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# CLINICAL—ALIMENTARY TRACT

## Development and Validation of a Symptom-Based Activity Index for Adults With Eosinophilic Esophagitis

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**See Covering the Cover synopsis on page 1193; see editorial on page 1212.**

**BACKGROUND & AIMS:** Standardized instruments are needed to assess the activity of eosinophilic esophagitis (EoE) and to provide end points for clinical trials and observational studies. We aimed to develop and validate a patient-reported outcome (PRO) instrument and score, based on items that could account for variations in patient assessments of disease severity. We also evaluated relationships between patient assessment of disease severity and EoE-associated endoscopic, histologic, and laboratory findings. **METHODS:** We collected information from 186 patients with EoE in Switzerland and the United States (69.4% male; median age, 43 y) via surveys (n = 135), focus groups (n = 27), and semistructured interviews (n = 24). Items were generated for the instruments to assess biologic activity based on physician input. Linear regression was used to quantify the extent to which variations in patient-reported disease characteristics could account for variations in patient assessment of EoE severity. The PRO instrument was used prospectively in 153 adult patients with EoE (72.5% male; median age, 38 y), and validated in an independent group of 120 patients with EoE (60.8% male; median age, 40.5 y). **RESULTS:** Seven PRO factors that are used to assess characteristics of dysphagia, behavioral adaptations to living with dysphagia, and pain while swallowing accounted for 67% of the variation in patient assessment of disease severity. Based on statistical consideration and patient input, a 7-day recall period was selected. Highly active EoE, based on endoscopic and histologic findings, was associated with an increase in patient-assessed disease severity. In the validation study, the mean difference between patient assessment of EoE severity (range, 0–10) and PRO score (range, 0–8.52) was 0.15. **CONCLUSIONS:** We developed and validated an EoE scoring system based on 7 PRO items that assess symptoms over a 7-day recall period. Clinicaltrials.gov number: NCT00939263.

*Keywords:* Disease Activity Measurement; Esophagus; Patient-Reported Outcome; Marker.

Eosinophilic esophagitis (EoE) is a young disease because only a little more than 2 decades have passed since this condition has been recognized as its own standing entity.[1,2] Some years ago, a panel of international experts

***Authors share co-first authorship.**

***Abbreviations used in this paper:*** **AMS, avoidance, modification and slow eating; CI, confidence interval; DSQ, dysphagia symptom questionnaire; EoE, eosinophilic esophagitis; Eos, eosinophils; EEsAI, Eosinophilic Esophagitis Activity Index; EGD, esophagogastroduodenoscopy; FDA, US Food and Drug Administration; GERD, gastroesophageal reflux disease; IQR, interquartile range; MDQ-30, Mayo Dysphagia Questionnaire 30-day; PatGA, patient global assessment; PRO, patient-reported outcome; Ref, reference; TS, trouble swallowing; VDQ, visual dysphagia question.**


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defined EoE as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[3] The prevalence of EoE currently is estimated at 1 in 2000 in the pediatric and adult populations of the United States and Europe.[4–7] Most adult patients suffer from dysphagia. However, patients also may report refractory heartburn and/or chest pain, which is located centrally and does not respond adequately to acid-suppressive medications.[8–10]

A standardized and validated patient-reported outcome (PRO) instrument assessing symptom severity in patients with EoE is needed urgently to define meaningful end points for clinical trials and to follow-up disease evolution in observational studies. Until now, EoE symptoms in adult patients have been evaluated in clinical trials using different PRO instruments. For example, Alexander et al[11] used the Mayo Dysphagia Questionnaire 30-Day (MDQ-30) version and found that swallowed fluticasone improved histologic characteristics, but not symptoms of EoE in adult patients. The MDQ-30 version was validated in a group of patients presenting with dysphagia and thoracic pain caused by various gastrointestinal diseases, but not specifically caused by EoE.[12] An ad hoc–constructed symptom assessment instrument was used by Straumann et al[13,14] in a placebo-controlled study to evaluate the efficacy of budesonide in adult EoE patients. Dellon et al[15] developed the dysphagia symptom questionnaire (DSQ), a 3-item electronic PRO administered daily to assess the frequency of dysphagia caused by eating solid food and relief strategies during the dysphagia episodes. This DSQ was evaluated in a group of 35 adolescent and adult EoE patients with clinically and histologically active disease.[15] Of note, none of these 3 instruments fulfill all the criteria currently required for an EoE PRO instrument. The assessment of dysphagia is particularly challenging because it depends not only on disease severity, but also on consistencies of foods consumed, and on behavioral adaptation strategies to living with dysphagia. Thus, any PRO instrument assessing dysphagia must take these factors into account.

Given the lack of standardized, validated PRO instruments, the results of clinical trials performed in EoE cannot be compared easily. This also might explain why different therapeutic trials document various degrees of association between patient-reported symptoms and endoscopic and histologic findings.[11,13,14] The current situation poses a major challenge for regulatory approval of EoE therapies.[16,17]

In this article, we describe the process of development and validation of a PRO instrument for adult EoE patients. The study was performed in accordance with the US Food and Drug Administration (FDA) guidelines.[16]

## Patients and Methods

### Study Overview

The adult Eosinophilic Esophagitis Activity Index (EEsAI) study was performed in 3 phases, which are illustrated in Supplementary Figure 1. During the first phase, a comprehensive list of relevant items to be potentially incorporated into the PRO, endoscopy, histology, and blood biomarker instruments was generated. During the second phase, the prototypes of standardized instruments were evaluated in one patient group (evaluation group). Data derived from the PRO instrument were used to derive a symptom severity score. During the third phase, the PRO instrument and the PRO score were validated in another group of adult EoE patients (validation group).

### Item Generation

We first established a conceptual framework for instruments to assess symptoms, behavioral adaptations, and biologic activity of adult EoE patients (Figure 1). For item generation, a review of the literature and the existing instruments to assess clinical, endoscopic, histologic, and biochemical EoE activity was performed, and expert opinion was provided using the Delphi technique (telephone conferences and e-mails). The Delphi technique allows geographically dispersed experts to reach a consensus on a particular complex task.[18] A Delphi group of adult EoE gastroenterologists (n = 9), allergists (n = 2), and pathologists (n = 2) from Switzerland and the United States contributed a list of items that they thought best reflected endoscopic (n = 6 items), histologic (n = 7 items), and biochemical activity (n = 5 items).

For the PRO instrument item generation, patient input was obtained by a mixed methods approach using open-ended patient symptom surveys (n = 135 patients), focus groups (n = 27 patients), as well as semistructured patient interviews (n = 24 patients). The qualitative methods of the development of the PRO instrument are described in detail in Appendix 2, Supplementary Tables 1–8, and Supplementary Figures 2–5 according to the consolidated criteria for reporting qualitative research guidelines.[19,20]

### Item Reduction and Formatting of the Instruments Assessing Biologic Activity

Delphi group members ranked each provided item assessing biologic EoE activity from 0 (not important) to 5 (very important). The number of items then was reduced by rank order from 7 to 5 items and from 5 to 3 items for histology and blood biomarkers, respectively. The number of items (n = 6) for endoscopy did not change. The generated instruments were distributed to the Delphi group, and multiple Delphi rounds were conducted to minimize interobserver variability, establish clear definitions, and to ensure that the final instruments reflect the consensus opinion.

### PRO Instrument

The EEsAI instruments were developed in such a way that PROs were assessed separately from items measuring biologic activity.[21–24] The PRO instrument included items on symptom severity and behavioral adaptations, which were recalled over 24 hours, 7 days, and 30 days, to determine the optimal recall period.

The PRO instrument contained 5 domains: a general domain to assess sociodemographic characteristics, 2 symptom domains to address symptoms that were dependent and independent of food intake, a comorbidities domain, and a medication domain. The PRO instrument consisted of 45 items. The domain addressing symptoms while eating or drinking included items on duration, frequency, and severity of dysphagia, time required for

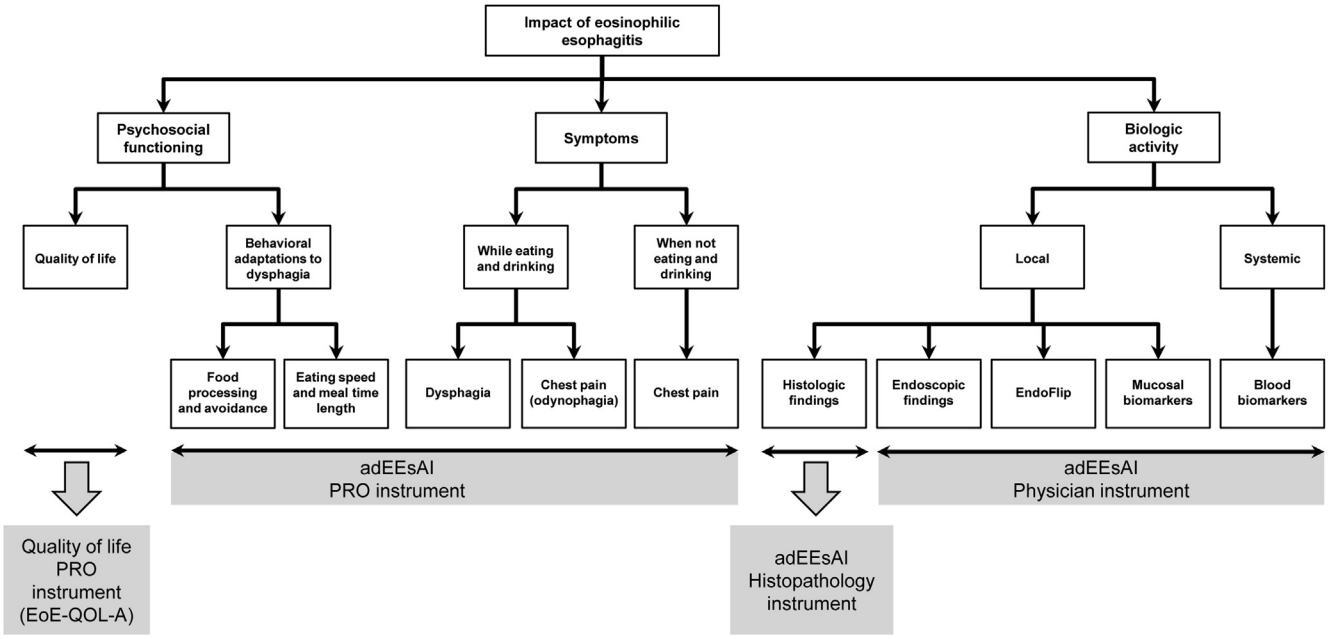


**Figure 1.** Conceptual framework for the development of EEsAI instruments. The EndoFlip or mucosal biomarkers, were not, as of yet, evaluated for the purposes of the EEsAI study. EndoFlip, Endolumenal Functional Lumen Imaging Probe.

meal intake, dysphagia upon consuming liquids, and pain when swallowing. The visual dysphagia question (VDQ) addressed the severity of dysphagia when consuming food of 8 distinct consistencies. The 8 food consistencies and examples of foods to illustrate those consistencies were as follows: (1) solid meat (such as steak, chicken, turkey, and lamb), (2) soft foods (such as pudding, jelly, and apple sauce), (3) dry rice or sticky Asian rice, (4) ground meat (hamburger and meatloaf), (5) fresh white untoasted bread or similar foods (such as doughnuts, muffins, and cake), (6) grits, porridge (oatmeal), or rice pudding, (7) raw fibrous foods (such as apples, carrots, and celery), and (8) French fries. The examples were chosen based on foods that are consumed in the United States, Europe, and Canada. The behavioral adaptations (avoidance, modification, and slow eating [AMS] of various foods) also were assessed in the context of consuming 8 distinct food consistencies. A domain addressing symptoms independent of eating or drinking included items on chest pain, heartburn, and acid regurgitation. The last 2 items were reproduced from the MDQ-30 with the permission of the copyright owners.[12]

Patients were asked to provide a Patient Global Assessment (PatGA) of EoE severity on an 11-point Likert scale, in which a score of 0 is defined as no symptoms and a score of 10 is defined as most severe symptoms. The PatGA was used as a main outcome parameter for every recall period. The PRO instrument was first created in English. Translation of the PRO instrument into German and French was performed in accordance with the World Health Organization guidelines for translation and adaptation of instruments.[25]

## *Instruments Assessing Endoscopic, Histologic, and Laboratory Findings*

The instrument for physicians consisted of 5 domains: a general domain for physician and patient characteristics, a gastroesophageal reflux disease (GERD) domain, an anti-eosinophil treatment domain, a blood biomarker domain, and an endoscopy domain. The instrument also incorporated the physician global assessment of EoE severity item. The physician global assessment took into account patients' symptoms (based on history taking), and endoscopic, histologic, and biochemical findings. The physician global assessment was assessed on an 11-point Likert scale, in which a score of 0 was defined as inactive EoE and a score of 10 was defined as most active EoE. The endoscopy domain of the physician instrument was designed based on the EoE Endoscopic Reference Score classification and grading system.[26]

The histopathology instrument contained 3 domains: a general domain for pathologists and 2 domains assessing EoE-associated histologic features in the distal and proximal esophagus. *Distal* was defined as the section of the esophagus 5 cm above the gastroesophageal junction, and *proximal* was defined as the section spanning the top half of the esophagus.

A detailed overview of the physician and histopathology instruments can be found in Supplementary Table 9.

## *Study Population*

The study was registered on clinicaltrials.gov (NCT00939263) and was approved by local institutional review boards and ethics committees. All authors had access to the study data and reviewed and approved the final manuscript.

Between April 2011 and December 2012 (evaluation group) and May 2013 and July 2014 (validation group), EoE patients were recruited from 1 ambulatory care clinic and 7 hospitals in Switzerland and the United States. Adult EoE patients (age, $\geq$17 y) in need of an esophagogastroduodenoscopy (EGD) for an initial diagnosis, for confirming a suspected diagnosis, or for monitoring previously diagnosed EoE were invited to participate in the study. Patients provided informed consent to participate in the study. EoE was diagnosed by investigators at all centers using published diagnostic criteria.[3] EoE patients

with concomitant GERD also were included if they were on continued proton-pump inhibitor therapy at the time of EGD. All patients underwent a standardized physical examination by a physician. EGD was performed and at least 8 biopsy specimens were obtained (4 from the proximal and 4 from the distal esophagus). Endoscopic findings were assessed according to the endoscopy atlas created by Hirano et al.[26] Levels of blood eosinophils also were measured. Patients completed the PRO instrument before undergoing an EGD. Gastroenterologists completed the instrument for physicians, and pathologists completed the histopathology instrument.

