

ORIGINAL ARTICLE

Gastroenterology: Eosinophilic Gastrointestinal Disorders

Monitoring pediatric eosinophilic esophagitis disease activity using an unsedated blind esophageal brushing model: A pilot study

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Abstract

Background: Recurrent upper endoscopies are essential for monitoring therapy response and disease activity in patients with eosinophilic esophagitis (EoE), leading to increased costs, procedural complications, and anesthesia exposure. The aim of this study was to examine an office-based model using serial sedation-free blind esophageal epithelial brushing (BEEB) to monitor therapy response through eosinophil-derived neurotoxin (EDN) levels and guide therapy plans in pediatric EoE patients.

Methods: EoE patients (≤ 21 years of age) were enrolled in this prospective study. Subjects were placed on dietary, pharmacologic, or combination therapy with the goal of inducing or maintaining remission. To assess response to sequential interventions, subjects underwent sequential sedation-free BEEBs through nasogastric tubes to measure EDN levels. Based on serial brushings, an individual plan of diet, medications, or a combination of both was created for each subject, and a final endoscopy was then performed to validate the accuracy of the individual plans.

Results: Twenty-four subjects completed the study. The average peak eosinophil count in patients with active EoE was 58.1 ± 30.8 eosinophils per high-power field and mean EDN level was $165.2 \pm 191.3 \mu\text{g/mL}$. A total of 42 BEEBs were completed. Individual therapy plans based on sequential BEEB were accurate in 19 out of the 24 patients (79%) and specifically nine out of 10 patients (90%) treated with elimination diets.

Conclusion: This study suggests that office-based sedation-free BEEBs can be used to monitor therapy response and disease activity in pediatric EoE patients.

KEYWORDS

children, histology, sedation-free, unsedated

1 | INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, antigen-driven, immune-mediated esophageal disease that is characterized by eosinophil-predominant inflammation and esophageal dysfunction triggered by antigens found

in specific foods and/or the environment.^{1,2} If left untreated, inflammation can induce remodeling and fibrosis of esophageal tissue, causing complications such as esophageal strictures and small caliber esophagus.³⁻⁷

The current gold standard for EoE diagnosis is upper endoscopy with biopsies to look for pathological

Abbreviations: EDN, eosinophil-derived neurotoxin; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, endoscopic reference score; EST, esophageal string test; NGT, nasogastric tube; PEC, peak eosinophil count.

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changes including elevated eosinophil density defined as ≥ 15 eosinophils per high power field (eos/hpf).^{4,7-9} After diagnosis, proton pump inhibitors, topical corticosteroids, food elimination diets, or biologics serve as treatments to induce remission.¹⁰⁻¹² A previous study showed that symptoms are not reliable markers of EoE disease activity.¹³ Thus, an EoE patient must undergo an esophagogastroduodenoscopy (EGD) with biopsies to determine if their disease is in remission after any changes in treatment plan or symptoms. Recurrent endoscopies lead to increased costs, potential for procedural complications, and exposure to anesthesia.^{14,15} Additionally, depending on the number of biopsies collected and the location of those biopsy sites, active inflammation can still be missed because EoE is a patchy disease.¹⁶ A less invasive and more cost-effective method of monitoring EoE disease activity is needed.

At our institution, performing blind esophageal brushings using a nasogastric tube (NGT) to measure eosinophil-derived neurotoxin (EDN) levels was found to be safe and well-tolerated in EoE patients, providing a possible alternative to recurrent endoscopies.¹⁵ In this study, we hypothesized that sedation-free blind esophageal epithelial brushing (BEEB) could accurately monitor EoE disease activity and guide therapy decisions.

2 | METHODS

2.1 | Subjects

Pediatric patients (≤ 21 years of age) who underwent routine endoscopy with biopsy at Arnold Palmer Hospital for Children in Orlando, FL and who were diagnosed with EoE were offered to be enrolled in an IRB-approved (IRB # 1241094-11), prospective study between September 2018 and May 2022. Criteria for diagnosis of EoE included esophageal dysfunction symptoms, ≥ 15 eos/hpf on esophageal biopsy, and exclusion of other causes of esophageal eosinophilia.⁹ Patients with esophageal atresia, esophageal stenosis, or a history of esophageal surgeries were excluded from the study. Active EoE was defined as ≥ 15 eos/hpf in one or more esophageal biopsies. EoE in remission was defined as < 15 eos/hpf present in all esophageal biopsies. Data including age at diagnosis, demographics, endoscopic findings, histologic findings, and therapy plans were collected.

