

A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation

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Background: Eosinophilic esophagitis (EE) is an increasingly recognized allergic disease entity that is difficult to distinguish clinically from other causes of esophagitis, especially gastroesophageal reflux disease (GERD). To our knowledge, there are no prospectively analyzed or validated symptom scoring tools for pediatric patients with EE and no prospective evaluation correlating symptoms with tissue inflammation.

Objectives: To prospectively analyze a symptom scoring tool's ability to distinguish pediatric patients with EE from those with GERD and from control patients with and without allergies and to correlate symptoms with tissue inflammation.

Methods: A prospective study of a symptom scoring tool given to patients with EE (n = 35 not receiving EE targeted therapy), patients with GERD (n = 27 not undergoing acid suppression), allergic control patients (n = 24), and nonallergic control patients (n = 14) at an academic pediatric hospital. Histology and endoscopy scores were correlated with symptom complaints.

Results: The total symptom score was higher among patients with EE (mean, 6.51; 95% confidence interval [CI], 5.50–7.53) and GERD (mean, 5.44; 95% CI, 4.64–6.25) than in allergic (mean, 0.92; 95% CI, 0.28–1.55) and nonallergic (mean, 1.00; 95% CI, 0.40–1.60) patients ($P < .001$). Patients with EE and GERD complained of more nausea/vomiting, abdominal pain, heartburn/regurgitation, and nocturnal awakening than control groups ($P < .001$). Only dysphagia (mean, 0.9 [95% CI, 0.7–1.2] in EE patients vs 0.4 [95% CI, 0.2–0.7] in GERD patients) and anorexia/early satiety (mean, 1.4 [95% CI, 1.2–1.6] in EE patients vs 0.8 [95% CI, 0.5–1.1] in GERD patients) discriminate EE from GERD ($P < .01$). These symptoms also correlated with the severity of histologic and endoscopic findings ($P < .05$).

Conclusion: Dysphagia and anorexia/early satiety identify pediatric patients with EE and correlate symptoms with tissue inflammation.

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INTRODUCTION

Eosinophilic esophagitis (EE) is a disease of increasing prevalence.^{1–4} Presenting symptoms are similar to those of gastroesophageal reflux disease (GERD) and include heartburn, abdominal pain, vomiting, poor appetite, and dysphagia.^{1,3}

Distinguishing EE clinically from other entities causing esophagitis, such as GERD, can be challenging; ultimately,

the diagnosis of EE depends on histopathologic findings.^{1,5,6} Typical histopathologic features are a patchy panesophageal eosinophilic infiltrate of at least 15 eosinophils per high-power field, epithelial basal zone hyperplasia, desquamation, eosinophil degranulation and clusters, and fibrosis with tissue remodeling of the lamina propria (LP).^{1,7,8} The endoscopic features of EE are characteristic but not specific for this disease; they include mucosal thickening, furrows, white plaques, concentric rings, and strictures.¹

Although retrospective pediatric studies have analyzed the finding of fibrosis in the context of dysphagia,⁹ the prospective correlation between pediatric patient symptoms and pathologic and/or endoscopic findings has not been studied. Although scoring systems have been reported,^{10,11} only a single reported validated dysphagia scoring system has been used in adult patients with EE; a recent quality-of-life study has been described in pediatric patients with EE.^{12–14} However, to our knowledge, there is no prospectively evaluated or validated pediatric symptom scoring tool for EE.

In this prospective study, we report the ability of a gastrointestinal (GI) symptom scoring tool^{15,16} to distinguish children with EE and GERD from children with other atopic and nonatopic disorders. Further, we demonstrate that the symptoms of anorexia/early satiety and dysphagia help to identify

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patients with symptomatic EE from patients with GERD. In addition, we positively correlate GI symptoms with endoscopic and histopathologic findings as evaluated by endoscopic and histologic scoring tools.