Histologic evaluation was performed by the local center pathologist. Five-micrometer sections were cut from paraffin blocks and stained with H&E for examination by light microscopy. The area of a high-power field and the percentage of the area covered by tissue were noted to allow for calculation of peak eosinophil counts/$mm^2$. To determine the peak eosinophil count, at least 5 levels of every esophageal biopsy specimen were surveyed under low power, and the eosinophils in the most densely infiltrated area were counted under high-power examination.

### Construction of the Visual Dysphagia Question and Avoidance, Modification, and Slow Eating Scores

The data obtained from the VDQ and AMS items were used to create a composite score. A sample calculation of the VDQ and AMS scores is provided in Appendix 3.

### Data Handling and Statistical Analysis

Data were double-entered by 2 researchers into the EpiData database (version 3.1; EpiData Association, Odense, Denmark) and imported into Stata (version 13, College Station, TX) for analysis. Descriptive results are presented as frequencies and corresponding percentages of the group total, or medians plus interquartile ranges (IQRs). We used multivariable linear regression analysis and analysis of variance models to identify redundant information and to obtain an equation for constructing a PRO score. In these analyses, the PatGA was used as the outcome, and responses to specific items in the instrument were used as predictors. These analyses allowed us to quantify the extent to which included items explained the variability in PatGA. The variables included in the final models were chosen on the basis of their relative contribution to the explanatory power of the models, coherence of parameter estimates, and expert opinion. We evaluated the fit of the models using the coefficient of determination ($R^2$). To validate the EEsAI PRO instrument, a second group of adult EoE patients was included, and the EEsAI PRO score was calculated based on the regression coefficients. The $R^2$ was calculated to assess the relationship between the EEsAI PRO score and the PatGA. A Bland–Altman plot was used to evaluate the agreement between the calculated EEsAI PRO score and the PatGA.

## Results

### Patient Characteristics

A total of 153 and 120 adult EoE patients were recruited for the evaluation and validation phases, respectively. The characteristics of these patients are shown in Table 1. Age at inclusion, sex, ethnicity, and education level were comparable between the 2 groups. When compared with the patients in the evaluation group, the patients in the validation group were more likely to have EoE symptom onset more than 5 years before inclusion in the study (67.2% vs 52.9%), to experience self-reported food allergies (50% vs 30.1%), and to receive EoE-specific therapies in the past 12 months before inclusion in the study (85.8% vs 58.8%); however, they were less likely to have concomitant GERD (15% vs 30.7%) or be treated with proton-pump inhibitor therapy (32.5% vs 55.6%).

### Predominant EoE Symptoms (Evaluation Group)

Table 2 illustrates the predominant symptoms of patients in the evaluation group, reported over the past 24 hours, 7 days, and 30 days. When recalled over the past 24 hours, 7 days, and 30 days, the median PatGA assessed on the 11-point Likert scale (range, 0–10) was 1 (IQR, 0–3), 2 (IQR, 1–4), and 2 (IQR, 1–4), respectively. Forty-one (27.5%), 91 (59.5%), and 126 (82.4%) patients reported trouble swallowing in the past 24 hours, 7 days, and 30 days, respectively. Overall, except for the meal duration, which remained relatively constant over the time periods examined, patients were more likely to experience dysphagia and pain events with increasing length of the recall period.

### Assessing Dysphagia Severity and Behavioral Adaptations When Ingesting Foods of Different Consistencies

The symptoms of patients in the evaluation group were analyzed for a 24-hour, 7-day, and 30-day recall period. The data from the VDQ and AMS items recalled over a 7-day recall period are shown in Supplementary Table 10. Generally, the severity of perceived dysphagia increased with increasing food consistency. For instance, 21 (13.7%) patients reported that they expected to experience severe difficulties when eating solid meat, and 11 (7.2%) patients reported the same when eating foods included in the raw foods category. In contrast, 5 (3.3%) and 6 (3.9%) patients reported that they expected to experience severe difficulties when consuming foods from the soft foods and grits and porridge categories, respectively. Increased time required to eat a certain food item was the most common complaint for EoE patients. For example, 103 patients (67.3%) experienced this phenomenon when eating solid meat, followed by 65 patients (42.5%) when eating ground meat, and 54 patients (35.3%) when eating bread. Food avoidance and food modification were reported less frequently for soft foods and were associated mostly with high-consistency foods, such as meat, and raw foods, such as vegetables. Similar trends were observed when data for the 24-hour and 30-day recall periods were analyzed (data not shown).

### Choosing the Appropriate Symptom Recall Period: Patient Input

Patients participating in the focus groups (n = 27) were asked to choose the best time period to recall their

**Table 1.** Patient Characteristics

| Characteristic | Evaluation group | | Validation group | |
|---|---|---|---|---|
| | Frequency | % | Frequency | % |
| Patients, n | 153 | 100.0 | 120 | 100.0 |
| Males | 111 | 72.5 | 73 | 60.8 |
| Age at inclusion, median (IQR; range) | 38 | 29–46; 17–71 | 40.5 | 31–49; 19–80 |
| Ethnicity | | | | |
| White | 148 | 96.7 | 114 | 95.0 |
| Non-white | 5 | 3.3 | 6 | 5.0 |
| Education | | | | |
| Compulsory schooling | 2 | 1.3 | 1 | 0.8 |
| Vocational training | 38 | 24.8 | 33 | 27.5 |
| Upper secondary education | 67 | 43.8 | 54 | 45.0 |
| University education | 46 | 30.1 | 32 | 26.7 |
| EoE symptom onset | | | | |
| 1–3 months ago | 1 | 0.7 | 0 | 0.0 |
| 4–11 months ago | 8 | 5.2 | 2 | 1.7 |
| 1–5 years ago | 63 | 41.2 | 38 | 31.7 |
| >5 years ago | 81 | 52.9 | 80 | 66.6 |
| Allergic diseases/allergies | | | | |
| Asthma | 53 | 34.6 | 42 | 35.0 |
| Rhinoconjunctivitis | 92 | 60.1 | 72 | 60.0 |
| Eczema | 18 | 11.8 | 34 | 28.3 |
| Food allergy | 46 | 30.1 | 60 | 50.0 |
| GERD | 47 | 30.7 | 18 | 15.0 |
| Diagnosis established | | | | |
| Clinically | 28 | 59.6 | 3 | 16.7 |
| Endoscopically | 11 | 23.4 | 6 | 33.3 |
| Based on pH-metric studies | 1 | 2.1 | 2 | 11.1 |
| Clinically and endoscopically | 7 | 14.9 | 5 | 27.8 |
| Concomitant medications | | | | |
| Proton-pump inhibitors | 85 | 55.6 | 39 | 32.5 |
| Histamine antagonists ($H_2$ receptor) | 7 | 4.6 | 1 | 0.8 |
| Histamine antagonists ($H_1$ receptor) | 25 | 16.3 | 18 | 15.0 |
| Inhaled corticosteroids for asthma | 4 | 2.6 | 4 | 3.3 |
| $\beta$2-adrenergic agonists for asthma | 20 | 13.1 | 2 | 1.7 |
| Leukotriene-receptor antagonists for asthma | 4 | 2.6 | 1 | 0.8 |
| EoE-specific treatments in the past 12 months | 90 | 58.8 | 103 | 85.8 |
| Hypoallergenic diets | 20 | 13.1 | 19 | 15.8 |
| Swallowed topical corticosteroids | 65 | 42.5 | 78 | 65.0 |
| Esophageal dilation | 30 | 19.6 | 26 | 21.7 |

symptoms reliably. The majority of patients indicated that the 7-day period was the best recall period (19 of 27; 70.4%), followed by the 14-day (5 of 27; 18.5%), 30-day (2 of 27; 7.4%), and 24-hour (1 of 27; 3.7%) periods.

### *Development of the PRO Score*

We modeled the PatGA recalled over 24-hour, 7-day, and 30-day periods by evaluating its strength and significance of association with the items in the PRO instrument. The following 7 items were chosen for inclusion in the PRO instrument based on their contribution to the explanatory power of the models, coherence of parameter estimates, and expert opinion: frequency of trouble swallowing, duration of trouble swallowing, pain when swallowing, VDQ, as well as 3 AMS items. Because the answers to the VDQ and 3 AMS items were scored to derive VDQ and AMS scores, respectively, the resulting 5 variables were used for the purposes of analyses presented later.

Frequency of trouble swallowing, duration of trouble swallowing, severity of pain when swallowing, the VDQ and AMS scores correlated positively with the PatGA for 3 recall periods. The data for the 7-day recall period are shown in Supplementary Figure 6. We used multivariable linear regression analysis and analysis of variance models to evaluate the contribution of chosen PRO variables to the PatGA. The results of these analyses are shown in Table 3. In general, the increasing severity of PRO variables mostly showed a positive and significant relationship with the PatGA for the 3 recall periods examined. For example, for the 7-day recall period, if a patient experienced daily episodes of trouble swallowing, the predicted PatGA increased by 2.61, when compared with 1.3 and 2.29 for trouble swallowing episodes experienced 1–3 and 4–6 times/week,

**Table 2.** Type and Frequency of EoE-Related Symptoms Assessed in the EEsAI PRO Instrument Over 3 Recall Periods (N = 153)

| Characteristic | Recall period | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 24 hours | | 7 days | | | 30 days | | |
| Median symptom severity (IQR; range) | 1 | 0–3; 0–10 | | 2 | 1–4; 0–10 | | 2 | 1–4; 0–10 |
| Frequency of trouble swallowing | | | | | | | | |
| Never | 111 | 72.5 | Never | 62 | 40.5 | Never | 27 | 17.6 |
| 1–3 times/day | 34 | 22.2 | 1–3 times/wk | 60 | 39.2 | 1–3 times/mo | 40 | 26.1 |
| ≥4 times/day | 7 | 4.6 | 4–6 times/wk | 15 | 9.8 | 1–3 times/wk | 52 | 34.0 |
| | – | – | | – | – | 4–6 times/wk | 19 | 12.4 |
| | – | – | Daily | 16 | 10.5 | Daily | 15 | 9.8 |
| Not applicable | 1 | 0.7 | | – | – | | – | – |
| Intensity of trouble swallowing | | | | | | | | |
| Everything was easy to swallow | 111 | 72.5 | | 53 | 34.6 | | 26 | 17.0 |
| Slight retching | 22 | 14.4 | | 69 | 45.1 | | 73 | 47.7 |
| Food stuck for ≤5 min | 7 | 4.6 | | 25 | 16.3 | | 37 | 24.2 |
| Food stuck for >5 min | 3 | 2.0 | | 4 | 2.6 | | 10 | 6.5 |
| Impacted food had to be removed | 6 | 3.9 | | 0 | 0.0 | | 3 | 2.0 |
| Missing | 4 | 2.6 | | 2 | 1.3 | | 4 | 2.6 |
| Duration of trouble swallowing | | | | | | | | |
| No troubles swallowing | 107 | 69.9 | | 56 | 36.6 | | 26 | 17.0 |
| <15 s | 24 | 15.7 | | 45 | 29.4 | | 49 | 32.0 |
| 16–59 s | 8 | 5.2 | | 29 | 19.0 | | 34 | 22.2 |
| 1–5 min | 3 | 2.0 | | 18 | 11.8 | | 28 | 18.3 |
| >5 min | 10 | 6.5 | | 5 | 3.3 | | 16 | 10.5 |
| Not applicable | 1 | 0.7 | | – | – | | – | – |
| Time required to eat a regular meal | | | | | | | | |
| <15 min | 24 | 15.7 | | 22 | 14.4 | | 20 | 13.1 |
| 16–30 min | 91 | 59.5 | | 88 | 57.5 | | 86 | 56.2 |
| 31–45 min | 30 | 19.6 | | 34 | 22.2 | | 37 | 24.2 |
| 46–60 min | 3 | 2.0 | | 3 | 2.0 | | 3 | 2.0 |
| >1 hour or refusal to eat | 3 | 2.0 | | 4 | 2.6 | | 5 | 3.3 |
| Not applicable | 2 | 1.3 | | 2 | 1.3 | | 2 | 1.3 |
| Frequency of pain when swallowing | | | | | | | | |
| Never | 137 | 89.5 | Never | 122 | 79.7 | Never | 106 | 69.3 |
| 1–3 times/day | 14 | 9.2 | 1–3 times/wk | 21 | 13.7 | 1–3 times/mo | 19 | 12.4 |
| ≥4 times/day | 2 | 1.3 | 4–6 times/wk | 6 | 3.9 | 1–3 times/wk | 16 | 10.5 |
| | – | – | | – | – | 4–6 times/wk | 9 | 5.9 |
| | – | – | Daily | 3 | 2.0 | Daily | 2 | 1.3 |
| Missing | 0 | 0.0 | Missing | 1 | 0.7 | Missing | 1 | 0.7 |

respectively. If, in addition, the duration of those trouble swallowing episodes lasted more than 5 minutes, the predicted PatGA increased by another 0.53.

Although the contribution of 5 PRO variables to the PatGA was similar, when the 7-day and 30-day recall periods were examined, the contribution of these variables was quite different when the 24-hour recall period was evaluated. For instance, for patients with the highest VDQ score quartile (score ranging from 7.6 to 10, which represents patients experiencing severe difficulties eating various foods), the predicted PatGA increased 6.19 for a 24-hour recall period, when compared with the increase of only 1.96 and 1.57 for the 7-day and 30-day recall periods, respectively. As such, for a 24-hour recall period, the VDQ score contributed approximately 3–4 times more to the predicted PatGA when compared with the same VDQ score for the 7-day and 30-day recall periods. On the other hand, the coefficients for the highest values of the AMS score were quite similar with 2.19 for the 24-hour, 2.15 for the 7-day, and 1.91 for the 30-day periods.

The regression model with 5 variables of the EEsAI PRO instrument explained 72% ($R^2 = 0.72$), 67%, and 58% of the variability in PatGA for the 24-hour, 7-day, and 30-day recall periods, respectively. Because $R^2$ can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance, only 5 independent variables that had a large effect were included in the model. Because the EEsAI PRO score for a 24-hour recall period was influenced strongly by a response to the VDQ, and the frequency of the events, such as pain and dysphagia, was also the lowest for the 24-hour recall period, we judged the 24-hour recall period to be less reliable for assessing EoE severity. Based on these statistical considerations and patient input, we concluded that a 7-day recall period represents the best choice for assessing patient-reported EoE severity by means of the EEsAI PRO score.

