Development of a validated patient-reported symptom metric for pediatric Eosinophilic Esophagitis: qualitative methods

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Abstract

Background

Previous non-validated attempts to measure symptoms in pediatric Eosinophilic Esophagitis (EoE) have not focused on outcomes patients and their families define as important. We sought to identify and validate key patient self-reported and parent proxy-reported outcomes (PROs) specific to EoE.

Methods

We developed methodology for focus and cognitive interviews based on the FDA guidelines for PROs, the validated generic PedsQL™ guidelines, and the consolidated criteria for reporting qualitative research (COREQ). Both child (ages 8-12 and 13-18) and parent-proxy (ages 2-4, 5-7, 8-12, and 13-18) interviews were conducted.

Results

We conducted 75 interviews to construct a new instrument, with items identified and developed from individual focus interviews, which were followed by cognitive interviews for face and content validation. Initial domains of symptom frequency and severity were developed, and open-ended questions were used to generate specific items during the focus interviews. Once developed, the instrument construct, instructions, timeframe, scoring, and specific items were systematically reviewed with a separate group of patients and their parents during the cognitive interviews. To capture the full impact of pediatric EoE, both histologic findings and PROs need to be equally important outcome measures.

Conclusion

We have developed the face and content validated Pediatric Eosinophilic Esophagitis Symptom Severity metric (PEESS™ version 2.0). The PEESS™ version 2.0 metric is now undergoing multisite national field testing as the next iterative instrument development phase.
Background

In pediatric eosinophilic esophagitis (EoE) there can be a wide range of symptoms: from the easily recognizable presentations of food bolus impaction and dysphagia, to the less obvious feeding disorders and abdominal pain [1]. Previous efforts to develop a questionnaire to measure pediatric EoE symptom severity have focused on correlations between non-validated symptom scores and histologic outcomes, specifically peak esophageal eosinophil counts [2,3]. To date, there have been no validated instruments that capture symptoms as patient and parent proxy-reported outcomes (PROs) developed specifically for pediatric EoE [1,4].

Pentiuk et al. developed the non-validated Pediatric Eosinophilic Esophagitis Symptom Severity Score (PEESS version 1.0) utilizing expert opinion and focusing on correlations between symptom scores and histologic outcomes [3]. In this study, Pentiuk and colleagues demonstrated that subjects with untreated EoE had higher PESS scores than treated subjects; however, symptom score and histology only weakly correlated [3]. Aceves and colleagues have also recently developed a symptom score through the modification of a metric utilized for acid peptic disorders [2]. However, this non-validated tool was again developed through expert opinion alone and focused on correlations to histology. In Aceves's study, the total symptom score was higher among patients with EoE and gastroesophageal reflux (GERD) than control patients (P<0.001). However, only symptoms of dysphagia and anorexia/early satiety were capable of significantly discriminating EoE from GERD (P<0.01). Patients with chief complaints other than dysphagia and anorexia did not have histology that directly correlated with the results of the modified symptoms scale.

These prior efforts to develop a symptom severity score for EoE depending solely on expert opinion have not taken into account patient perceptions of symptom severity or response to treatment, which are increasingly important to improving health outcomes and quality of life [4]. Therefore, there is a significant need for severity indices to be developed as patient or parent proxy-reported outcomes. Well designed and validated PROs have been increasingly recognized as key outcome measures for the treatment of chronic disease over the past decade. For example, the recent pediatric asthma randomized
clinical trial for the medication ciclesonide utilized both patient symptoms and QOL metrics as key outcome measures, and demonstrated improvements in QOL and symptoms scores in the treated groups relative to the placebo controls [5]. The National Institutes of Health identified PROs as key components in the clinical research “toolbox” and have launched the Patient Reported Outcomes Measurement Information System (PROMIS, http://www.nihpromis.org/default.aspx) in an attempt to provide healthcare workers and researchers with instruments to objectively measure the disease characteristics that patients and their families deem critically important for their day-to-day health [6-12, 18]. It is clear that a pediatric EoE symptom severity scale would provide a valuable new tool with which to better analyze the outcomes in pediatric EoE that are relevant to families.