METHODS

Patients

Patients attending Dermatology, Allergy, or Eosinophilic Gastrointestinal Disorders clinics at Rady Children's Hospital, San Diego, California, were asked to complete a 7-point symptom score questionnaire (Fig 1). Untreated patients with GERD referred from the gastroenterology clinic were asked to complete the symptom questionnaire at the time of their upper endoscopy. Children were divided into 4 groups: (1) those without allergy (nonallergic controls), (2) those with allergy but without EE or GERD (allergic non-EE controls), (3) those with GERD who were not receiving acid suppression therapy, and (4) those with EE who were not receiving EE-directed therapy. Allergy, asthma, allergic rhinitis, and/or food allergy was diagnosed by an allergy and immunology physician (S.A. or J.F.B.) using skin prick testing (wheal/flare diameter of 3/5 mm greater than saline), serum-specific IgE level (>0.35 kU/L), and/or pulmonary function testing results in conjunction with a clinical history and physical examination. Patients with GERD-like symptoms (eg, regurgitation, heartburn, and pain) who had fewer than 7 eosinophils per high-power field (magnification $\times 400$) using light microscopy on esophageal mucosal biopsy specimens and who may have distal erosive esophagitis on endoscopy were considered to have GERD. Patients with peak counts of more than 20 eosinophils per high-power field on esophageal biopsy specimens were considered to have EE. Parents and children were instructed to fill in the scoring tool together. To evaluate symptom duration, the patient medical record was reviewed for first documentation of symptoms. The study was approved by the Rady Children's Hospital and the Uni-

versity of California, San Diego, Human Research Protection Program. Written informed consent/assent was obtained from all participants.

Symptom Score

A simple symptom scoring tool previously used for acid-peptic disorders in children was modified.^{15,16} This score included 7 categories (heartburn/regurgitation, abdominal pain, nocturnal awakening, nausea/vomiting, anorexia/early satiety, dysphagia/odynophagia, and GI bleeding) (Figure 1), each scoring between 0 and 2 points (maximum, 14 points). Zero points were awarded if symptoms were absent, 1 if the symptoms were mild and did not disrupt daily activities, and 2 if the symptoms were severe enough to disrupt daily activities. Previous GI bleeding was considered mild (1 point) if there was no associated anemia or hemodynamic changes and considered severe (2 points) if it occurred more than once, caused anemia, or required a blood transfusion.

Upper GI Tract Endoscopy Score

This score included 4 categories that composed the typical endoscopic features of EE: pallor, white plaques, linear furrows, and concentric rings or stricture. The esophageal appearance was recorded at 3 levels: proximal (3 cm below the cricopharyngeal muscle), midpoint (the mid point between the gastroesophageal junction and the cricopharyngeal muscle), and distal (3 cm above the gastroesophageal junction). Zero points were scored if the feature was absent, 1 if the feature was present at any 1 or 2 levels, and 2 if the feature was present at all 3 levels. Therefore, the maximum number of points was 8.

Histology Score

This score was calculated from biopsy specimens taken at 3 different esophageal levels (distal, mid, and proximal) by an investigator (R.O.N.) blinded to the patient's diagnosis. All features were evaluated on hematoxylin-eosin-stained sec-

1. Does your child ever have a burning sensation in the chest (heartburn)?
Does your child ever feel food coming back up into his or her throat?
2. Does your child complain about stomach pains?
Is your child often irritable for no apparent reason (you suspect belly pain)?
3. How often does your child complain about feeling like throwing up?
How often does your child throw up?
4. How often does your child eat too little or get full before finishing his or her meal?
5. How often does your child wake up during the night from belly pain?
6. How often has your child noticed blood in his or her stool during the last 3 months?
7. Does your child have difficulties swallowing?
Does swallowing feel painful to your child?
Please distinguish between problems swallowing liquids and solids.

Figure 1. Symptom scoring tool. Answers were scored on a scale of 0 (not at all), 1 (mild; no problem with daily activities, medicines as needed), or 2 (severe; regularly interferes with daily activities or requires daily medicines).