2.2 | Study design

Enrolled patients were placed either on an elimination diet and/or medication for management of their disease based on mutual decisions made by the families and the managing physicians. To assess response to

What is Known

- In eosinophilic esophagitis (EoE) patients, eosinophils deposit eosinophil-derived neurotoxin (EDN) on the luminal surface of the esophagus.
- EDN measured at $10 \mu\text{g/mL}$ and higher in esophageal brushing samples obtained through a nasogastric tube (NGT) is highly sensitive (97%) and specific (89%) for the diagnosis of active EoE.
- Blind esophageal epithelial brushing obtained via an NGT is safe and well tolerated.

What is New

- Blind esophageal epithelial brushing can be used successfully to monitor therapy response and disease activity in pediatric patients with established EoE, especially those on elimination diets.

interventions, subjects underwent sedation-free BEEBs instead of serial endoscopies. Subjects underwent sequential BEEBs when sequential interventions were made. Based on serial brushings, an individual plan of diet, medications, or a combination of both was created for each subject, and a final endoscopy was then performed to validate the accuracy of the individual plans. The primary endpoint was to determine the accuracy of the therapy plans created based on sequential BEEBs.

Pharmacologic modifications included adjusting doses or frequency of medications. For patients on elimination diets, modifications were made by introducing or restricting specific foods.

2.3 | Blind esophageal brushing via NGT

Blind esophageal brushings were performed using disposable cytology brushes (Kimberly-Clark # 60,314) inserted through an NGT (CORTRAK[®] # 20-9431TRAK2). NGT placement in the distal esophagus was determined using Strobel's formula [distance from the nares to the lower esophageal sphincter = $5 + 0.252 \times \text{height (cm)}$] and was confirmed by X-ray. Once the NGT with cytology brush was in position, the brush was advanced through the NGT. The brush was opened and closed 10 times to collect esophageal mucosal specimens from the distal esophagus and the process was repeated while withdrawing the NGT in 2 cm increments to obtain samples from the entire esophagus (Figure 1). For details of the procedure, see Smadi et al.¹⁵

