Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease

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Background: The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0) measures patient-relevant outcomes. However, whether patient-identified domains (dysphagia, gastroesophageal reflux disease [GERD], nausea/vomiting, and pain) align with clinical symptomology and histopathologic and molecular features of eosinophilic esophagitis (EoE) is unclear.
Objective: The purpose of this study was to determine whether clinical features of EoE, measured through PEESS v2.0, associate with histopathologic and molecular features of EoE. This represents a novel approach for analysis of allergic diseases, given the availability of allergic tissue biopsy specimens.
Methods: We systematically recruited treated and untreated pediatric patients with EoE (aged 2-18 years) and examined parent proxy–reported symptoms using the PEESS v2.0. Clinical symptomology was collected by questionnaire. Esophageal biopsy samples were quantified for levels of eosinophils, eosinophil peroxidase (EPX) immunohistochemical staining, and mast cells. Molecular features were assessed by using the EoE Diagnostic Panel (94 EoE-related gene transcripts). Associations between domain scores and clinical symptoms and biological features were analyzed with Wilcoxon rank sum and Spearman correlation.
Results: The PEESS v2.0 domains correlated to specific parent-reported symptoms: dysphagia ($P = .0012$), GERD ($P = .0001$), and nausea/vomiting ($P < .0001$). Pain correlated with multiple symptoms ($P < .0005$). Dysphagia correlated most strongly with overall histopathology, particularly in the proximal esophagus ($P \leq .0049$). Markers of esophageal activity (EPX) were significantly associated with dysphagia (strongest $r = 0.37$, $P = .02$). Eosinophil levels were more associated with pain ($r = 0.27$, $P = .06$) than dysphagia ($r = 0.24$, $P = .13$). The dysphagia domain correlated most with esophageal gene transcript levels, predominantly with mast cell–specific genes.

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Conclusion: We have (1) established a validated, parent proxy–reported measure for pediatric EoE, the PEESS v2.0; (2) verified that the parent proxy effectively captures symptoms; (3) determined that the dysphagia domain most closely aligns with symptoms and tissue-based molecular biomarkers; (4) established that symptoms correlate with EPX staining; and (5) observed association between mast cells and dysphagia. (J Allergy Clin Immunol 2015;135:1519-28.)

Key words: *Allergy, reflux, quality of life, surveys, mast cells, molecular genetics, pediatrics, microarray, patient-reported outcomes*

Eosinophilic esophagitis (EoE) is a chronic allergic inflammatory disease driven by food antigen exposure. Although a variety of histologic features, including eosinophil and mast cell accumulation and deposition of their granule contents in tissue, as well as epithelial hyperplastic and remodeling changes, have been noted, the importance of each of these histologic findings for discrete symptoms has been unclear. Clinical outcome end points, such as disease-specific patient-reported outcomes (PROs), are increasingly being recognized as essential for linking disease processes with key effector mechanisms and developing treatments that effectively improve clinically relevant features.[1,2] We recently developed the Pediatric EoE Symptom Score (PEESS v2.0) in an effort to identify and uniquely measure relevant outcomes that patients with EoE and their families identified as important.[3] Input from patients and their families established that the 20 questions from the PEESS v2.0 could be consolidated into 4 major domains: dysphagia, gastroesophageal reflux disease (GERD), nausea/vomiting, and pain.[3] To further validate these domains, it is important to demonstrate that the domains align with clinical symptomology and histopathologic features.

EoE is typified by eosinophil-predominant infiltration of the esophagus (≥15 eosinophils per high-power field [hpf] in at least 1 hpf in esophageal biopsy specimens) that is not responsive to prolonged, high-dose acid suppression with proton pump inhibitors.[4] However, esophageal changes are not limited to the number of eosinophils and might also depend on the extracellular content of eosinophil granule proteins, such as eosinophil peroxidase (EPX), which might have a functional role in EoE.[5] In addition, a unique esophageal gene expression profile exists in patients with EoE, and the magnitude of its expression is proportional to the quantity of inflammatory cells (eg, eosinophils and mast cells).[6,7] This early work implicates T_H2 inflammatory responses (eg, IL-13 and eotaxin-3), as well as expression of mast cell–specific genes, in EoE pathogenesis.[7-10] Importantly, the gene expression profiles of a specific set of 94 genes can discriminate EoE from non-EoE.[11] However, whether the underlying clinical symptomology, histology, and molecular profiles relate to specific clinical manifestations has not been established.

The purpose of this study was (1) to validate patient-defined domains of the parent proxy–reported PEESS v2.0 questionnaire, (2) to determine which histologic features correlate most strongly and specifically with distinct clinical symptoms, and (3) to gain insight into disease pathophysiology by deeply probing molecular transcript expression as a function of distinct clinical symptoms.

Abbreviations used
CCHMC: Cincinnati Children's Hospital Medical Center
CLC: Charcot-Leyden crystal galectin
CPA3: Carboxypeptidase A3
EDP: EoE diagnostic panel
EoE: Eosinophilic esophagitis
EPX: Eosinophil peroxidase
GERD: Gastroesophageal reflux disease
GPR160: G protein–coupled receptor 160
HPGDS: Hematopoietic prostaglandin D synthase
hpf: High-power field
IL5RA: IL-5 receptor α
IQR: Interquartile range
LRRC31: Leucine-rich repeat containing 31
PEESS v2.0: Pediatric EoE Symptom Score
PRO: Patient-reported outcome
SAMS1N: SAM domain SH3 domain and nuclear localization signals 1
SLC26A4: Solute carrier family 26 (anion exchanger), member 4
VEGFA: Vascular endothelial growth factor A

TABLE I. Characteristics of the pediatric EoE study cohort

Characteristic	Statistics
No.	46
Age ± SD (y)	8.2 ± 4.2 (median, 6.9; range, 2.4-17)
Age at diagnosis (y)	6.1 ± 4.4 (median, 4.4; range, 0.8-17)
Sex (% male)*	100
Race (% white)*	97.8
Duration since histologic diagnosis ± SD (y)	2.4 ± 1.6 (range, 0.2-7.3)
Treatment (%)	93.5
Diet only (%)	30.4
Swallowed steroids only (%)	28.3
Diet and swallowed steroids (%)	34.8
Peak eosinophil count (median)	35.5 (IQR, 7.8-88.8; range, 0-295)
Disease activity† (% of cohort)	
Active disease count (eosinophils ≥ 1 /hpf)	71.7
Intermediate count (15 > eosinophils ≥ 6 hpf)	6.5
Low count (6 > eosinophils > 0)	15.2
None (eosinophils = 0)‡	6.5
Distal eosinophil count (median)	27.5 (IQR, 7.8-77.3; range, 0-295)
Proximal eosinophil count (median)	4 (IQR, 0-35; range, 0-295)

*Inclusion of only male and primarily white subjects was an inclusion criterion for the analysis set to minimize heterogeneity.
†Activity was based on the peak eosinophil count (eg, maximum of the proximal and distal counts).
‡All subjects with no eosinophils were treated.

METHODS

Study subjects

Pediatric patients had a confirmed diagnosis of EoE, which was defined as the presence of upper gastrointestinal tract symptoms and an endoscopy with 15 or more eosinophils/hpf in proximal or distal esophageal tissue biopsy specimens per consensus recommendations.[12] Additional data collected included a parent-reported clinical symptom questionnaire and an endoscopic sample collection (see the Methods section in this article's Online Repository at www.jacionline.org). Consent was obtained by a study staff member and was completed either in same-day surgery or in the outpatient clinic. Assent was obtained for