Table 1. Histopathology Scoring Tool

Feature	Scoring key
Epithelium: No. of eosinophils	0: 0 per hpf; 1: 1–10 per hpf; 2: 11–20 per hpf; 3: 21–40 per hpf; 4: 41–60 per hpf; and 5: ≥ 61 per hpf
Basal zone hyperplasia	0: <20%; 1: 21%–50%; 2: 51%–75%; and 3: >75%
Dilated intercellular spaces	0: absent; and 1: present
Epithelial desquamation	0: absent; and 1: present
Eosinophil clusters	0: absent; and 1: present
Degranulated eosinophils	0: absent; and 1: present
Lamina propria: No. of eosinophils	0: 0 per hpf; 1: 1–5 per hpf; 2: 6–20 per hpf; 3: >20 per hpf
Lamina propria fibrosis	0: absent; 1: mild; 2: moderate; and 3: severe
Total score	18 possible

Abbreviation: hpf, high-power field.

tions in routinely processed endoscopic biopsy specimens. There were 9 to 16 tissue sections per slide. The slides were scanned at low power, and the regions containing the densest eosinophilic infiltrate were analyzed for eosinophil counts. Eosinophils were counted at a magnification of $\times 400$ in 5 high-power fields in regions with the highest concentration of eosinophils by scanning, and the maximal eosinophil count was recorded. The histologic scoring system uses 8 recognized histologic features of EE, and points were assigned according to the degree of eosinophilic infiltrate or the presence and/or severity of the specific feature, such as basal zone hyperplasia or degranulated eosinophils (Table 1). The maximum score for each esophageal level was 18 (maximum of 12 in biopsy specimens without an LP). The average epithelial score was calculated by summing the score at each level and dividing by the number of levels for which biopsy specimens were available (3 in most patients with EE and GERD). A subepithelial region from 70 to 150 μm immediately beneath the epithelium was evaluated for fibrosis in biopsy specimens that had at least greater than 3 high-power fields of LP for evaluation. Fibrosis severity was scored (range, 0–3) by a blinded investigator (R.O.N.) based on the number of fibroblasts, the thickness of collagen bundles, and collagen accumulation, as previously described.⁷

Statistical Analysis

Total scores and score subcomponents were compared among more than 2 groups using a 1-way analysis of variance and the Kruskal-Wallis test and between 2 groups using a Mann-Whitney test statistic for unpaired variables; Spearman correlation coefficients were generated using commercially available statistical software packages (NCSS, Kaysville, Utah; and GraphPad Prism, San Diego, California). $P < .05$ (2-tailed) was considered statistically significant.

RESULTS

Patient Characteristics

Fourteen nonallergic control patients and 24 allergic control patients without EE were recruited from the pediatric dermatology and allergy clinics, respectively. Children with GERD ($n = 27$) and with histologically confirmed EE ($n = 35$) completed the symptom score (Table 2). None of the patients received medication or dietary therapy for GERD or EE at data collection. Patients with EE underwent therapy for concurrent allergic diseases (3% taking inhaled corticosteroid, 23% taking albuterol intermittently, and 6% taking antihistamine) or avoided food for anaphylaxis (14%) at symptom collection. Of the patients with EE, 9 (26%) were receiving

Table 2. Patient Characteristics

Characteristic	Nonallergic controls (n = 14)	Allergic controls without EE (n = 24)	Patients with GERD (n = 27)	Patients with EE (n = 35)
Age, mean (95% CI), y	9.6 (7.3–12.1)	9.2 (7.4–10.9)	8.7 (6.7–10.5)	8.8 (7.0–10.5)
Male sex, % (No.)	54 (8)	45 (11)	52 (14)	56 (20)
Allergic status, % (No.)				
Asthma	0	54 (13) ^a	15 (4)	26 (9) ^a
Allergic rhinitis	0	83 (20) ^a	44 (12)	68
Food allergy	0	21 (5) ^a	7 (2)	31 (11) ^a
Symptom duration	NA	NA	23 mo	40 mo ^a

Abbreviations: CI, confidence interval; EE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; NA, not applicable.