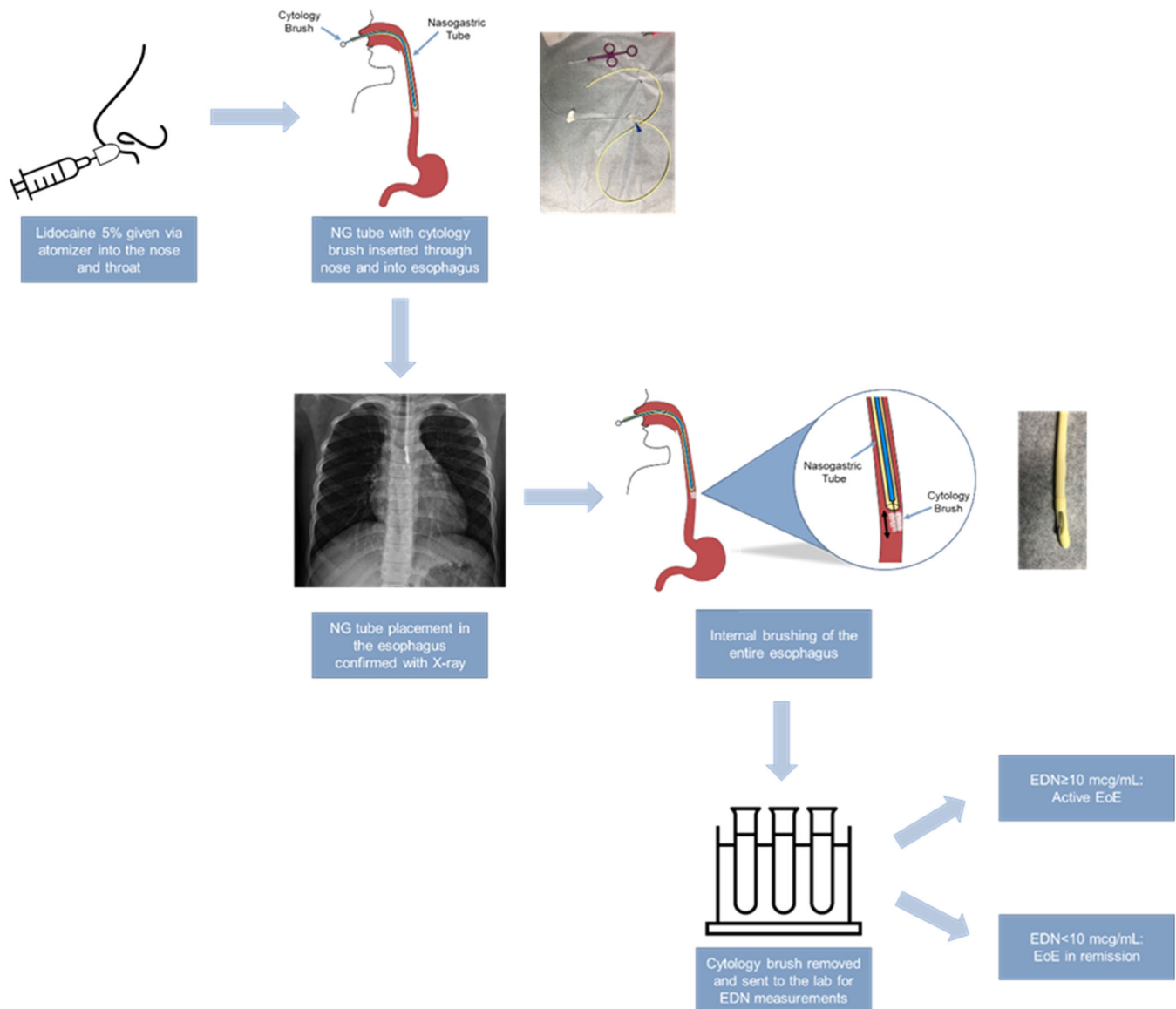


FIGURE 1 Unsedated blind esophageal brushings via nasogastric tube procedure. EDN, eosinophil-derived neurotoxin; EoE, eosinophilic esophagitis; NG, nasogastric.

2.4 | EGD with biopsy

Endoscopy with esophageal biopsies was performed using our standard institutional protocol. A minimum of four proximal and distal esophageal biopsies were collected for each patient. Endoscopic reference score (EREFS) scores were documented by the performing physician to assess disease activity. Biopsies were reviewed by pathologists blinded to the endoscopic findings, brushing results, and treatment status. Peak eosinophil counts (PEC) per high-powered field with a diameter of 0.54 mm (eos/hpf) were reported for both the proximal and distal esophagus.

2.5 | Esophageal brushing via EGD

Esophageal brushing during EGD was performed under direct endoscopic visualization, using standard cytology

brushes (Kimberly-Clark # 60 314) to collect epithelial specimens from the entire esophagus. Brushing specimens were obtained before esophageal biopsies. The brushes were cut (2–3 in. from the end), placed in empty tubes, frozen immediately, and transferred to our Pediatric Gastroenterology Translational Laboratory for batch analysis.

2.6 | Sample extraction

EDN was extracted from the brushings and levels were measured using an enzyme-linked immunosorbent assay at the Pediatric Gastroenterology Translational Laboratory in Orlando, FL. The absorbance in each microwell was measured at 450 nm using a microplate reader. The concentration of EDN was calculated using the standard curve. EDN levels ≥ 10 $\mu\text{g/mL}$ indicated

active EoE disease and levels $<10 \mu\text{g/mL}$ indicated EoE in remission. Samples were batched and processed weekly and EDN results were available within a week of esophageal brushing. Details of the procedure can be found in Smadi et al.¹⁵

2.7 | Statistical analysis

Descriptive statistics were performed. Continuous variables were reported as means and standard deviations. Categorical variables were reported as percentiles. Statistical testing was conducted in Microsoft Excel.

3 | RESULTS

3.1 | Subjects

The study was offered to those who met inclusion criteria and 30 subjects were enrolled. Among the enrolled, 24 subjects completed the study. We did not keep records of those who were offered and refused to participate in this pilot study. Six subjects did not complete the study because they did not undergo a final endoscopy to validate the therapy plan created by BEEB. The data of the 24 subjects who completed the study only is presented. The average age of subjects at diagnosis of EoE was 7 years old. A history of atopy was recorded in 58.3% of participants. The most common presenting symptoms at diagnosis were reflux symptoms (37.4%), which included heartburn, recurrent throat clearing, and regurgitation. Only one subject presented with food impaction (Table 1).