**Table 3.** Linear Regression Coefficients, 95% CIs, and *P* Values for the Models of PatGA of the EoE Activity Recalled Over the 24-Hour, 7-Day, and 30-Day Periods

| | Recall period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 24 hours | | | 7 days | | | | 30 days | | | |
| Characteristic | Coefficient[a] | 95% CI | *P* | | Coefficient[a] | 95% CI | *P* | | Coefficient[a] | 95% CI | *P* |
| Frequency of trouble swallowing | | | .01 | | | | < .0001 | | | | .0001 |
| Never | 0.00 | Ref. | | Never | 0.00 | Ref. | | Never | 0.00 | Ref. | |
| 1–3 times/day | 1.30 | (0.50 to 2.09) | | | – | – | – | 1–3 times/mo | 0.31 | (-0.62 to 1.23) | |
| ≥4 times/day | 0.86 | (-0.91 to 2.63) | | 1–3 times/wk | 1.30 | (0.74 to 1.86) | | 1–3 times/wk | 1.28 | (0.26 to 2.29) | |
| – | – | – | – | 4–6 times/wk | 2.29 | (1.40 to 3.18) | | 4–6 times/wk | 2.49 | (1.26 to 3.73) | |
| – | – | – | – | Daily | 2.61 | (1.66 to 3.56) | | Daily | 2.46 | (1.09 to 3.83) | |
| Duration of trouble swallowing | | | .03 | | | | .41 | | | | .52 |
| ≤5 min | 0.00 | Ref. | | | 0.00 | Ref. | | | 0.00 | Ref. | |
| >5 min | 1.64 | (0.16 to 3.13) | | | 0.53 | (-0.76 to 1.83) | | | 0.30 | (-0.61 to 1.20) | |
| Pain when swallowing | | | .10 | | | | .0001 | | | | .0001 |
| No | 0.00 | Ref. | | | 0.00 | Ref. | | | 0.00 | Ref. | |
| Yes | 0.78 | (-0.16 to 1.73) | | | 1.27 | (0.66 to 1.87) | | | 1.17 | (0.58 to 1.75) | |
| VDQ score | | | <.0001 | | | | .02 | | | | .01 |
| 0 | 0.00 | Ref. | | | 0.00 | Ref. | | | 0.00 | Ref. | |
| 0.1–2.5 | 0.14 | (-0.66 to 0.93) | | | 1.02 | (0.22 to 1.81) | | | 0.40 | (-0.60 to 1.39) | |
| 2.6–5.0 | 2.00 | (1.02 to 2.98) | | | 1.63 | (0.69 to 2.56) | | | 1.64 | (0.50 to 2.78) | |
| 5.1–7.5 | 3.22 | (1.66 to 4.78) | | | 1.81 | (0.43 to 3.20) | | | 1.62 | (-0.05 to 3.29) | |
| 7.6–10.0 | 6.19 | (4.21 to 8.17) | | | 1.96 | (0.45 to 3.47) | | | 1.57 | (-0.23 to 3.37) | |
| AMS score | | | .20 | | | | .01 | | | | .10 |
| 0 | 0.00 | Ref. | | | 0.00 | Ref. | | | 0.00 | Ref. | |
| 0.1–2.5 | -0.04 | (-0.73 to 0.66) | | | -0.57 | (-1.24 to 0.10) | | | -0.35 | (-1.13 to 0.43) | |
| 2.6–5.0 | -0.16 | (-1.16 to 0.85) | | | -0.06 | (-0.98 to 0.86) | | | -0.42 | (-1.43 to 0.59) | |
| 5.1–7.5 | 0.20 | (-1.34 to 1.73) | | | 0.77 | (-0.59 to 2.12) | | | 0.39 | (-1.15 to 1.93) | |
| 7.6–10.0 | 2.19 | (0.28 to 4.10) | | | 2.15 | (0.46 to 3.84) | | | 1.91 | (0.01 to 3.81) | |
| Constant[b] | 0.39 | (-0.21 to 0.98) | .20 | | 0.38 | (-0.14 to 0.89) | .15 | | 0.88 | (0.20 to 1.55) | .01 |
| $R^{2c}$ | **0.72** | | | | **0.67** | | | | **0.58** | | |

CI, confidence interval; Ref, reference.

[a]The coefficient represents the change in the value of the predicted PatGA for each category change of the independent variable. For example, for a 7-day recall period, the predicted PatGA increased by 1.3 if the patient reported having frequency of trouble swallowing of 1–3 times a week (category of never was the reference category). Similarly, the predicted PatGA increased by 2.29 and 2.61 points, if instead of not having any trouble swallowing (never), the patient reported having frequency of trouble swallowing of 4–6 times/wk and daily, respectively. In this analysis, with frequency of trouble swallowing, duration of trouble swallowing, and so forth, as independent variables and predicted PatGA as the dependent variable, the adjusted regression coefficient for the duration of trouble swallowing represents the amount of variation in predicted PatGA that is owing to the effects of duration of trouble swallowing alone, after frequency of trouble swallowing has been taken into account. For example, for a 7-day recall period, if the patient experienced daily episodes of trouble swallowing (with a predicted PatGA increase of 2.61 points), his/her predicted PatGA increased by another 0.53 points, if the duration of those trouble swallowing episodes was longer than 5 minutes.

[b]The constant represents the value of the predicted PatGA when all 5 values of independent variables are set to reference category.

[c]The coefficient of determination, $R^2$ is a measure of the extent to which the regression model describes the observed data. The closer the $R^2$ is to 1, the more precise the regression model is. Because $R^2$ can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance, only independent variables that have a large effect have been included in the model. This also was performed to ensure that the statistical model is clinically meaningful and can be interpreted easily.

### *Relationship Between Patient-Assessed EoE Severity and Biologic EoE Activity*

We observed a positive association between endoscopic/histologic alterations and PatGA, which is illustrated by box plots in Figure 2. We did not find a correlation between PatGA and peripheral blood eosinophil counts ($r = 0.045$; $P = .67$).

### *Validation of the Score as Well as Practicability and Content Validity of the Instrument*

To validate the PRO score obtained during the evaluation phase, we calculated it for every EoE patient recruited in the validation group and compared it with the PatGA. The plot in Figure 3*A* shows that the EEsAI PRO score for the 7-day recall period predicted 65% of the variability in PatGA, which closely compares with the 67% variability in PatGA that is explained by the EEsAI PRO score in the evaluation group. The Bland–Altman plot (Figure 3*B*) evaluates the agreement between the calculated EEsAI PRO score and the PatGA. A mean difference of only 0.15 between the PatGA and EEsAI PRO score was observed. The upper and lower 95% limits of agreement were 3.06 and -2.75, respectively. Two versions of the validated 7-day EEsAI PRO score are shown in Table 4: (1) the original PRO score that ranges from 0 to 8.52, and (2) the user-friendly EEsAI PRO score that ranges from 0 to 100.

To evaluate the practicality and content validity of the validated EEsAI PRO instrument, we again contacted the 27 patients who participated in the focus groups. First, we evaluated the time patients needed to complete the EEsAI PRO instrument. When completing the instrument for the first time, patients required a median of 8 minutes (IQR, 7–9 min; range, 4–10 min). When asked "How difficult was it for you to complete this questionnaire?" patients responded with a median score of 1 (IQR, 0–2; range, 0–6) on an 11-point Likert scale where 0 represents no difficulties at all and 10 represents very difficult. To evaluate content validity, patients were asked the Likert scale question: "Does this questionnaire measure the complaints you have had/you currently have due to EoE?" Patents responded with a median score of 8 (IQR, 7–9; range, 4–10), where 10 represents perfectly and 0 represents not at all.

## Discussion

Eosinophilic esophagitis is a young disease, and, to date, no validated PRO instruments reliably assessing disease activity have been approved by the regulatory authorities in the United States and Europe.

In this article, we describe the process of the development and validation of the adult EEsAI PRO instrument that assesses EoE symptom severity. We developed the EEsAI PRO instrument according to FDA guidelines.[16] Patient surveys, focus groups, and semistructured interviews were used to gain patient input to inform PRO instrument development. The resulting PRO instrument was evaluated in the first group of adult EoE patients. As a gold standard, we used patient assessment of disease severity (PatGA) to develop the EEsAI PRO instrument score. Based on statistical considerations and expert input, 7 PRO items were selected. These items explained 67% of the total variability in the PatGA over a 7-day recall period. The EEsAI PRO instrument was validated in a second group of patients, and these 7 items explained 65% of the variability in PatGA.

Assessment of dysphagia is a challenge because this symptom depends not only on the severity of the disease, but also on the consistency of the ingested foods. Moreover,

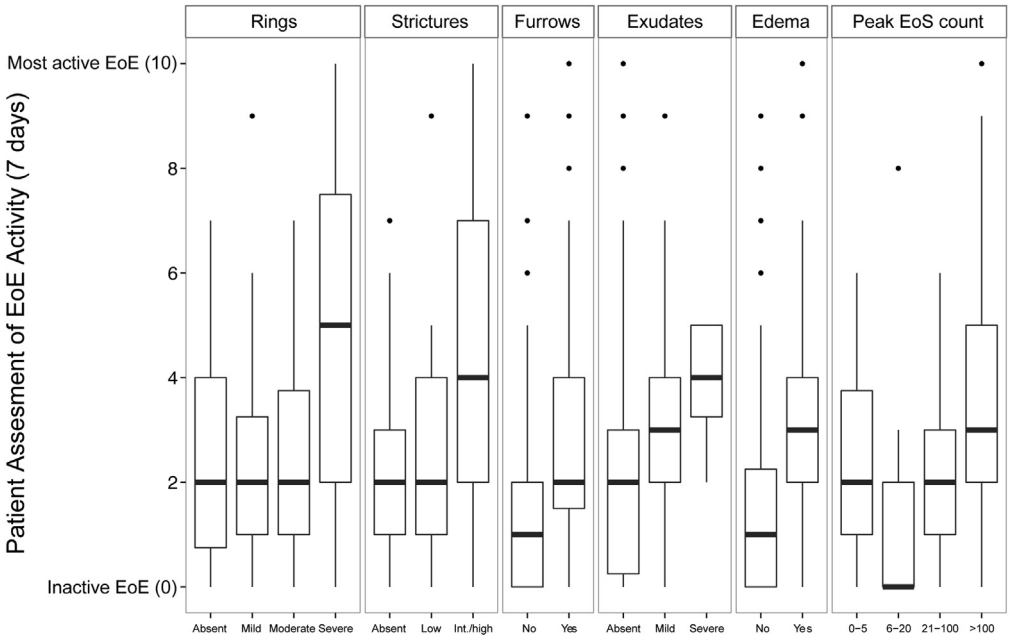


**Figure 2.** Box plots of patient-assessed EoE severity distribution by endoscopic/histologic activity. The box contains the 25th–75th percentiles of values, the *horizontal line* in the middle of the box represents the median. Eos, eosinophils.

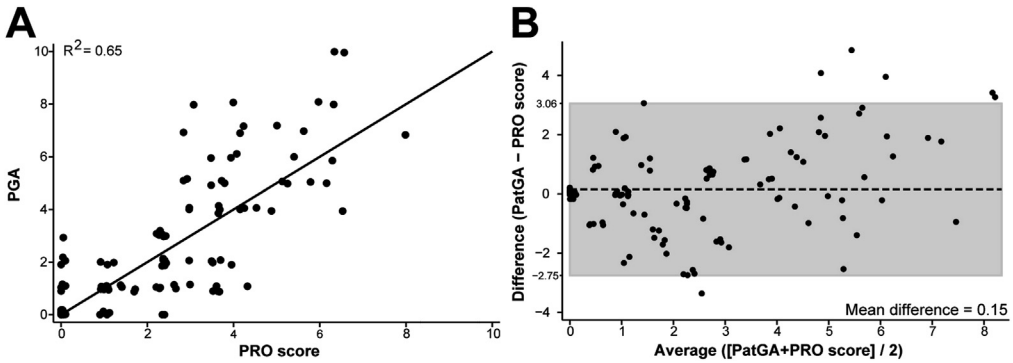


**Figure 3.** (*A*) The correlation plot between the EEsAI PRO score and the PatGA in the validation group. (*B*) The Bland–Altman plot for the agreement between the EEsAI PRO score and the PatGA in the validation group. The *grey box* indicates the 95% limits of agreement.

patients suffering from dysphagia rapidly develop behavioral adaptation strategies. The EEsAI PRO instrument assesses dysphagia caused by eating foods of different consistencies (VDQ), and takes into account behavioral adaptation strategies. The food consistencies of the VDQ are well defined, and the foods used to illustrate those consistencies frequently are eaten in Western countries. Because the VDQ includes items from various food groups, the EEsAI PRO instrument can be used to assess dysphagia in individuals with, among others, vegetarian dietary patterns, food intolerances, and in patients on elimination diets. Based on patient input, the EEsAI PRO instrument is a content-valid measure of EoE symptom severity and easy to complete.

**Table 4.** EEsAI PRO Score for the 7-Day Recall Period

| Item | Score (based on regression coefficients) | Score (total set to 100) |
|---|---|---|
| Frequency of trouble swallowing | | |
| Never | 0 | 0 |
| 1–3 times/wk | 1.30 | 15 |
| 4–6 times/wk | 2.29 | 27 |
| Daily | 2.61 | 31 |
| Duration of trouble swallowing | | |
| ≤5 min | 0 | 0 |
| >5 min | 0.53 | 6 |
| Pain when swallowing | | |
| No | 0 | 0 |
| Yes | 1.27 | 15 |
| VDQ score | | |
| 0 | 0 | 0 |
| 0.1–2.5 | 1.02 | 12 |
| 2.6–5.0 | 1.63 | 19 |
| 5.1–7.5 | 1.81 | 21 |
| 7.6–10.0 | 1.96 | 23 |
| AMS score | | |
| 0 | 0 | 0 |
| 0.1–2.5 | 0 | 0 |
| 2.6–5.0 | 0 | 0 |
| 5.1–7.5 | 0.77 | 9 |
| 7.6–10.0 | 2.15 | 25 |
| Total | 8.52 | 100 |

NOTE. The score based on regression coefficients that ranges from 0 to 8.52 is shown in column 1. For clinical ease of use, a total of the score based on the regression coefficients was set to 100 and values for each category were adjusted accordingly. This score is shown in column 2.