^a $P < .05$.

acid suppression therapy. The mean age (9.6, 9.2, 8.7, and 8.8 years for the nonallergic control, allergic control without EE, GERD, and EE groups, respectively) and sex (8 [54%], 11 [45%], 14 [52%], and 20 [56%] male in the nonallergic control, allergic control without EE, GERD, and EE groups, respectively) of the patients among the 4 groups were not significantly different. Most patients in each group ($\geq 77\%$) were older than 5 years. Consistent with previous studies, patients with EE had a longer *disease duration* (defined as the onset of symptoms to the time of scoring tool completion) than patients with GERD (40 vs 23 months; $P = .01$).

Endoscopic Scores

Patients with EE had significantly higher total upper GI tract endoscopy (EGD) scores than patients with GERD (3.69 [95% confidence interval {CI}, 3.03–4.36] vs 0.44 [95% CI, 0.23–0.65]; $P < .001$). Patients with EE had more frequent and more severe endoscopic findings in all EGD scoring subcomponents, with scores of 0.63 vs 0 ($P < .001$) for plaques, 1.42 vs 0.44 ($P < .001$) for pallor, 1.45 vs 0.04 ($P < .001$) for linear furrows, and 0.15 vs 0 for rings in patients with EE vs patients with GERD, respectively. Although 5 patients with GERD had distal erosive esophagitis, none of the patients with EE had erosions on endoscopy.

Symptom Scores

The total symptom scores for nonallergic controls (mean, 1.00; 95% CI, 0.40–1.60) and allergic controls without EE (mean, 0.92; 95% CI, 0.28–1.55) were lower than for patients with GERD (mean, 5.44; 95% CI, 4.64–6.25) or patients with EE (mean, 6.51; 95% CI, 5.50–7.53) ($P < .001$). In addition, the GERD and EE groups both complained of more heartburn/regurgitation, nausea/vomiting, abdominal pain, nocturnal awakening, anorexia/early satiety, and dysphagia than either control group ($P < .001$ for all categories) (Fig 2).

Although both patients with EE and GERD could be easily distinguished from both groups of control patients through individual symptoms and the total symptom score, we sought to determine which specific symptoms were capable of identifying pediatric patients with EE from pediatric patients with GERD. Although symptoms of heartburn/regurgitation, abdominal pain, and nausea/vomiting did not distinguish patients with GERD from patients with EE, the EE group complained significantly more of anorexia/early satiety (mean, 0.81 vs 1.37; $P = .01$) and dysphagia (mean, 0.44 vs 0.94; $P = .006$) than the GERD group (Fig 2, top panel). Of the EE group, 22 (63%) complained of dysphagia for solids, 10 (29%) for liquids, and 8 (23%) for both solids and liquids. The odds ratio for having EE and dysphagia was 12 (95% CI, 4–43); for having EE and anorexia/early satiety, 8 (95% CI, 3–28); and for having EE and dysphagia plus anorexia/early satiety, 15 (95% CI, 6–68) ($P < .001$ for each). In addition, the positive predictive value for distinguishing EE when anorexia/early satiety and dysphagia are used together is 79%. Thus, it is likely that anorexia/early satiety and dysphagia are important clinical indicators of EE.

