the patient in a sitting position. After retrieval of the mesh, the string was cut, and the Cytosponge specimen was placed in a methanol-based preservative fluid-filled container (PreservCyt; Cytyc Co, Marlborough, MA) and kept at room temperature until transportation to the laboratory.

Sample processing. The container was first vortexed to concentrate tissue at the bottom of the container. This was followed by centrifugation of the cellular material at the bottom of the container for 10 minutes at 2500 rpm, yielding a pellet of 3–4 mL in a Falcon (Thermo Fisher Scientific, Waltham, MA) tube. The pellet was removed, and repeat centrifugation of the supernatant was performed to yield more cells that were combined with the original pellet. The pellet was then suspended in Plasma-Lyte (Baxter International, Deerfield, IL). A 5:1 ratio of plasma:thrombin was then added to another Falcon tube with the tissue to create a clot, and the specimen was then processed routinely in paraffin to create a cell block for analysis. Staining of paraffin sections for