PROs must be assessed in a defined recall period, but its choice depends on the following factors: (1) intended use of the instrument (conceptual framework), (2) the ability of the patient to remember the required information, (3) the extent to which the patient with a certain illness is burdened when completing the instrument, (4) the nature of the disease and the symptoms, and (5) the study design.[27] The choice of a short recall period may lead to underestimation of symptom severity when symptoms have a day-to-day fluctuation, or else may place undue burden on the patient if patients are too ill to complete the questionnaire frequently. However, a long recall period may overestimate or underestimate the true health status of the patient. Based on patient preferences and statistical considerations presented in this study, the 7-day symptom recall period appears to be the most suitable for this chronic condition.

In recent years, several PRO instruments have been developed to assess EoE symptom severity. The Straumann Dysphagia Index does not assess dysphagia caused by eating foods of different consistencies and does not take into account behavioral adaptations to living with dysphagia.[13,14] The MDQ-30 day version assesses dysphagia caused by various esophageal diseases, but it has not been developed for EoE specifically.[11,12] By using the DSQ, Dellon et al[15] recently evaluated dysphagia to solid food in a group of 35 adolescent and adult EoE patients. However, the term solid food was not defined in the article. In our study, we noted important differences in dysphagia severity and behavioral adaptations to dysphagia when patients consumed solid food of different consistencies. For example, 75% of patients expected to experience dysphagia as a result of consumption of solid meat, whereas only 17% of patients expected to experience dysphagia when eating grits or porridge. Standardizing the assessment of dysphagia by ingestion of a defined test meal is one way to avoid the complexities associated with the definition of solid food. However, such an approach may not be entirely practical and may raise ethical concerns associated with the exposure

of the patients to the risk of food bolus impactions.[28] The VDQ can be thought of as a hypothetical test meal that potentially avoids the ethical issues associated with the ingestion of a defined test meal. In contrast to findings reported by Dellon et al,[15] we found that patients frequently reported behavioral adaptations to dysphagia such as food modification, food avoidance, and slow eating. For example, 67% of EoE patients reported eating solid meat more slowly than other people eating this type of food. The EEsAI PRO instrument assesses dysphagia caused by eating foods of distinct consistencies and also takes into account behavioral adaptations.

We observed a positive relationship between endoscopic and histologic alterations and patient-assessed EoE severity. We suspect that patients are, to a lesser extent, sensitive to mild endoscopic/histologic alterations when compared with moderate/severe alterations. This relative lack of sensitivity to mild EoE alterations may explain why the positive correlations between EoE symptom severity and endoscopic and histologic findings have been documented in some,[13,14,29] but not other, studies[11,30] in both adult and pediatric patients. The observed inconsistencies in the correlations between PRO and biologic items also may be related to the fact that dysphagia and behavioral adaptations in these studies has not been assessed in the context of various food consistencies. Finally, the assessment of endoscopic and histologic alterations in adult EoE has not been standardized in these studies. The recent work by Hirano et al[26] represents an important milestone in standardizing the assessment of endoscopic alterations in EoE. At present, the presumed pathophysiological mechanisms leading to EoE symptoms involve mucosal inflammation that is associated with dysmotility and/or mechanical restriction owing to subepithelial fibrosis. We have yet to assess the relationship between symptom severity as captured by the EEsAI PRO instrument and the esophageal compliance that can be measured by the Endolumenal Functional Lumen Imaging Probe (EndoFLIP; Crospon, Inc, Carlsbad, CA).[31,32] For the purposes of clinical trials, it seems prudent to include both PRO and biologic end points because untreated eosinophil-predominant esophageal inflammation is associated with the generation of esophageal strictures that ultimately lead to symptoms.[31,33]

Our study had several strengths, but some limitations as well. We present data from an international multicenter study to develop and validate an activity index for adult EoE patients. We followed the recommendations of the FDA for PRO instrument development.[16] Although the DSQ applies a scoring algorithm that involves giving a discrete arbitrarily chosen value to each item response,[15] the scores for individual items of the EEsAI PRO instrument are based on the regression coefficients of the linear regression modeling using PatGA (the current gold standard for patient-perceived symptom severity) as the outcome. The EEsAI PRO instrument is an EoE-specific instrument designed to assess dysphagia caused by eating 8 different food consistencies and behavioral adaptations to living with dysphagia. As such, the validated EEsAI PRO instrument can be used to measure EoE symptom severity in patients who do not eat certain food categories, such as vegetarians or patients on specific elimination diets. The EEsAI PRO instrument is validated, content-valid, and easy to complete.

Regarding limitations, the EEsAI PRO instrument was evaluated and validated for adult patients only (age, $\geq$17 y). The EEsAI PRO instrument is about to be used in an upcoming randomized, placebo-controlled, clinical trial that will provide data on responsiveness. We also evaluated and validated the PRO instrument for a 24-hour recall period, in case completion of the PRO instrument on a daily basis might be preferred in certain studies. These data will be published elsewhere. The development of an electronic PRO (hand-held device) certainly will make the instrument even more user-friendly.

In summary, we report on the development and validation of the adult EEsAI PRO instrument to assess EoE symptom severity over a 7-day recall period. The EEsAI PRO instrument is content-valid and is easy to complete. The development and validation of an instrument for standardized assessment of EoE symptom severity is a matter of paramount importance for guiding clinical decision making and for defining the outcome parameters for clinical trials as well as epidemiologic studies.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.08.028.

## References


1. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109–116.
2. Straumann A, Spichtin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr 1994;20:1419–1429.
3. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.
4. Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr 2011;52:300–306.
5. **Hruz P, Straumann A**, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. J Allergy Clin Immunol 2011;128:1349–1350.
6. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009;7:1055–1061.
7. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014;12:589–596.

8. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med 2004;351:940–941.
9. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–1669.
10. Straumann A, Rossi L, Simon HU, et al. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? Gastrointest Endosc 2003;57:407–412.
11. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012;10:742–749.
12. Grudell AB, Alexander JA, Enders FB, et al. Validation of the Mayo Dysphagia Questionnaire. Dis Esophagus 2007;20:202–205.
13. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–1537.
14. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400–409.
15. Dellon ES, Irani AM, Hill MR, et al. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmcol Ther 2013;38:634–642.
16. US Food and Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims. Available at: www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed: December 3, 2013.
17. Fiorentino R, Liu G, Pariser AR, et al. Cross-sector sponsorship of research in eosinophilic esophagitis: a collaborative model for rational drug development in rare diseases. J Allergy Clin Immunol 2012;130:613–616.
18. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008–1015.
19. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349–357.
20. Mayring P. Qualitative content analysis. Forum: qualitative social research, 1(2), Article 20. 2000. Available: http://nbn-resolving.de/urn:nbn:de:0114-fqs0002204.
21. Erickson P, Willke R, Burke L. A concept taxonomy and an instrument hierarchy: tools for establishing and evaluating the conceptual framework of a patient-reported outcome (PRO) instrument as applied to product labeling claims. Value Health 2009;12:1158–1167.
22. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 2007;10(Suppl 2):S125–S137.
23. Bottomley A, Jones D, Claassens L. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. Eur J Cancer 2009;45:347–353.
24. McLeod LD, Coon CD, Martin SA, et al. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res 2011;11:163–169.
25. Process of translation and adaptation of instruments. Available at: http://www.who.int/substance_abuse/research_tools/translation/en/. Accessed: May, 2011.
26. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. Gut 2013;62:489–495.
27. Norquist JM, Girman C, Fehnel S, et al. Choice of recall period for patient-reported outcome (PRO) measures: criteria for consideration. Qual Life Res 2012;21:1013–1020.
28. Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clin Gastroenterol Hepatol 2008;6:598–600.
29. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010;139:418–429.
30. Pentiuk S, Putnam PE, Collins M, et al. Dissociation between symptoms and histologic severity in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2009;48:152–160.
31. **Schoepfer AM, Safroneeva E**, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation, in a time-dependent manner. Gastroenterology 2013;145:1230–1236.
32. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011;140:82–90.
33. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–585.


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Please contact Alain M. Schoepfer for inquiries about permission to use the EEsAI instruments in a study.

**Conflicts of interest**

Alain Schoepfer has received research grants from AstraZeneca AG, Aptalis Pharma, Inc, Dr Falk Pharma GmbH, Glaxo Smith Kline, plc, Nestlé SA, and Novartis; he received consulting fees from Aptalis Pharma, Inc, and Dr Falk Pharma, GmbH. Alex Straumann has received research grants from AstraZeneca AG, Aptalis Pharma, Inc, Dr Falk Pharma GmbH, Glaxo Smith Kline, plc, Nestlé SA, Novartis and Regeneron Pharmaceuticals, Inc; he received consulting fees from Actelion Pharmaceuticals Ltd, Bühlmann Laboratories AG, Dr Falk Pharma GmbH, Genentech, Inc, Glaxo Smith Kline, plc, Meritage Pharma, Inc, Merck & Co, Inc, Nestle SA, Novartis AG, Oxagen, Ltd, Pfizer, Inc, Receptos, Inc, Regeneron Pharmaceuticals, Inc; he also received speaker fees from Takeda Pharmaceutical Company, Ltd; Radoslaw Panczak has received consulting fees from Aptalis Pharma, Inc; Claudia Kuehni has received research grants from AstraZeneca AG, Aptalis Pharma, Inc, Dr Falk Pharma GmbH, Glaxo Smith Kline, plc, and Nestlé SA; Yvonne Romero has collaborated on projects supported by Aptalis Pharma, Inc, and Meritage Pharma, Inc, and has received royalties for commercial use of the MDQ-30; Ikuo Hirano has received research grants from Meritage Pharma, Inc, and consulting fees from Aptalis Pharma, Inc, Meritage Pharma, Inc, and Receptos, Inc; Jeffrey Alexander has received consulting fees from Meritage Pharma, Inc, and Aptalis Pharma, Inc, and research grant from Merck & Co, Inc; he has received royalties for commercial use of the MDQ-30, and also has a financial interest in Meritage Pharma, Inc; Glenn Furuta has received consulting fees from Pfizer, Inc, Meritage Pharma, Inc, Knopp, and Biosciences, LLC, and has received royalties from UpToDate, Inc, and is also a founder of EnteroTrack, LLC; Evan Dellon has received research grants from AstraZeneca, AG, and Meritage Pharma, Inc, he has received consulting fees from Aptalis Pharma, Inc, Novartis, Receptos, Inc, and Regeneron Pharmaceuticals, Inc; John Leung has received research grants from Meritage Pharma, Inc; Margaret Collins has received consulting fees from Aptalis Pharma, Inc, Biogen Idec, Meritage Pharma, Inc, Novartis, and Receptos, Inc; Sandeep Gupta has received consulting fees from QOL, Receptos, Inc, and Meritage Pharma, Inc, and speaker fees from Abbott Laboratories and Nestlé SA. Seema Aceves is a co-inventor of oral viscous budesonide (patent held by University of California, San Diego), and also has received royalties for oral viscous budesonide from Meritage Pharma, Inc, owns stocks in Meritage Pharma, Inc, and has received consulting fees from Receptos, Inc, and Regeneron Pharmaceuticals, Inc; Felicity Enders receives royalties for commercial use of the MDQ-30; Marcel Zwahlen has received research grants from AstraZeneca AG, Aptalis Pharma, Inc, Dr Falk Pharma GmbH, Glaxo Smith Kline, plc, and Nestlé SA; and Ekaterina Safroneeva has received consulting fees from Aptalis Pharma, Inc, and Novartis. The remaining authors disclose no conflicts.

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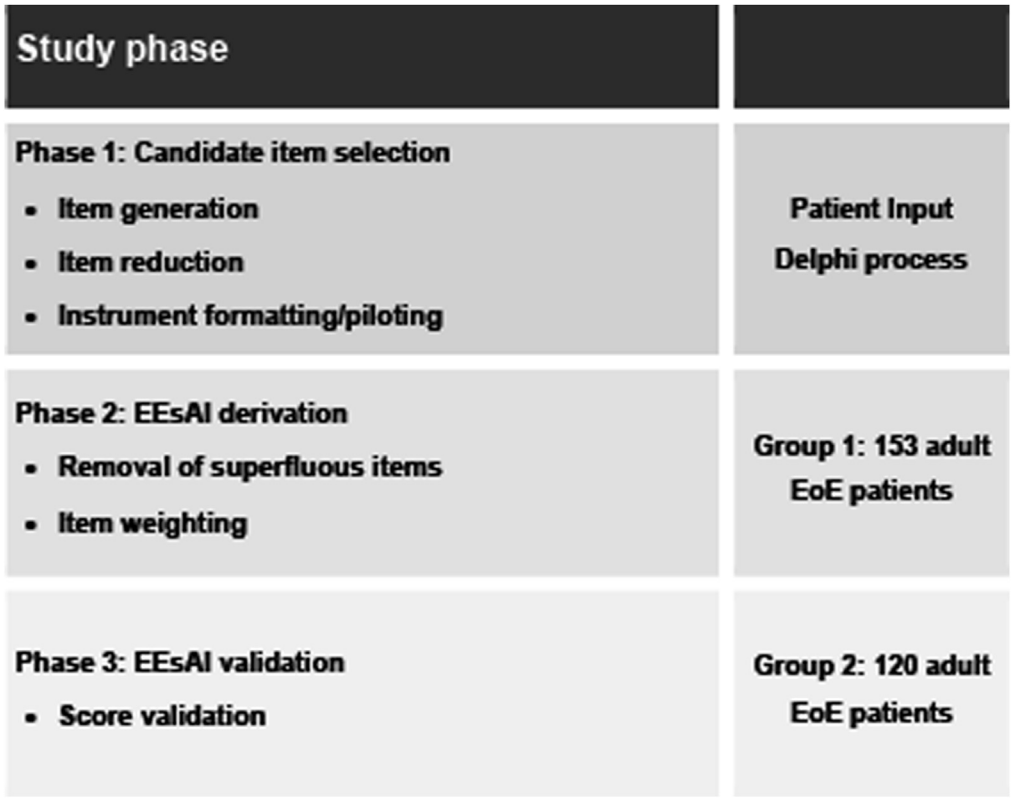
# Appendix 1




**Supplementary Figure 1.** Timetable for the adult EEsAI study.

# Appendix 2

# Development and Validation of a Symptom Activity Index for Adults with Eosinophilic Esophagitis: Qualitative Methods

This section describes in detail the qualitative methods used to develop and validate the EEsAI PRO instrument. Findings are reported according to the Consolidated Criteria for Reporting Qualitative Research.[1]

## Patients and Methods

The EEsAI study is registered under clinicaltrials.gov (NCT00939263) and was approved by the institutional review boards and ethics committees of the participating centers. The qualitative work reported in this article was conducted in Switzerland (cantons of Bern and Solothurn) and at Northwestern University (Chicago, IL). All participants provided written informed consent.