As a first step in the development process of a new PRO instrument, face and content validity must be established. Basic PRO validation requires feedback from patients and their parents to determine if the instrument’s item content captures the disease features they believe the instrument should measure. Content validity is established using qualitative research methodologies to investigate whether the PRO instrument and its respective items measure the disease of interest from the patients’ perspective. To capture outcomes from patients’ perspectives, the FDA literature on PROs indicates that it is important to establish content validity before evaluating other measurement properties. Rigorous face and content methodology is an essential step to define metrics as PROs, and testing other measurement properties will not replace or rectify problems with eliciting patient and parent proxy focused outcomes [6].

As the primary objective of this study, we sought to identify key EoE patient and parent proxy-reported symptoms, and to develop a validated EoE PRO symptom metric though a series of focus and cognitive interviews as qualitative metrics of face and content validation.

Methods

FDA guidelines on PRO development, the validated generic PedsQL™ guidelines, and the consolidated criteria for reporting qualitative research (COREQ) were used to develop the methodology for face and content validation [6,13,14].
Research Team

The research team was composed of experts in the field of EoE including: specialty physicians from the fields of Allergy and Gastroenterology with advanced training in clinical research methodologies and two Ph.D. psychologists with specific expertise in qualitative research and PRO methodology. The entire team developed all interview guidelines, whereas specific interviewers were trained in qualitative methodology. The research team reviewed transcriptions of the interview audiotapes.

Participants

Participants were identified from local and referral populations. It was critical to assess patients’ and families’ concerns that were specific to EoE, not those related to other co-morbidities. Therefore, pediatric patient participants were restricted to those with a confirmed diagnosis of EoE and without other co-morbidities, including: inflammatory bowel disease, celiac disease, psychiatric disorder, and/or therapy with psychiatric/behavioral medication.

Focus Interviews

The methodologies for focus interviews have been described previously [12, 15]. Briefly, our research team developed a script of semi-structured open-ended questions (Table 1). Interviewers facilitated the participants’ answers by focusing discussion on the topics under consideration while being nondirective and nonevaluative. Interviews lasted approximately one hour, comprising a total of 36 subjects divided evenly among children ages 8-12 and 13-18 and parents of children ages 2-4, 5-7, 8-12, and 13-18. This age stratification was in alignment with the PedsQL™ guidelines (http://www.pedsqol.org), considered the gold standard for pediatric PRO metrics [16]. In general, children in the 8-12 and 13-18 year age groups described and discussed their symptoms related to EoE. Three focus interviews in the 5-7 year age group were also attempted. However, children in this younger age group were not able to fully describe and discuss their symptoms. Therefore, only parent proxy PRO measures were developed for children in the 2-4 and 5-7 year old age groups. Children ages 8-12 and 13-18 were interviewed separately from their parents.
All sessions were audio-recorded, transcribed verbatim, and analyzed by the research team. Responses were grouped according to domains of interest, age ranges, and patient vs. parent proxy groups. Content and themes were then derived by consensus among the research team. Disagreements were resolved by further discussion.

**Expert Opinion**

Items derived from the focus interviews were integrated into a preliminary draft of the PEESS™ version 2.0. Local and national EoE experts in the fields of allergy, gastroenterology, and psychology then reviewed this draft. To retain the focus of the PEESS™ v2.0 on patient self-reported and parent proxy-reported outcomes, experts were allowed only to discuss general concerns and suggest (not delete) additional items. This additional information was then reviewed with a separate cohort of subjects in the cognitive interview phase.

**Cognitive Interviews**

A different cohort of 39 subjects divided evenly among children ages 8-12 and 13-18 and parents of children ages 2-4, 5-7, 8-12, and 13-18 were interviewed. Cognitive interviews were designed to elicit information regarding the clarity and rationale of the directions, the individual items, the domains, and the response choices, as well as overall comments on the relevance and complexity of the questionnaire. Subjects completed the PEESS module v1.0, reviewed the PEESS™ version 2.0 preliminary draft derived from the focus interviews, and provided feedback utilizing the previously described respondent debriefing methodology [13]. Briefly, cognitive probes and items generated by focus interview subjects and national experts were assimilated into a protocol from the existing methodological literature by Varni and colleagues (Table 2). An item-by-item summary of each section of the questionnaire, including recommendations for modifications, was prepared from transcribed audiotapes and interviewer notes. Using the same methodology as described for the focus interviews, items and content generated were revised. Reading level was assessed using the Flesch Reading Easiness and the Flesch–Kincaid Grade Level scores and used to further revise question language and grammar. A summary of the content validation methodology is provided in Figure 1.
Results