3.2 | Initial EGD

During initial EGD, no patients had stricturing disease. Mean EREFS score was 2.4 ± 1.5 . Three patients had grossly normal endoscopies. The average PEC in all subjects during initial endoscopy was 58.1 ± 30.8 eos/hpf. Mean EDN level was $165.2 \pm 191.3 \mu\text{g/mL}$ (Table 1).

3.3 | Blind esophageal brushings and treatment

A total of 42 blind brushings were completed amongst all patients (Table 2). The number of blind esophageal brushings each patient underwent ranged from 1 to 4 with an average of 1.8 esophageal brushings per patient. After the final blind esophageal brushing, 10 patients were treated with food elimination diets, eight were managed with medications, and six were on combination therapy. No significant adverse events including perforation, vomiting, bleeding, or significant pain occurred in any of the subjects. Time to perform

TABLE 1 Demographics and characteristics of subjects.

	Number of patients (%)
<i>N</i>	24
Mean age at diagnosis (years)	7
Male sex	19 (79%)
Race	
Caucasian	16 (66.7%)
Hispanic	3 (12.5%)
African American	2 (8.3%)
Other	3 (12.5%)
History of atopy	14 (58.3%)
Presenting symptom	
Abdominal pain	4 (16.7%)
Dysphagia	5 (20.8%)
Vomiting	6 (25%)
Food impaction	1 (4.2%)
Reflux symptoms	9 (37.5%)
Feeding difficulties	4 (16.7%)
Poor weight gain	5 (20.8%)
Initial endoscopy	Mean (SD)
PEC (eos/hpf)	58.1 (30.8)
EREFS	2.4 (1.5)
EDN ($\mu\text{g/mL}$)	165.2 (191.3)

Abbreviations: EDN, eosinophil-derived neurotoxin; EREFS, endoscopic reference score; PEC, peak eosinophil count.

BEEB including X-rays to confirm placement was 20 ± 5 min. The position of the brush needed adjustment based on X-rays in 15 cases (35%). There was no need to remove the brush totally in any case. The procedure tolerance was assessed by the physician based on the ability to complete BEEB in all 42 cases.

3.4 | Final endoscopy

A final endoscopy was performed to validate therapy plans created based on sequential BEEBs. For example, subject # 15 (Table 2) followed a food elimination diet and underwent blind brushing when EDN was low consistent with EoE in remission. Then he introduced foods, one food at a time for 8 weeks, followed by esophageal brushing after each introduction. EDN remained low after introducing fish, and soy serially, and increased to above $10 \mu\text{g/mL}$ level after egg introduction. The conclusion was that egg is a trigger for this subject. He did not want to

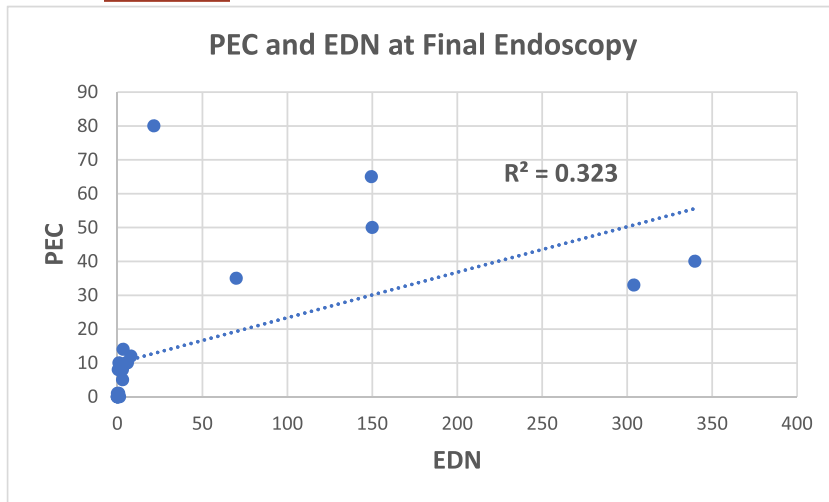


FIGURE 2 Correlation between brushing and histology during final endoscopy. EDN, eosinophil-derived neurotoxin measured in esophageal epithelial brushing ($\mu\text{g/mL}$); PEC, peak eosinophil count (eosinophils/high power field).

introduce dairy due to anaphylaxis. He remained on an egg- and dairy-free diet and underwent a final endoscopy, which revealed EoE in remission based on histology. In this case, the therapy plan created based on serial BEEBs was accurate.