### *Research Team and Reflexivity*

The research team was composed of experts in the field of EoE (A.M.S., A.S., I.H., and N.G. are practicing gastroenterologists), general internal medicine (E.K.), mucosal immunology (E.S.), veterinary medicine (E.M.), epidemiology (R.P. and M.Z. are epidemiologists, and C.E.K. is a pediatric pulmonologist and epidemiologist), PRO design (K.K. and B.S. are PRO specialists), statistics (M.C.), and psychology (T.H.T. and K.M.), with specific expertise in qualitative research. The research team also included a research assistant (N.A.H.).

The interviewers (T.H.T., K.M., and B.S.) were trained in qualitative methodology as part of university studies and research activities; the interviewer (E.K.) and the facilitators (A.M.S. and A.S.) underwent training in qualitative research methodology for the purposes of this study. Those performing content analysis (E.S., A.M.S., N.H., and E.M.) received training in qualitative research methodology for the purposes of this study. Some of the authors were experienced at performing research (T.H.T., C.E.K., M.Z., and E.S. have conducted research on various aspects of EoE for >5 years, and R.P., M.C., E.M., and N.A.H. have conducted EoE research for at least 1 year). Some of the authors underwent background training on various aspects of EoE related to this study specifically for the purposes of this study (K.K., K.M., and B.S.). Some of the authors are experts and have published extensively on EoE (A.S., A.M.S., I.H., and N.G.).

Patients participating in the survey had an established relationship with treating physicians (A.S., I.H., and N.G.). Patients participating in the survey were informed about the purpose and research interests of the research team through a letter that described the purpose of the study. Patients who participated in the focus groups had an established relationship with the treating physician (A.S.), but no previous relationship with A.M.S. and K.M. Before the focus groups, patients were provided with information about the study and the research interests of the research team (A.M.S. and A.S.). Patients participating in the face-to-face semistructured interviews had an established relationship with the treating physicians (I.H., N.G.), but no previous relationship with the other physician (E.K.).

### *Study Design*

**Theoretical framework.** Given the fact that there is no single gold standard to gain patient input for PRO development, we chose a mixed methods approach by gathering patient input by means of surveys, focus groups, and individual interviews (Supplementary Figure 2). The content analysis was performed using a deductive category application approach described by Mayring.[2,3] This method allows separation of the data from the text and systematic reduction of the information.[2–4] We followed the Consolidated Criteria for Reporting Qualitative Research guidelines when reporting the results of this study.[1]

**Participant selection and setting.** The diagnosis of EoE was established according to published criteria.[5] Patients with EoE and concomitant gastroesophageal reflux disease who were receiving treatment with at least a standard dose of proton pump inhibitors were included in the study.

*Patients participating in the survey.* A total of 110 EoE patients from Switzerland (A.S.) and 287 EoE patients from Northwestern Medical Center (Chicago, IL) (I.H. and N.G.) were asked to participate in the study. EoE patients were sent questionnaires by mail. Patients completed these at a place of their choice and returned the completed questionnaires by mail.

*Patients participating in the focus groups.* Thirty-two EoE patients were approached during a routine clinical visit in an EoE clinic (Olten County, Switzerland), and invited (by A.S.) to participate in the focus groups. Five patients declined the invitation. Twenty-seven EoE patients were interviewed in 3 focus groups (n = 9 for each focus group). Interviews were conducted at the EoE clinic in Olten, Switzerland. Except for the interviewer (K.M.) and 2 facilitators (A.M.S., A.S.), no one else was present at the time of the focus group discussions.

*Patients participating in the individual patient interviews.* A total of 30 patients were approached during a routine clinical visit at a university-based gastroenterology practice and invited (by I.H. and N.G.) to participate in the face-to-face patient interviews. Six patients declined to participate. Interviews were conducted at Northwestern Medical Center (Chicago, IL).

**Data collection.** *Eosinophilic esophagitis symptom questionnaire used in the survey.* The EoE symptom questionnaire consists of 7 close-ended questions designed to address participants' age, sex, country of citizenship, education, and current occupation, and 2 open-ended questions assessing EoE-related symptoms and their severity (Supplementary Table 1). For each open-ended question, we provided an example of the way an answer to this question might be given and a space of 4 lines for a description of a single symptom or complaint. We also provided an 11-point

Likert scale for patients to rank the severity of a given symptom (Supplementary Figure 3). For each open-ended question, a space for a description of up to 6 concerns or symptoms was provided. Patients were asked to write any other additional symptoms they might have experienced on a separate sheet of paper, if they were to run out of space. The questionnaire was developed in German (Olten County is located in the German-speaking part of Switzerland). The EoE symptom questionnaire in German was translated into US English, as described by Acquadro et al.[6] During the pilot study, 15 study participants were asked to complete the questionnaires. After the completion of the questionnaires, patients were interviewed to provide feedback. Patients judged the questionnaires to be appropriate to capture EoE-related symptoms and easy to complete.

*Focus groups.* Subjects participated in the focus group guided by an experienced psychologist (K.M.) to learn about the patient's symptoms and other experiences with EoE. Facilitators were present as well (A.M.S. and A.S.). A priori themes, such as symptoms during food intake or symptoms when not eating or drinking, behavioral adaptations to living with dysphagia, impairment in social and professional activities, experience with treatments and endoscopies, as well as other concerns, were developed based on the existing literature, the experience of the research team, or were adopted and/or reproduced directly from a study by Tufts et al with permission of the senior investigator (I.H.).[5,7–11] The open-ended questions were constructed in German, a translation of these questions into English is provided in Supplementary Table 2. Three repeat focus groups were performed in the Swiss dialect of the German language. The focus groups lasted between 1.5 and 2 hours. All sessions were audiorecorded, translated, and transcribed in German because the Swiss dialect of German is not a written language. The research team reviewed transcriptions of the focus groups. The transcripts were analyzed by the lead investigator (A.S.) and the research team (E.S., E.M., and N.A.H.). Field notes were taken (A.S.). Transcripts were not returned to participants for further comments. Because no new theme had arisen during the past 2 focus groups, no additional focus group interviews were performed.

The patients participating in the focus group interviews for item generation were contacted at later time points to provide feedback about the best recall period to assess EoE symptoms, to assess the content validity, and the practicability of the EEsAI PRO instrument.

*Individual patient interviews.* Twenty-four EoE patients underwent individual face-to-face semistructured interviews guided by a trained physician (E.K.) to inquire about the symptoms and other experiences with EoE. No facilitator was present during the individual interviews. Interviews were conducted in English. The set of questions has been published previously by Taft et al.[11] An individual patient interview lasted between 50 and 60 minutes. After the interview, patients underwent a debriefing with the interviewer to better understand various reasons behind patients' responses. Field notes were taken by the interviewer after the individual patient sessions. All interviews and debriefing sessions were audiorecorded and transcribed. The transcripts were analyzed by the local investigators (E.K., T.H.T., I.H., and N.G.) and the research team in Switzerland (E.S., N.A.H., and A.M.S.).

**Analysis and findings.** *Development and description of the code book.* Based on a review of the existing literature and the proposals of the multidisciplinary research team, the conceptual model was developed (Supplementary Figure 4), and the preliminary version of the codebook was derived.[5,7–11] The input from patients and the expert discussions were designed to elicit concepts related to patient experiences with EoE symptoms to help develop an EoE symptom severity instrument.

*Data analysis.* We conducted a computer-assisted content analysis according to Mayring using ATLAS.ti software, version 5.0 (ATLAS.ti, GmbH, Berlin, Germany).[2,3] We established definitions and coding rules for each main code category and its subcode categories before the coding (see development and description of the code book). The unit of analysis was defined as all words and sentences related to the description of a single symptom or a problem (written within the 4 lines provided per discomfort). The complete transcripts of surveys, focus groups, and individual patient interviews were read by 2 coders (A.M.S. and E.S.). Because questionnaires were completed in 2 languages, 3 coders with proficiency in English and German analyzed the material. Categories were discussed among coders until mutual agreement was reached. One researcher (E.S.) analyzed all the material using these code categories, and categories were revised or expanded, if necessary, to saturate the content of the material provided. As a formative check of reliability, we clarified definitions, as well as new and obsolete codes, until consensus about saturation was reached. The final codes were applied to all the text (Supplementary Table 3). As a part of summative reliability check, the final matching of the main code and subcode categories, as well as their validity, were discussed by a research team, and agreement was reached when opinions differed. Given the fact that Taft et al[11] already described the impact that EoE has on several psychosocial domains, we specifically analyzed the transcripts of semistructured interviews for a description of the physical complaints and those psychosocial domains related to adaptations to living with dysphagia.

The sociodemographic data were entered in a database created in EpiData, version 3.1 (EpiData Association, Odense, Denmark). Descriptive analyses were performed using Stata, version 11.2 (Stata Corporation, Austin, TX).

# Results

## *Response Rate Characteristics of the Study Population*

Supplementary Table 4 provides an overview of the sociodemographic characteristics of the study sample overall, which consists of patients having participated in the surveys, in the focus group interviews, and in the individual patient interviews. A total of 397 consecutive EoE patients

were addressed by treating physicians to participate in the survey in Switzerland and the United States. Response rates were 19.2% (55 of 287 patients) in the United States and 72.7% (80 of 110 patients) in Switzerland. The results are based on the responses provided by 135 patients. Of a total of 617 statements, 467 (75.7%) described symptoms while eating (a statement represents one answer written within the 4 lines provided per discomfort). Fifty-three patients (39.3%) reported only discomfort related to eating or drinking. For focus groups, 32 Swiss patients were invited, with 5 patients declining to participate (response rate, 84%). For semistructured face-to-face interviews, 30 US patients were approached, with 6 patients declining to participate (response rate, 80%). All patients had a confirmed EoE diagnosis at the time of participation in the study.

### Qualitative Analysis

**Major themes.** Three key themes and 2 subthemes emerged: the definitions of dysphagia and dysphagia characteristics; dysphagia caused by different foods, pills, and beverages; and behavioral adaptations to living with dysphagia (2 subthemes: strategies aimed to avoid impaction and strategies dealing with impaction once it occurred). The key domains and their relationships are illustrated in Supplementary Figure 5.

*Definition of dysphagia and dysphagia characteristics.* In Supplementary Table 5, a sample quotation of the description of dysphagia events and the specific characteristics of these events provided by the patients are shown. Participants described dysphagia in terms of difficulty swallowing, solids/liquids passing slowly or not smoothly, a feeling of tightness, and most commonly as impaction events, characterized by food being stuck or lodged in the esophagus or else by choking on food. Dysphagia events were described by patients to be occurring in the throat and chest or esophagus. We were able to identify various characteristics and attributes of dysphagia, such as the duration, frequency, and severity of dysphagia events. The duration of dysphagia events ranged from a few seconds, to minutes, to many hours, especially if impacted food had to be removed by endoscopy. The frequency of dysphagia ranged from infrequent events, to those occurring a few times a week, and, finally, to those occurring every day and every time one eats. Patients often mentioned that various disease treatments diminished the frequency or the severity of the dysphagia events.

*Dysphagia caused by eating different foods, pills, and drinking beverages.* Patients frequently described dysphagia events caused by eating certain foods, drinking beverages, or swallowing pills. In Supplementary Table 6, the sample quotation of the describing dysphagia events caused by eating foods, swallowing pills, and drinking beverages is shown. Of all the foods causing dysphagia, meat was mentioned most frequently, followed by bread and rice. However, other foods, such as uncooked fruits and vegetables, ground meat, French fries, and pasta also caused trouble swallowing in patients with EoE. Patients also described dysphagia caused by swallowing large pills. In addition, drinking liquids also caused dysphagia events. Patients also were likely to specify that alcoholic beverages were causing these events. Finally, patients occasionally mentioned foods that do not cause dysphagia and are easy to swallow.

Patients also used various adjectives to describe foods that cause dysphagia, of these "solid" and "dense" were most frequent, but "heavy," "tough," or "thick" also were used. Mostly, these adjectives were used in the context of dysphagia caused by eating meat, although other foods also were mentioned. Similarly, the adjectives "fibrous" and "course" also were used frequently to describe foods causing dysphagia; most frequently these adjectives were used to describe uncooked vegetables, but these also occasionally were used in the context of eating meat. Finally, the adjective "dry" was used frequently to describe dry foods, such as popcorn and chips, that also caused dysphagia, but this adjective also frequently was used in the context of dysphagia events caused by eating meat.

*Behavioral adaptations to living with dysphagia.* Over the years, patients have developed various strategies to avoid impaction events or to deal with them, especially to avoid going for emergency treatment. Examples of these strategies are shown in Supplementary Table 7. The following strategies for avoiding impaction events were used by EoE patients: food avoidance, food processing, eating carefully/slowly, and drinking liquids to wash down the food. Patients mostly avoided eating meat, although rice, bread, and vegetables also were described as foods to be avoided. Patients also processed their foods to avoid food impaction events, of which the most common strategy was to cut meat into small pieces before consuming it. Other strategies involved peeling apples before eating them or eating foods with sauces to facilitate swallowing. Patients also described that eating slowly, carefully, taking smaller bites out of their foods, and chewing carefully helped them to avoid impaction episodes. Patients also mentioned that eating quickly would lead to dysphagia episodes; we interpreted these statements as an indication that eating slowly was a strategy to avoid dysphagia. Finally, many patients mentioned that they nearly always had something to drink during mealtimes. The strategies of dealing with impaction events also frequently were mentioned by patients. For the purposes of coding, these strategies had to be used in the context of impaction events, described as foods "sticking" or "lodging itself" in the chest, esophagus, or throat. These strategies included trying to induce "choking," "coughing," or vomiting of impacted food. Waiting for impaction to resolve itself was also a very common strategy. Patients also used liquids to wash down impacted food. This strategy was different from the strategy of avoiding impaction by drinking liquids, which was defined as something occurring regularly when eating. Liquids frequently were described as either helping to resolve impaction events or not. Patients also used other strategies, such as relaxing, walking, and performing a physical activity, such as jumping, to try to resolve the impaction event.

**Other themes.** Other themes identified in the process of our analysis included swallowing-associated pain, non–swallowing-associated pain, allergic reactions related to

food intake, gastroesophageal reflux disease-like symptoms, and treatments. In Supplementary Table 8, the sample quotation for these themes is shown.