Focus Interviews Patient Self-Report

Children in the 8-12 and 13-18 year groups focused on pain and difficulties with eating food. Regarding frequency, most children described this as how “often” a particular symptom was occurring. Regarding severity, all children described this as how “bad” a particular symptom was. We were surprised to find how clearly children could discern the feeling of nausea from vomiting or abdominal pain. Most children also acutely described heartburn and regurgitation. In addition, children frequently described dysphagia as trouble swallowing or the sensation of food getting stuck.

Focus Interviews Parent Proxy-Report

Although similar to patient self-reported symptoms, parent proxy-reported concerns often differed regarding perceptions of symptom severity. In addition, parents focused more on amounts of food eaten than children. Parents also described issues with frequency and severity of symptoms as separate from the overall question of how much of a problem a particular symptom was for their child.

Expert Opinion

National EoE experts were particularly helpful regarding dysphagia and the various ways that patients and parents described this important symptom. In addition to items asking about trouble swallowing and feelings of food getting stuck, items were added regarding needing to drink liquids to help swallow food and extended time needed to eat food compared to others.

Focus Interview Item and Instrument Draft Development

Thirty-six focus interview transcripts were analyzed. Content and themes derived by consensus among the research team are summarized in Table 3. Once developed, the instrument construct, instructions, timeframe, scoring, and items were systematically reviewed with a different group of patients and their parents during the cognitive interviews.

Cognitive Interview Patient Self-Report

Results from the separate cohort of children with EoE in the 8-12 and 13-18 year groups who participated in the cognitive interview respondent debriefing are summarized in Table 3. In general,
participants thought that the PEESS™ version 2.0 preliminary draft was much easier to understand than the PEESS v1.0. In response to questions raised about the language of the severity score response choices, a visual analog scale was presented to participants. The feedback regarding this addition was uniformly positive, with participants asserting that the draft was much easier to interpret with the insertion of the visual analog scale. For items such as vomiting, nausea, and heartburn, participants thought that having explanations of these terms in parentheses allowed for easier comprehension.

**Cognitive Interview Parent Proxy-Report**

A separate cohort of parents of children ages 2-4, 5-7, 8-12, and 13-18 was identified and interviewed separately from their children. Overall, responses to the PEESS™ version 2.0 preliminary draft were very positive, with participants reporting the response choices as much easier to understand than those in the PEESS v1.0. The addition of several questions regarding dysphagia was also positively received, and participants thought it was important to include all additional questions. The items “eating less food than others” and “needing more time to eat” were particularly important to parents of children in the 2-4 and 5-7 year age groups. Questions were raised about the overall layout of the instrument; many parents (as well as patients) thought that having frequency and severity of particular items side by side rather than on two separate pages would facilitate measuring each symptom comprehensively (Figure 2).

**Final Data Analysis and Construction of the PEESS v2.0**

After the 39 cognitive interviews were concluded, each interview transcript was reviewed in conjunction with the 36 focus interview transcripts (75 total interviews). Results are illustrated in Figure 2 and summarized in Table 3. If two or more participants did not like a particular item or shared a particular concern, the item was reviewed and modified by the research team. We modified additional language and item constructs based on Flesch Reading Easiness and Flesch–Kincaid Grade Level [16]. For example, items 5 and 6 were changed from the grammatically correct “stomachaches” and “bellyaches’ to the grammatically incorrect “stomach aches” and “belly aches.” This adjustment increased the Flesch Reading Ease score and decreased the Flesch-Kincaid Grade level, suggesting that the items were easier to comprehend. Disagreements were resolved by discussion, and the PEESS™ v2.0 was developed.
Discussion

Patient and parent proxy-reported outcomes are critical components for evaluating the impact of current and planned treatments for pediatric EoE. We report the first description of a face- and content-validated patient self-report and parent proxy-report of pediatric EoE symptom-specific outcomes (PEESS™ v2.0).