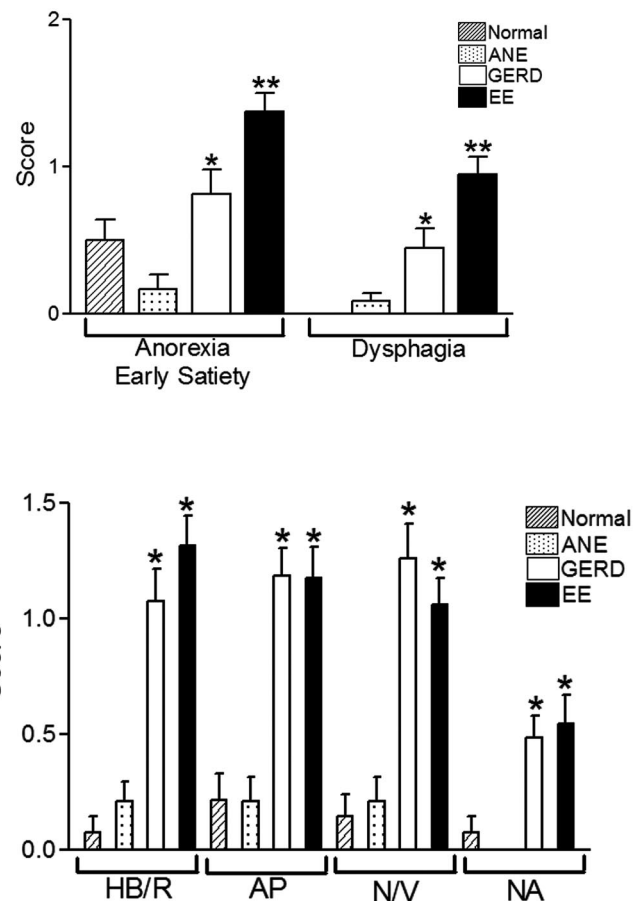


Figure 2. Distinguishing symptoms in patients with eosinophilic esophagitis (EE). Symptom scores in nonallergic and allergic controls without EE compared with patients with gastroesophageal reflux disease (GERD) and EE. * $P < .05$ for patients with GERD or EE compared with control patients. ** $P < .05$ for patients with GERD compared with patients with EE. ANE indicates anorexia/early satiety; AP, abdominal pain; HB/R, heartburn/regurgitation; NA, nocturnal awakening; N/V, nausea/vomiting.

Correlation of Symptoms With EGD and Histopathologic Findings

We used our histology and EGD scoring tools to determine if subjective symptoms in patients with EE correlated with objective findings on endoscopy and histology. Data were collected for patients with EE and GERD using a scoring tool for EGD that grades on the distribution and presence of pallor, linear furrows, white plaques, and concentric rings or strictures. Histologic data were collected using a scoring tool that grades on the presence and/or severity of epithelial findings of eosinophil numbers, clusters, and degranulation; basal zone hyperplasia; dilated intercellular spaces to total 12 possible epithelial points; LP fibrosis; and eosinophil numbers to total 6 possible LP points (Table 1). Of patient biopsy specimens, 17 from those with EE and 5 from those with GERD showed LP.

Histologic findings in both the epithelium and LP correlated well with the endoscopic features. The average epithelial score correlated with endoscopic findings of furrows/thickening, pallor, plaques, and the total EGD score (Table 3). By comparison, only furrows/thickening correlated with the maximum LP histology score (Table 4).

The average epithelial score correlated with the complaints of dysphagia plus anorexia/early satiety (Table 4). By comparison, the maximal LP score correlated significantly only with the symptom complaint of dysphagia ($r = 0.45$, $P = .04$). Other than anorexia/early satiety and dysphagia, none of the other clinical symptoms had a significant correlation with any histologic or endoscopic finding.

DISCUSSION

Herein, we report the first prospective analysis of a pediatric scoring tool in 4 groups of patients: controls with and without allergy compared with patients with GERD and EE. With the exception of GI bleeding, all of the symptom features easily distinguished healthy and allergic patients without EE from those with GERD or EE. This finding is important. Also, dysphagia and/or anorexia/early satiety should raise the clinical index of suspicion for either GERD or EE in pediatric patients.