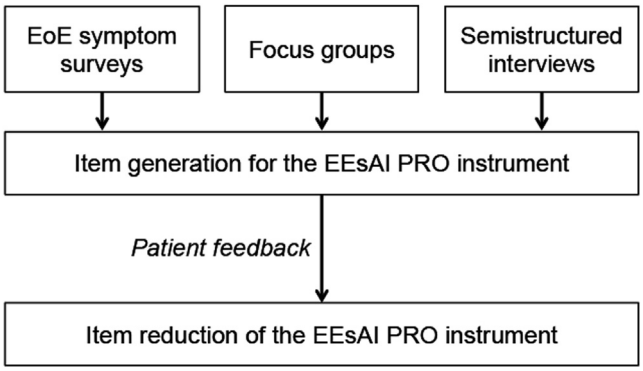
Patients mentioned that swallowing and particularly episodes of impaction were associated with pain mostly occurring in the chest/esophagus, although sometimes also in the belly/stomach. Characteristics of these swallowing-associated pain episodes, such as description of pain, frequency, duration, or severity, also were described. Similarly, non–swallowing-associated pain (and its characteristics), defined for the purposes of coding as pain occurring outside the time of eating or drinking and not occurring at the time of impaction, also was mentioned by the patients. Patients also described allergic reactions related to food. For the purposes of coding, this was defined as itching, swelling, or irritation of the mouth. Patients described this occurrence when consuming fruits, dairy, and wheat products, such as bread and beer. Finally, patients mentioned experiencing gastroesophageal reflux disease–like symptoms, including heartburn and acid regurgitation, often described as "reflux" or "acid reflux."

As treatments, patients mentioned endoscopic disimpactions, dilation, as well as treatments with anti-acid/gastroesophageal reflux medications and swallowed topical corticosteroids. Mostly patients mentioned treatment with medications and dilation in the context of feeling better after these treatments, although side effects of corticosteroid intake, such as fungal infection, also were described. In case of food impactions requiring endoscopic removal, these were mentioned in the context of being unable to swallow one's saliva and worrying, fearing, or panicking during these extreme episodes. Other treatments were mentioned in connection with other allergic disorders, such as asthma.

Although assessing the themes related to psychosocial function outside of disease-modifying behavior was outside the scope of our study, patients mentioned that they were concerned, often panicking, when experiencing episodes of food impaction. Patients also mentioned that they were concerned about meal times both at home and when eating out, especially in the presence of company.

## Supplementary References


1. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349–357.
2. Mayring P. Qualitative content analysis. Forum: qualitative social research, 1(2), Article 20. 2000. Available: http://nbn-resolving.de/urn:nbn:de:0114-fqs0002204.
3. Mayring P. Qualitative inhaltsanalyse: grundlagen und techniken. 11. Auflage, Beltz Pädagogik Verlag, Weinheim, Basel, 2010.
4. Gläser J, Laudel G. Life with and without coding: two methods for early-stage data analysis in qualitative research aiming at causal explanations. Forum: Qualitative Social Research 2013;14(2). Accessed: May 22, 2014.
5. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011; 128:3–20.
6. Acquadro C, Conway C, Giroudet C, et al. Linguistic validation manual for patient-reported outcomes (PRO) instruments. Lyon, France: Mapi Research Trust, 2004.
7. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109–116.
8. Straumann A, Spichtin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr 1994;20:1419–1429.
9. Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr 2011; 52:300–306.
10. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med 2004;351:940–941.
11. Taft TH, Kern E, Keefer L, et al. Qualitative assessment of patient-reported outcomes in adults with eosinophilic esophagitis. J Clin Gastroenterol 2011;45:769–774.




**Supplementary Figure 2.** Patient input.

**QUESTIONS RELATING TO EOSINOPHILIC ESOPHAGITIS**

**DISCOMFORT WHILE EATING**

Please describe any discomfort that you have experienced while eating or drinking that is due to eosinophilic esophagitis.

*Please try to explain your symptoms as precisely and clearly as possible. For example: If you have pain, where exactly is the pain? In your throat, stomach, chest, etc.? How long does the pain last? How intense is the pain? How often do you have pain, etc.?*

*If you have more than 6 symptoms, please describe them in detail on a separate sheet of paper.*

*A score of 0 (not annoying) indicates that you don't have the symptom, while a score of 10 (very annoying) indicates that the symptom is very strong, almost unbearable.*

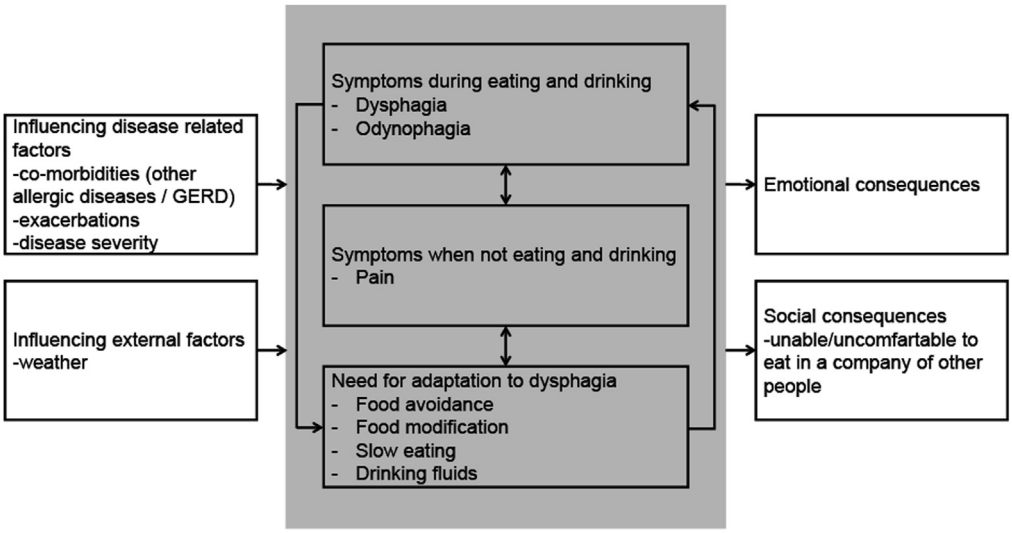
Example:

*When I eat French fries, I feel a tightness in my throat that lasts 10-20 seconds; afterwards, I have to drink water to wash down the food.*

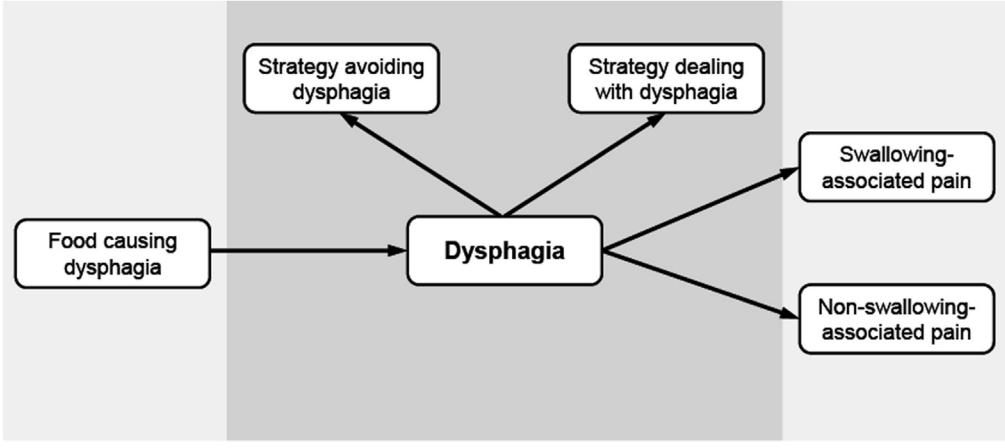
| Not annoying | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | very annoying |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ☐ | ☐ | ☐ | ☐ | ☑ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |

| Not annoying | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | very annoying |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | |

**Supplementary Figure 3.** Extract of the survey to gain patient input on EoE-related symptoms.




**Supplementary Figure 4.** Conceptual model of the study.




**Supplementary Figure 5.** Key domains of EoE-related symptoms.

**Supplementary Table 1.** Open-Ended Questions Used in the Patient Survey to Gain Input on Eosinophilic Esophagitis–Related Symptoms

| Question | Wording of the question |
|---|---|
| Open-ended question 1. Discomfort while eating | Please describe any discomfort that you have experienced while eating or drinking that is caused by eosinophilic esophagitis. |
| Open-ended question 2. Discomfort not related to eating or drinking | Please describe any discomfort related to eosinophilic esophagitis that occurs at times when you are not eating or drinking. In other words, symptoms that occur between meals. |
| Defining the question | *Please try to explain your symptoms as precisely and clearly as possible.* |
| Providing examples for the definition | *For example: If you have pain, where exactly is the pain? In your throat, stomach, chest, and so forth? How long does the pain last? How intense is the pain? How often do you have pain, and so forth?* |
| Explaining the procedure | *If you have more than 6 symptoms, please describe them in detail on a separate sheet of paper.* |
| Explaining the severity scoring for each symptom | *A score of 0 (not annoying) indicates that you do not have the symptom, whereas a score of 10 (very annoying) indicates that the symptom is very strong, almost unbearable.* |
| Giving an example of how it would look like when being filled | Supplementary Figure 3 (example for question 1) |

**Supplementary Table 2.** Semistructured Questions for Focus Groups

| | |
|---|---|
| Question 1. | How would you describe to someone else what EoE is?[a] |
| Question 2. | How old were you when you were diagnosed with EoE? |
| Question 3. | What sources did you use to learn more about EoE?[a] |
| Question 4. | What symptoms did you have because of your EoE? Please describe first the symptoms that occurred during meal times and then the symptoms that occurred independent of meal times. |
| Question 5. | Have you avoided or do you avoid certain foods? |
| Question 6. | Have you modified/changed certain foods? |
| Question 7. | Have you eaten longer than other people? If yes, how long do you need to eat a meal? |
| Question 8. | What impact EoE has on your professional life? |
| Question 9. | What impact EoE has on your social life? |
| Question 10. | What impact EoE has on your activities, including sports, in your spare time? |
| Question 11. | What was your experience with endoscopies and foods that got stuck?[a] |
| Question 12. | Since being diagnosed with EoE, have you told anyone about it?[a] |
| Question 13. | Did you undergo allergy testing?[a] |
| Question 14. | What are your concerns regarding the long-lasting evolution of your EoE? Do you worry about cancer? Do you worry about new episodes of foods getting stuck?[a] |
| Question 15. | What have your experiences been with swallowed steroids? Diets? Stretching of the esophagus?[a] |
| Question 16. | What is the most difficult thing about having EoE?[a] |
| Question 17. | Compared with any other current medical problems you once had, where does EoE stand?[a] |

[a]These questions were adopted or reproduced directly from a study by Tufts et al[11] with permission of the senior investigator.

**Supplementary Table 3.** Coding Tree

| Main code | Subcodes |
|---|---|
| Dysphagia | Definition: impaction |
| | Definition: tightness |
| | Definition: difficulty swallowing |
| | Definition: solids/liquids passing slowly or not smoothly |
| | Location: throat |
| | Location: chest/esophagus |
| | Duration |
| | Frequency |
| | Severity |
| | Unable to swallow/build-up of saliva |
| Dysphagia caused by different foods, pills, and beverages | Description: compact/solid |
| | Description: dry |
| | Description: fibrous |
| | Foods specified: meat |
| | Foods specified: bread |
| | Foods specified: pill |
| | Foods specified: raw fibrous |
| | Foods specified: rice |
| | Foods specified: French fries |
| | Foods specified: pasta |
| | Other/unspecified |
| | Beverages specified: alcohol-containing |
| | Beverages: other/unspecified |
| Foods not causing dysphagia | |
| Strategies avoiding impaction | Food avoidance |
| | Food processing |
| | Eat slowly/trigger: hasty eating |
| | Washing food down: helps |
| | Washing food down: does not help |
| Strategy dealing with dysphagia event | Choke/cough impacted food out |
| | Vomit impacted food |
| | Waiting until impaction resolves itself |
| | Washing food down: helps |
| | Washing food down: does not help |
| | Other strategies mentioned/not specified |
| Swallowing-associated pain | Location: throat |
| | Location: chest/esophagus |
| | Location: belly/stomach |
| | Description: burning |
| | Duration |
| | Frequency |
| | Severity |
| | Circumstances: with food impaction |
| | Circumstances: with food but no impaction |
| | Circumstances: with beverages |
| Non–swallowing-associated pain | Circumstances |
| | Description |
| | Location: chest |
| | Location: belly/stomach |
| | Location: throat |
| | Duration |
| | Frequency |
| | Severity |
| Allergic manifestations | Allergies related to food: location, throat |
| | Allergies related to food: location, esophagus |
| | Allergies related to food: duration of event |
| | Foods causing allergies |
| | Afflictions mentioned: allergic reactions not for food |
| | Symptom: itching/scratching/irritation |
| | Symptom: throat swelling |
| | Symptom: tightness |

**Supplementary Table 3.** Continued

| Main code | Subcodes |
|---|---|
| Treatments | Anti-acid/GERD medications |
| | Dilation |
| | Endoscopic disimpaction |
| | Swallowed topical corticosteroids |
| | Diet |
| | Not specified |
| | Treatments for concomitant allergic diseases |
| Gastroesophageal reflux disease–like symptoms | Definition: heartburn |
| | Definition: acid regurgitation/reflux |
| | Definition: gastroesophageal reflux disease |
| | Location: chest |
| | Circumstances |
| | Duration |
| | Frequency |
| | Severity |
| | Pain |
| Other concerns | Symptom: sweating |
| | Symptom: vomiting |
| | Symptom: problems breathing/choking |
| | Symptom: pressure on the chest |
| | Symptom: nausea |
| | Symptom: foreign body sensation |
| | Symptom: clearing ones throat |
| | Symptom: belching/gas/burping |
| | Overall duration of disease/symptoms |
| Psychological concerns | Psychological factors: worry about potential impaction |
| | Psychological factors: feelings during impaction |
| | Psychological factors: reduced enjoyment of mealtimes |
| | Psychological factors: other |