In the development of the PEESS™ v2.0, the variety of symptoms reported by pediatric EoE patients and their families was surprising. The existing literature reports that adult EoE patients often describe varying degrees of dysphagia, whereas children often describe pain without dysphagia as their only symptom [1, 3]. Characterization of dysphagia from multiple perspectives was critical to capturing this important symptom. Patients and parent proxies were often unaware that they (or their child) were experiencing dysphagia as assessed by items such as “trouble swallowing” or “food getting stuck while eating.” However, the addition of items including “taking a long time to eat food” and “needing to drink a lot of water while eating food” captured the more subtle descriptions of dysphagia.

Utilizing two distinct cohorts for the focus interviews and cognitive interviews also yielded invaluable information and allowed further refinement of patient self-reported and parent proxy-reported perspectives. In particular, clarification and increased reading ease of directions, addition of a visual analog scale, language modification, and the changes in instrument layout were all developed from the cognitive interviews.

Conclusions

Currently, pediatric EoE is assessed using number of eosinophils per high powered field in an esophageal endoscopic biopsy specimen as the primary outcome variable. Symptoms are at best reported as secondary outcomes utilizing physician directed questions, without any attention to PROs [5,17]. It is currently well described that the severity of histologic inflammation in EoE as measured by tissue eosinophil counts might not correlate with the degree of symptoms [3]. For example, initial data in the pediatric Reslizumab (Cinquil®) study suggests that patient symptoms and HRQOL do not correlate with histologic esophageal inflammation [18]. In a condition without known risk of malignancy or reduced life
expectancy, both histologic findings and PROs need to be equally important outcome measures to assess
the total health of the patient. Face and content validation of the PEESS™ v2.0 are important first steps to
establishing patient self-report and parent proxy-report symptom assessments as key factors in pediatric
EoE for patients, families, researchers, and care providers alike.

**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>COREQ</td>
<td>Consolidated Criteria for Reporting Qualitative Research</td>
</tr>
<tr>
<td>EoE</td>
<td>Eosinophilic Esophagitis</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal Reflux Disease</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>PEESS™ v2.0</td>
<td>Pediatric Eosinophilic Esophagitis Symptom Severity Metric</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient Reported Outcomes</td>
</tr>
<tr>
<td>PROMIS</td>
<td>Patient Reported Outcomes Measurement Information System</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
</tbody>
</table>

**Competing Interests**

Cincinnati Children’s Hospital Medical Center and Dr. James P. Franciosi hold the copyright and the
trademark for the PEESS™ v2.0 and may receive financial compensation from the Mapi Research Trust,
which is a nonprofit research institute that charges distribution fees to for-profit companies that use the
PEESS™ v2.0™.
Author’s Contributions

JPF: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, revising manuscript critically for important intellectual content, final approval of the version to be published, acquisition of funding.

KAH: substantial contributions to conception and design, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval of the version to be published.

CWD: acquisition of data, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval of the version to be published.

ABG: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, revising manuscript critically for important intellectual content, final approval of the version to be published.

AJG: substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, revising manuscript critically for important intellectual content, final approval of the version to be published.

JPA: substantial contributions to conception and design, revising manuscript critically for important intellectual content, final approval of the version to be published, Acquisition of funding.

MER: analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval of the version to be published, acquisition of funding.

JWV: substantial contributions to conception and design, revising manuscript critically for important intellectual content, final approval of the version to be published.

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References


**Figure Legends**

**Figure 1: Cognitive Interview Flowchart**

Focus interview transcripts of pediatric patients with EoE and their parents were used to develop the items and domains for the PedsQL™ EoE Module. Cognitive interviewing was conducted with a separate cohort pediatric patients and their parents in the 5 – 7, 8 12, and 13 – 18 year old age groups, while parent proxy-reports were also obtained in the 2 – 4 year age group.