For the final endoscopy, the average EREFS was 1.1 ± 1.6 . Mean PEC was 14.7 ± 22.5 eos/hpf and EDN was 37.8 ± 95.1 $\mu\text{g/mL}$. The therapy plans based on BEEB were accurate in 19 out of 24 patients (79%) and specifically nine out of 10 patients (90%) treated with food elimination diets (Table 2). EDN obtained during final endoscopy correlated with PEC ($R^2 = 0.32$) with a perfect agreement ($\kappa = 1$) using EDN at 10 $\mu\text{g/mL}$ and PEC at 15/hpf as cutoffs (Figure 2).

4 | DISCUSSION

This is the first pediatric study that has investigated unsedated serial BEEB as a noninvasive method for monitoring EoE disease. In this study, we found that serial BEEBs were successful in developing therapy plans in the majority (79%) of pediatric EoE patients. Serial BEEBs were highly accurate (90%) in identifying food triggers in those treated with food elimination diet.

Other less invasive tests than endoscopy have been studied to monitor esophageal inflammation including the esophageal string test (EST), Cytosponge cell collection device, and mucosal impedance measurements.^{17–20} Transnasal endoscopy is a good alternative to sedated endoscopy but is still considered invasive. Diagnostic sensitivity of a single esophageal biopsy is around 73% in EoE patients, suggesting that some cases can be missed.²¹ Epithelial brushing, like the EST and Cytosponge, can sample larger areas of the esophagus than a single biopsy can. Obtaining pan-esophageal samples may improve identification of active inflammation since EoE is a patchy disease.¹⁶ A unique feature of esophageal brushing when compared to other

noninvasive methods to assess EoE disease activity is that it obtains epithelial rather than luminal samples. Also, this procedure does not require the ability to swallow a pill. Thus, this method can be performed on relatively young children depending on patient tolerance.

The BEEB method provides several advantages to standard endoscopy. This method allows for more frequent monitoring of therapeutic efficacy than can be achieved through recurrent endoscopies. No sedation is needed for this procedure, decreasing patient sedation exposure and its risks. Additionally, it can be performed in a standard clinic if an X-ray is accessible. The only other equipment required are NGT and cytology brush, making it a cost-effective alternative to endoscopy with sedation for pediatric patients. Furthermore, the procedure is fast and requires no recovery time, allowing patients to return to work or school the same day. Esophageal brushing was overall well tolerated in patients. No significant adverse events including perforation, vomiting, bleeding, or significant pain occurred in any of the subjects. A total of 42 blind brushings were performed on 24 patients. We estimated that at least 18 endoscopies were saved using the serial BEEBs instead of serial endoscopies in the study.

Though BEEB provides several promising features, it does have limitations. Initial diagnosis of EoE still requires endoscopy with biopsy to exclude other diseases and to identify fibrostenotic disease. Thus, blind esophageal brushing should not be used for initial diagnostic purposes, but rather only for monitoring response for treatment. Caution must be used when using blind brushing in patients with fibrostenotic disease due to the risk of perforation. In our study, none of the patients had a history of fibrostenotic disease. Additionally, patient tolerance is a major factor in the successful completion of brushing. Physicians must choose patients wisely when deciding who should undergo the procedure. One limitation of this pilot study is the lack of acceptance rate to participate by patients and their families. We plan to study this in a

bigger study. Another limitation is the need to confirm the position of the brush by X-ray.

Our pilot study included only 24 patients, but we believe this number is adequate because EDN blind brushing has already been tested in a large population in a previous study.¹⁵ In one case, we determined the success of our prediction using EDN levels as “unknown” because steroids and a stricter food elimination diet were introduced due to worsening symptoms during the interval between blind brushing and final EGD. Thus, a conclusion could not be determined in this patient. The cases where therapy plans based on serial BEEBs were not accurate might be related to inadequate tissue sampling due to poor contact of the brush with the esophageal mucosa. In the future, to overcome this, a wider brush can be trialed, which would provide a larger surface area of contact with the mucosa. There was no failure due to intolerance of the procedure.

5 | CONCLUSION

This study suggests office-based, sedation-free blind esophageal brushing can be used to monitor therapy response and disease activity in pediatric patients with established EoE.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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