**Supplementary Table 4.** Characteristics of the Study Population

| Source of input Country | Patient survey | | | | Focus groups | | Interviews | |
|---|---|---|---|---|---|---|---|---|
| | Switzerland | | United States | | Switzerland | | United States | |
| Patient numbers | N | % | N | % | N | % | N | % |
| Responders | 80 | 100 | 55 | 100 | 27 | 100 | 24 | 100 |
| Sex | | | | | | | | |
| Men | 62 | 77.5 | 31 | 56.4 | 19 | 70.4 | 17 | 70.8 |
| Women | 18 | 22.5 | 24 | 43.6 | 8 | 29.6 | 7 | 29.2 |
| Age at time of questionnaire completion, *y* | 43.4 ± 14.4 | | 43.2 ± 10.6 | | 45.8 ± 14.5 | | 39.1 ± 11.4 | |
| Education[a] | | | | | | | | |
| Compulsory schooling[b] | 1 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vocational training[c] | 35 | 43.7 | 5 | 9.1 | 12 | 44.4 | 0 | 0 |
| Upper second. education[d] | 31 | 38.8 | 23 | 41.8 | 12 | 44.4 | 3 | 12.5 |
| University education[e] | 13 | 16.3 | 27 | 49.1 | 3 | 11.2 | 21 | 87.5 |
| Migration[f] | | | | | | | | |
| No migration background | 74 | 92.5 | 54 | 98.2 | 27 | 100 | 24 | 100 |
| Migration background | 6 | 7.5 | 1 | 1.8 | 0 | 0 | 0 | 0 |

[a]Education systems are different in Switzerland and the United States. We compared the different levels according to the International Standard Classification of Education (ISCED).
[b]Basic education in both countries took 9 years (ISCED codes 1 and 2).
[c]Secondary education consisted of high school, vocational training, apprenticeship, grammar school (leads in Switzerland to a Maturity Degree and is the regular pathway to university education), teachers' college (in Switzerland was the regular pathway to be a primary school teacher until very recently) (ISCED codes 3 and 4).
[d]First-stage tertiary education. In Switzerland this was a bachelor's degree, or additional schooling that leads to higher degrees/managerial jobs in specific professions (eg, in economics, social work, engineering, journalism, and so forth). In the United States this was some college but no degree, associate's degree, bachelor's degree (ISCED codes: Switzerland, 5.1–5.6, 5.8; United States, 5.1–5.3).
[e]University education consisted of a University degree (eg, master's degree, doctorate degree, medicine/MD, law/JD/LLB) (ISCED codes: Switzerland, 5.7, 5.9–5.14, 6; United States, 5.4–5.8, 6).
[f]Migration background was defined as a participant who moved to Switzerland/United States after birth, or was not a Swiss/US citizen at the time of the questionnaire completion, or became a Swiss/US citizen after birth.

**Supplementary Table 5.** Dysphagia and its Characteristics

| Definition of dysphagia | | | |
|---|---|---|---|
| Impaction | Tightness | Difficulty swallowing | Solids/liquids passing slowly or not smoothly |
| There are times when I will eat sandwiches and bites will get stuck for about 30 seconds | When I eat red meat, I occasionally have a feeling of tightness or impaction | Sometimes eating chicken or other meats is tough to swallow | When I eat chicken I feel it either slowly go down or get stuck in my throat |
| When taking medication sometimes the pills get temporarily stuck in my throat | When I eat red meat, I feel a tightness in my throat, oftentimes I need to walk around and swallow continuously to allow swallowing the food | When eating I sometimes just have a hard time swallowing. Throat does not clog but closes just enough to make eating and drinking difficult | Sometimes meat or very heavy foods do not go down smoothly |
| Sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (>5 min) to completely be swallowed (move down into stomach) | Before treatment I would experience a painful and complete constriction of my throat, a complete choking sensation Nothing would relieve it, only a few minutes for it to clean | Symptoms are better or less obvious now that I take Nexium a day. Do not seem to choke or have as much difficulty while swallowing after eating | Earlier, when I was experiencing symptoms, I had trouble swallowing. Things, especially sandwiches, would get stuck or slow down before getting to my stomach |
| When I eat rice, I have difficulty swallowing or sometimes it feels like it gets stuck in my throat | Sometimes when I eat, I feel a tightness in my upper chest, back of throat. I drink a lot of water virtually every time | I have trouble swallowing: very, very painful and many choking experiences | When I eat at every meal, it does not matter what type of food, I notice that the food goes down the esophagus somewhat slowly |
| Most of my symptoms are related to choking on foods: very painful | | If I am very stressed or upset, I find some difficulty in swallowing liquids | |

| Dysphagia characteristics | | | |
|---|---|---|---|
| Dysphagia duration | Dysphagia frequency | Dysphagia severity | Dysphagia Location |
| When I eat food (various things), sometimes it gets stuck in my throat for a few seconds, then goes down | Tightness in my throat when eating hamburgers, sandwiches too quickly. Infrequent symptoms | Symptoms are better or less obvious now that I take a Nexium a day. Do not seem to choke or have as much difficulty while swallowing after eating | Esophagus: sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (>5 min) to completely be swallowed (move down into stomach) |
| When I eat bread (or bagels) I feel a tightness in my throat/upper chest. It usually goes away after 20–30 seconds. I stop eating and focus on relaxing and may drink water to make it go away | Before treatment I would experience a painful and complete constriction of my throat, a complete choking sensation. Nothing would relieve it, only a few minutes for it to clean. This would happen relatively often, 1 or 2 times per week, after eating “dense” foods | Occasionally when I eat, I feel a tightness that is severe. I hope when I drink something that it will go away | Throat/chest: pork (especially pork chops) always cause tightness in throat/chest. It lasts 30+ seconds but my throat/chest will feel sore for a while |

**Supplementary Table 5.** Continued

| Dysphagia characteristics | | | |
|---|---|---|---|
| Dysphagia duration | Dysphagia frequency | Dysphagia severity | Dysphagia Location |
| I have to take smaller bites, wait until it (food) goes down, then I can eat again. It takes about 5 seconds between bites | Most frequently when I have a problem the food will get stuck for 10–20 seconds. Sometimes I try to get it down by swallowing water, which may or may not work. There is a slight discomfort and tightness in my esophagus but I can always tell that it will go down and eventually it does go down by itself. I can usually start eating again after that. If I have a second incident during the same meal, I will stop eating. That occurs maybe 50% of the time | Most frequently when I have a problem the food will get stuck for 10–20 seconds. Sometimes I try to get it down by swallowing water, which may or may not work. There is a slight discomfort and tightness in my esophagus but I can always tell that it will go down and eventually it does go down by itself. I can usually start eating again after. If I have a second incident during the same meal, I will stop eating. I rate this symptom as a 4 (on a scale from 0 to 10), unless it reoccurs during the same meal, then it is a 6 | Throat: pieces of meat have gotten severely stuck in my throat, producing the feeling of choking, but obviously not in the airways. Happens several times per year |
| When eating meat, I would have a problem if I swallowed too big of a bite. It would get stuck in my throat and sometimes be stuck for hours. 80% of the time it would only be stuck for a few minutes | My most recent symptom is various types of solid foods getting stuck in my throat. It will not go down with dry swallowing, but will go down with 1–2 drinks of liquid. It happens once or 2twice a week | | Throat: dry chicken (white meat) causes tightness in my throat/chest that lasts 10–20 seconds |

**Supplementary Table 6.** Dysphagia Caused by Different Foods, Pills, and Beverages

| Meat | Pills | Bread | Other foods/unspecified |
|---|---|---|---|
| Periodically meat will remain in my esophagus for several minutes and coughing or throwing up seem to be the only solution | Difficulty swallowing pills because of a history of dysphagia with larger pills. More a mental annoyance that I get concerned about swallowing pills. I take a "gummy" chewable multivitamin instead of a pill | Sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (>5 min) to completely be swallowed (move down into stomach) | When I eat items such as crackers, peanuts, popcorn, and so forth the material that is finely chewed gets stuck in my throat. This material is not easily washed down with water |
| Sometimes eating chicken or other meats is tough to swallow | When I take pills, they must be very small or it will get stuck in my throat. Nothing like water helps, so I must try to throw up the pill | When I eat meat or breads, they are hard to pass down my esophagus. My passage becomes restricted and I am forced to wait until the food passes (30 min to 3 h) or try to physically throw up the blockage | Earlier, when I was experiencing symptoms, I had trouble swallowing. Things, especially sandwiches, would get "stuck" or slow down before getting to my stomach. They would clear with liquids |
| Sometimes when I eat meat, I feel a scratch in my throat or a light tightness that remains until I wash it down with a fluid | Cannot swallow pills, that is how I first came across my problem, got stuff in my esophagus and had severe choking for several hours | When I eat food (various things) sometimes it gets stuck in my throat for a few seconds and then goes down (examples of foods may be bread) | When I eat potato chips, sometimes chip fragments hang up in my throat. Generally, they pass naturally |
| When I eat meat too much too quickly I have to wait to let the food pass | | | |

| Pasta | Raw fibrous foods | Rice | Ground meat |
|---|---|---|---|
| When I eat bread or pasta, especially if I do not chew it into small pieces, it gets stuck in my upper chest/just past my throat and I wait 15–20 seconds for it to pass before I can drink water. It often causes tightness in my chest | When I eat carrots, I feel them stick at the top of my throat until I wash them down with water | When I eat rice, I have difficulty swallowing or sometimes it feels as if it gets stuck in my throat | Tightness in my throat when eating hamburgers, sandwiches too quickly. Infrequent symptoms |
| If I eat pasta (wheat) with a thick sauce or lots of cheese it feels like a sticky lump in my throat and lasts 30+ seconds | Have to peel apples to eat | When I eat rice and it is dry and it gets stuck, so I stay away | In the past I have had tightness in my throat while eating various things like chicken, hot dogs, steak, hamburger, and so forth. Increases with fluid. Sometimes lasts 5 seconds to 10 min or until food passed through |

| French Fries | Beverages | Alcoholic beverages |
|---|---|---|
| Throat: I cannot swallow pills and certain foods may get stuck such as French fries. There is no pain. I chew my food more than most and cannot drink liquids as fast (this is without stretching and medication [fluticasone]) | When I drink diet soda I sometimes get a painful lump in my chest, it feels like the liquid gets stuck | The difficulties swallowing have subsided in the past 2 years and do not currently exist. In the past, I had problems when eating rice, meat, and drinking wine |

**Supplementary Table 6.** Continued

| French Fries | Beverages | Alcoholic beverages |
|---|---|---|
| French fries and peanuts are difficult to swallow and require water to wash down the food | When I drink liquids quickly, the liquid often catches in my throat | Sometimes, when drinking a glass of wine, it feels as if my esophagus narrows down |
| Beyond steak and French fries, I cannot identify certain foods as being special offenders | Several times per week, even water does not go down smoothly | When I eat fast, bread, meat or while drinking alcohol, I sometimes get food stuck |
| **Description, dense/solid** | **Description, dry** | **Description, course/fibrous** |
| When I eat certain foods my throat closes, or clogs, so that I cannot swallow or eject it. Not certain what foods cause this but typically steak or heavier meats. Have to wait for clog to subside or have emergency treatment | When I eat chicken and it is dry, it sticks in my throat and I must drink and cough to get it moved | Coarse foods like raw vegetables such as carrots, broccoli, get stuck in my throat, so I avoid them. It is very difficult to dislodge food stuck in my throat, drinks or coughing do not work much |
| Also could not eat solid anything for several months | When I eat rice and it is dry it gets stuck so I avoid it | I also could no longer swallow fibrous vegetables, such as spinach, beans, celery, and so forth |
| If I am off my medication, it feels as if food gets caught in my throat with dense foods (eg, meats) | When I eat dry food (lately corn chips), the food sometimes gets hung up in my throat. I have to wash it down with water | |

**Supplementary Table 7.** Behavioral Adaptation to Living With Dysphagia

| Strategies to avoid impaction | | | |
|---|---|---|---|
| Food avoidance | Food processing | Eating slowly (trigger, hasty eating) | Washing food down |
| After 15+ esophageal dilations, I still have some problems eating. Always have to have water to wash food down. Have to chew a lot and still take small bites. Certain foods I still stay away from | When I eat steak, I have to cut it into tiny pieces for fear that it may get stuck in my throat | When I eat, at every meal, it does not matter what type of food, I notice that the food goes down the esophagus somewhat slowly. I have to take smaller bites, wait until it goes down, then I can eat again. It takes about 5 seconds between bites. No pain at all | Always have water with me just in case. Have trouble with popcorn, nuts, corn, tough meat, thick cheeses, and bread. Sweets go down easy, except caramel, which is too thick. Have not had peanut butter in more than 15 years |
| I avoid the steak in pepper and all steak for that matter because I feel it is tough to swallow | Have to peel apples to eat | When going out to eat, have to be careful what I order because I eat so slowly and just being careful about food going down. Most of the time, I have to take home half or three quarters of the meal because everyone else is finished | Whenever I eat anything, I always have to have something to wash the food down |
| When I eat rice and it is dry it gets stuck so I avoid it<br>Coarse foods like raw vegetables such as carrots, broccoli, get stuck in my throat, so I avoid them | Eat only foods with sauces, so that I can swallow them easily | Always have a drink while eating and almost have to eat carefully, slowly | Always have to have water to wash the food down |

| Strategies dealing with impaction | | | | |
|---|---|---|---|---|
| Choke/cough/vomit impacted food out | Waiting until impaction resolves itself | Washing food down: helpful | Washing food down: not helpful | Other strategies mentioned/not specified |
| If coughing and drinking does not dislodge food and I cannot swallow my saliva, after 10 minutes I panic and will try to induce vomiting to dislodge food | When I eat meat or breads, they are hard to pass down my esophagus. My passage becomes restricted and I am forced to wait until the food passes (30 min to 3 h) or try to physically throw up the blockage. When blockage occurs I am subject to spit a lot of saliva | My most recent symptom is various types of solid foods getting stuck in my throat. It will not go down with dry swallowing, but will go down with 1–2 drinks of liquid. It happens once or twice a week. It will happen even with a breath mint that I have started to chew | When I take pills, they must be very small or it will get stuck in my throat. Nothing like water helps, so I must try to throw up the pill | There are times when I will eat sandwiches and bites will get stuck for about 30 seconds. Repeated swallowing and walking tend to help |