**Figure 2: Face Validation & Layout Design**

Based on patient and parent proxy feedback through focus interviews and separate cognitive interviews, the instrument layout and overall design went through several iterative drafts. As an example, participants favored having frequency and severity of particular items side by side rather than on two separate pages.
Table 1: Focus Interview Open-ended Questions

<table>
<thead>
<tr>
<th>Participant</th>
<th>Questions</th>
</tr>
</thead>
</table>
| Child (Parent) | What symptoms do you (does your child) have that you relate to EE?  
Not eating?  
Pain in chest?  
Burning in chest?  
Trouble swallowing (eating food)?  
Vomiting/throwing up?  
What is the most frequent symptom?  
How often does this occur?  
What is the worst symptom?  
How often does this occur?  
How often do you call your (your child’s) doctor?  
Because of your (your child’s) symptoms, do you (s/he) have trouble in school? Work?  
Playing with friends?  
What trouble do you (your child) have eating food? |


Table 2: Cognitive Interview Respondent Debriefing

<table>
<thead>
<tr>
<th>Subject</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Directions</strong></td>
<td>How would you make the directions more clear/easy to understand?</td>
</tr>
<tr>
<td></td>
<td>What does &quot;in the past month&quot; mean to you?</td>
</tr>
<tr>
<td></td>
<td>When you see &quot;the past month&quot;, what days did you include?</td>
</tr>
<tr>
<td><strong>Items</strong></td>
<td>In your own words, what do you think this question is asking?</td>
</tr>
<tr>
<td></td>
<td>What does this question mean to you? What did you think of when answering this question?</td>
</tr>
<tr>
<td></td>
<td>Was this question easy to understand? Are there any specific words that are difficult to understand?</td>
</tr>
<tr>
<td></td>
<td>How would you change the words to make it more clear?</td>
</tr>
<tr>
<td></td>
<td>Was this item hard to answer? If yes, why?</td>
</tr>
<tr>
<td></td>
<td>How did you choose your answer?</td>
</tr>
<tr>
<td><strong>Domains</strong></td>
<td>In your own words, what do you think this group of questions is asking about?</td>
</tr>
<tr>
<td></td>
<td>How do you think these items are related?</td>
</tr>
<tr>
<td></td>
<td>Are there any questions that do not belong in this group?</td>
</tr>
<tr>
<td><strong>Response Choices</strong></td>
<td>What do you think about the response choices?</td>
</tr>
<tr>
<td><strong>Overall Assessment</strong></td>
<td>How would you make the response choices clearer or easier to understand?</td>
</tr>
<tr>
<td></td>
<td>Are there things that we forgot to ask about that you think are important?</td>
</tr>
<tr>
<td></td>
<td>Overall thoughts/opinions of the questionnaire?</td>
</tr>
<tr>
<td></td>
<td>Anything you would change in the questionnaire as a whole?</td>
</tr>
<tr>
<td>Item</td>
<td>Focus interviews patient reported symptoms</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>General</td>
<td>Patients described how often symptoms occurred and how bad symptoms as different concepts</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>8 reported chest pain.</td>
</tr>
<tr>
<td>Heartburn</td>
<td>4 reported heartburn, 1 reported reflux, 4 reported “burning in chest”</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5 reported abdominal pain, 8 reported “stomachaches/ pain”</td>
</tr>
<tr>
<td>Dysphagia/ Food Impaction</td>
<td>3 reported dysphagia, 16 described “trouble swallowing” 4 reported feeling of “food getting stuck”</td>
</tr>
<tr>
<td></td>
<td>Needing a drink to help swallow food. Some participants did not know that this was a symptom of EoE.</td>
</tr>
<tr>
<td></td>
<td>Needing more time to eat than other children the same age.</td>
</tr>
<tr>
<td></td>
<td>Feeling like food gets stuck in throat or chest</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 reported vomiting, 5 reported “throwing up”</td>
</tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Summary of Content Validation Methodology
Focus Interview developed

PEESS v 2.0

Physician developed

PEESS v 1.0

Cognitive Interview developed

PEESS v 2.0

Validated PEESS® v 2.0

Figure 2: Face validation & Layout Design