Although dysphagia has been a reported clinical symptom in adult and pediatric patients with EE,^{1-6,9-11} our data demonstrate that patients with EE and GERD can be identified from one another by the severity of this symptom. Previously reported scoring tools have not focused on anorexia/early satiety as a symptom feature.¹⁰⁻¹⁴ However, our data would suggest that this is an important discriminating feature of EE vs GERD in pediatric patients and that these features should be scored as separate items in future tools.

Most patients in each study group were children older than 5 years. As such, this scoring tool is best applicable to school-aged children. Parents and children were asked to fill out the symptom questionnaire together and, as such, our scoring tool does not reflect the differences in symptom perception between the child and his or her caregiver. In

Table 4. Correlation of Symptoms With Histologic and Endoscopic Findings

Feature	Average epithelial score, <i>r</i> value	Maximum lamina propria score, <i>r</i> value
Maximum lamina propria score	0.57 ^a	NA
Endoscopic features		
Pallor	0.62 ^a	0.44
Furrows/thickening	0.82 ^a	0.64 ^a
White plaques	0.64 ^a	0.28
Concentric rings	0.13	0.32
Symptoms		
Heartburn/regurgitation	0.15	0.16
Abdominal pain	-0.10	0.31
Nausea/vomiting	-0.01	-0.27
Anorexia/early satiety	0.21	-0.06
Nocturnal awakening	-0.18	0.02
Dysphagia	0.19	0.45 ^a
Dysphagia plus anorexia	0.32 ^a	0.30
Total symptom score	0.05	0.30

Abbreviation: NA, not applicable.

^a $P < .05$.

children younger than 5 years, some of the symptoms were likely inferred by the parent based on the child's behavior.

There are currently no surrogate disease markers for the severity of esophageal inflammation in patients with EE, and a recent study demonstrates that symptoms do not correlate directly with eosinophil numbers.¹⁸ Although some physicians attempt to use symptoms as a surrogate marker for disease activity in those with EE, the relationship between symptoms and inflammation has not been clearly delineated.^{1,17,18} As such, monitoring of true disease activity requires an endoscopy with biopsy and a subsequent histologic evaluation.^{1,17} For the first time, we demonstrate in a prospective study that the findings of dysphagia and anorexia/early satiety correlate with inflammatory features in the epithelium and LP. This finding is particularly important given that these are the 2 clinical features that also help identify pediatric patients with EE from those with GERD. None of the patients with EE examined in this study were receiving disease-targeted therapy in the form of elimination diets, topical corticosteroids, or, in the case of patients with GERD, acid-blocking medications. Despite 26% of the patients with EE taking an acid-blocking medication at the time of symptom evaluation, all complained of significant symptoms. Thus, it will be important to determine which symptom constellations resolve after therapy that effectively abrogates esophageal inflammation.

In summary, we have shown that pediatric patients with EE and GERD can be identified from one another based on complaints of dysphagia and anorexia/early satiety and either EE or GERD and they can be distinguished from healthy or allergic patients without EE based on almost any of the clinical features in the scoring tool. We also have demon-

Table 3. Endoscopic Characteristics^a

Endoscopic feature	Patients with GERD (n = 27)	Patients with EE (n = 35)
Pallor	44 (12)	83 (29) ^b
Plaques	4 (1)	89 (31) ^b
Furrows	0	40 (14) ^b
Rings	0	9 (3)
Total EGD score, mean (95% CI)	0.44 (0.23-0.65)	3.69 (3.03-4.36) ^b

Abbreviations: CI, confidence interval; EE, esophageal esophagitis; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease.

^a Data are given as percentage (number) of each group unless otherwise indicated.

^b $P < .05$.

strated that these particular symptoms correlate with histologic findings of eosinophilia, basal zone hyperplasia, dilated intercellular spaces, and LP fibrosis. As such, it will be important to expand questions targeting dysphagia and anorexia/early satiety in future symptom scoring tools and to evaluate changes in these symptoms after therapy.

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