**Supplementary Table 7.** Continued

| Strategies dealing with impaction | | | | |
|---|---|---|---|---|
| Choke/cough/vomit impacted food out | Waiting until impaction resolves itself | Washing food down: helpful | Washing food down: not helpful | Other strategies mentioned/not specified |
| Periodically meat will remain in my esophagus for several minutes and coughing or throwing up seem to be the only solution | When I eat certain foods my throat closes, or clogs, so that I cannot swallow or eject it. Not certain what foods cause this but typically steak or heavier meats. Have to wait for clog to subside or have emergency treatment | When eating I use to feel as if the food would not go all the way down and I had to drink something to wash the food down. Discomfort ended once food was washed down | When I eat items such as crackers, peanuts, popcorn, and so forth, the material that is finely chewed gets stuck in my throat. This material is not easily washed down with water | Food sticks near my neck, at the base of my throat. I have to slap my chest or jump up and down to move it |
| I have had 3 impactions that I now am aware of. I felt like I was choking. My throat was tight. After several times throwing up, I felt better but was unable to eat. Afraid I could not swallow | I have had 2 total food impactions that have had to be removed by endoscopy. Both times not even liquids would go down and I had to spit up my swallowed saliva. Before going to the hospital, I tried the Heimlich and waited several hours to see if the food would go down on its own | When I eat chicken and it is dry. It sticks in my throat and I must drink and cough to get it moved | I have found that sucking on ice works better than liquid, which can make it worse | |

**Supplementary Table 8.** Other Themes

| Allergic reactions related to food | Swallowing-associated pain | Non–swallowing-associated pain | Gastroesophageal reflux disease symptoms |
|---|---|---|---|
| When I eat most foods, such as fruits, I feel my throat swelling, ears itching, and throat itching as well | I have trouble swallowing; very, very painful and many choking experiences | Stomach upset. The pain can last several hours. The pain is about a 2–8 (on a 10-point scale), depending on the type of food, but it is annoying. The pain may last half an hour or longer. I avoid these foods | I sometimes experience heartburn and reflux as a result of the food that I eat |
| When I eat foods with my specific allergen (dairy), or foods that have residuals on them, I have trouble swallowing, and my throat feels swollen shut | When I drink diet soda I sometimes get a painful lump in my chest, it feels as if the liquid gets stuck. It burns and is very painful | Before being diagnosed I used to get severe pain in the middle of my chest right at the bottom of my rib cage. The pain would last all day and was very annoying. Was very hard on me and my family | When lying down at bedtime or during sleep I am sometimes awakened with heartburn, reflux, and stomach pain |
| Many fresh fruits and vegetables irritate my mouth, throat, and stomach | Swallowing nonstick foods gives me pain in the chest<br>I have chest pain from food blockage when I eat certain foods that block my esophagus. Pain is mild but goes away once food passes | A reoccurring chest pain/cramp, comes on suddenly | I occasionally have acid reflux, mostly at night |

| Treatment | | | |
|---|---|---|---|
| Endoscopic disimpaction | Dilations | Anti-acid/GERD medications | Swallowed topical corticosteroids |
| Three times in the past 10 years I have gone to the hospital after many attempts at freeing meat, the only solution then (after several hours) is an upper endoscopy | About a year ago, I had an endoscopy and stretching, which helped for a few months | Before starting daily Pepcid (famotidine), 20-mg dose, I had trouble swallowing many types of meats and dry foods. Sometimes I would have to force the food up, or drink water to force the food down | I am currently using the fluticasone inhaler, so I have not had any symptoms recently |
| If food does get caught, there is a burning where my throat hits my stomach. I have been scoped in the ER 3× because of this issue. I have had 9 total upper GIs because of this | I have had my throat stretched twice in the past. The first time was a piece of steak lodged in my throat for 24 h. It then was removed before the first balloon dilatation. When it was lodged, no liquid would pass through | When I used to eat chicken or other drier cuts of meat, regardless of the size of bite I take, or how much I chew it up, I would have difficulty swallowing it and need to wash it down immediately with water. Since going on an anti-acid reflux regimen, I have not experienced this problem (only on exceptionally rare occasion) | Before I regularly used Flovent (fluticasone), I occasionally was unable to swallow food, most often meat, that was lodged in my throat. When it happened, I often had to go to the emergency room to dislodge the food |
| I have had 2 total food impactions that have had to be removed by endoscopy. Both times not even liquids would go down and I had to spit up my swallowed saliva | After 15+ esophageal dilations, still have some problems eating. Always have to have water to wash food down. Have to chew a lot and still take small bites. Certain foods I still stay away from | I used to get periodic (ie, monthly) tightness in the center of my chest, a stabbing pain. It would last anywhere between 5 and 15 min. I have not experienced this since taking anti-acid medication daily | I cannot swallow pills and certain foods may get stuck such as French fries. There is no pain. I chew my food more than most and cannot drink as fast (this is without stretching and medication [fluticasone]) |

## Appendix 3

The data obtained from the VDQ were used to create a composite score. The degree of perceived difficulties when eating a given food consistency was graded between 0 for no difficulties and 3 for severe difficulties. These grades for each food consistency were summed in the numerator of the score and divided by the maximum sum of grades that could be attained for each subject, which depended on the number of food consistencies consumed by a subject in a given recall period.

For the AMS score, answers to 3 items exploiting the pattern of behavioral adaptation were scored for each food consistency consumed by the subject. If patients recorded no behavioral changes, a score of 0 was assigned; when reporting eating slower than others, a score of 1 was assigned; when reporting the modification of certain food consistencies, a score of 2 was assigned; when reporting both eating slower than others and modifying certain food consistencies, a score of 3 was assigned; if the subject completely avoided one or several food consistencies because of EoE symptoms, a score of 5 was assigned. Scores for all consumed food consistencies were summed up in the numerator and divided by the maximum sum of scores that could be attained by a given subject. The VDQ and AMS scores range from 0 to 10.

We provide a sample calculation of VDQ (equation 1) and AMS (equation 2) scores for patient X, who reported that he/she ate all 8 food consistencies and expected to experience moderate difficulties eating solid meat; mild difficulties eating dry rice, ground meat, fresh white untoasted bread, and French fries; and no difficulties eating soft foods, grits/porridge/rice pudding, and raw fibrous foods. In the past 7 days, the patient reported that he/she modified solid meat and French fries, but not other foods. The patient did not avoid any foods. However, the patient ate solid meat, ground meat, fresh white untoasted bread, and French fries slower than other people eating these same foods, but not other foods. The verb "modified" was illustrated with the following examples: put the food in the blender, cut it into small pieces, dunk it in liquid, or mash it. Patient X had a VDQ score of 2.5 and an AMS score of 2.

### *Equation 1: VDQ Score*

$$VDQ = \frac{N_1 \times 1 + N_2 \times 2 + N_3 \times 3}{D \times 3} \times 10$$

Where $N_1$ is the number of food consistencies graded with mild difficulties, $N_2$ is the number of food consistencies graded with moderate difficulties, $N_3$ is the number of food consistencies graded with severe difficulties, and D is the number of relevant food consistencies (different than not applicable).

For patient X, $N_1 = 4$, $N_2 = 1$, $N_3 = 0$, and $D = 8$.

$$VDQ = \frac{4 \times 1 + 1 \times 2 + 0 \times 3}{8 \times 3} \times 10 = 2.5$$

### *Equation 2: AMS Score*

$$AMS = \frac{N_1 \times 1 + N_2 \times 2 + N_3 \times 3 + N_4 \times 5}{D \times 5} \times 10$$

Where $N_1$ is the number of food consistencies with a response of yes to eating slowly only, $N_2$ is the number of food consistencies with a response of yes to modification only, $N_3$ is the number of food consistencies with a response of yes to both eating slowly and modification, $N_4$ is the number of food consistencies with a response of yes to avoidance only, and D is the number of relevant food consistencies (different than not applicable).

For patient X, $N_1 = 2$ (ground meat and fresh white untoasted bread), $N_2 = 0$, $N_3 = 2$ (solid meat and French fries), $N_4 = 0$, and $D = 8$.

$$AMS = \frac{2 \times 1 + 0 \times 2 + 2 \times 3 + 0 \times 5}{8 \times 5} \times 10 = 2$$

# Appendix 4

## Supplementary Tables and Figures

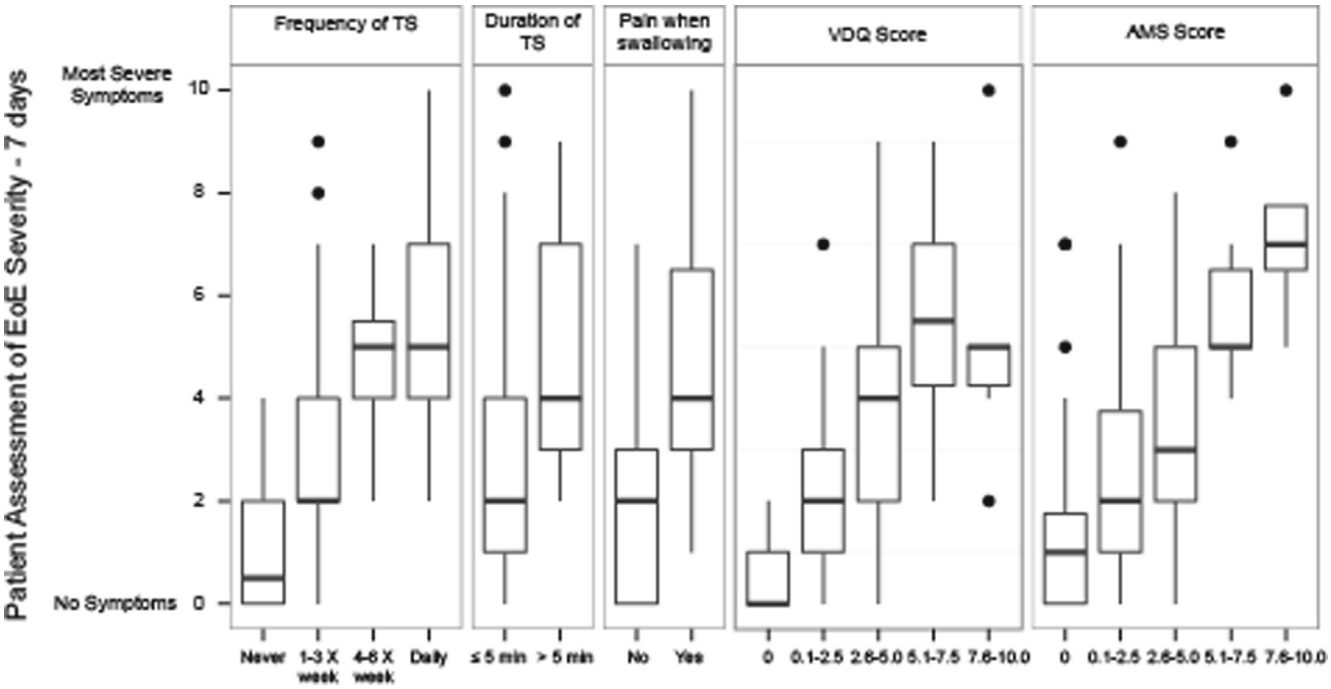
**Supplementary Table 9.** Description of the Physician and Histology Instruments

| | Physician instrument | Histology instrument |
|---|---|---|
| Derivation | Delphi | Delphi |
| completed by | Physician and study coordinator (if applicable) | Pathologist |
| Number of items | 39 close-ended items | 22 close-ended items |
| Type of items | 5 items: dichotomous scale | 3 items: dichotomous scale |
| | 1 item: Likert scale | 0 items: Likert scale |
| | 21 items: multiple nonhierarchical options | 13 items: multiple nonhierarchical options |
| | 12 items: multiple hierarchical options | 6 items: multiple hierarchical options |
| Average completion time | 30 minutes | 10 minutes (without histologic evaluation) |
| Overall assessment variable | Physician global assessment of EoE activity (11-point Likert scale) | |
| Domains | EoE treatment strategies | Distal esophagus |
| | Treatment with steroids | Eosinophil peak number |
| | Elimination diets | Distribution of eosinophils in a high-power field |
| | Dilation | Percentage of high-power field covered by the tissue |
| | Blood biomarkers | Sample orientation |
| | Eosinophil serum levels | Distribution of inflammation |
| | IgE | Presence of abscesses |
| | IL5 | Basal layer enlargement |
| | Endoscopic features | Lamina propria fibrosis |
| | Endoscopic features described by Hirano et al[26] with some modifications | Proximal esophagus |
| | GERD | Same as described earlier |
| | Presence of GERD | General |
| | GERD-like symptoms | Qualification and experience of the participating pathologist |
| | Barrett's esophagus | |
| | Hiatal herniation | |
| | Fundoplication surgery | |
| | General | |
| | Qualification and experience of the participating gastroenterologists | |

**Supplementary Table 10.** Symptom Severity and Behavioral Changes When Eating Foods From Eight Distinct Consistencies as Assessed by the Visual Dysphagia Question (n = 153)

| | Solid meat | | Ground meat | | Fresh bread | | Dry rice | | Raw food | | French fries | | Grits, porridge | | Soft foods | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Difficulties eating | | | | | | | | | | | | | | | | |
| No | 37 | 24.2 | 81 | 52.9 | 69 | 45.1 | 69 | 45.1 | 85 | 55.6 | 89 | 58.2 | 127 | 83.0 | 141 | 92.2 |
| Mild | 56 | 36.6 | 37 | 24.2 | 45 | 29.4 | 52 | 34.0 | 39 | 25.5 | 39 | 25.5 | 13 | 8.5 | 6 | 3.9 |
| Moderate | 39 | 25.5 | 26 | 17.0 | 24 | 15.7 | 22 | 14.4 | 16 | 10.5 | 11 | 7.2 | 2 | 1.3 | 1 | 0.7 |
| Severe | 21 | 13.7 | 8 | 5.2 | 8 | 5.2 | 8 | 5.2 | 11 | 7.2 | 8 | 5.2 | 6 | 3.9 | 5 | 3.3 |
| Do not know | 0 | 0.0 | 0 | 0.0 | 6 | 3.9 | 1 | 0.7 | 1 | 0.7 | 4 | 2.6 | 4 | 2.6 | 0 | 0.0 |
| Missing | 0 | 0.0 | 1 | 0.7 | 1 | 0.7 | 1 | 0.7 | 1 | 0.7 | 2 | 1.3 | 1 | 0.7 | 0 | 0.0 |
| Behavior | | | | | | | | | | | | | | | | |
| Modification | 23 | 15.0 | 6 | 3.9 | 7 | 4.6 | 5 | 3.3 | 10 | 6.5 | 7 | 4.6 | 0 | 0.0 | 1 | 0.7 |
| Avoidance | 17 | 11.1 | 13 | 8.5 | 11 | 7.2 | 16 | 10.5 | 18 | 11.8 | 7 | 4.6 | 5 | 3.3 | 1 | 0.7 |
| Eating slower | 103 | 67.3 | 65 | 42.5 | 54 | 35.3 | 51 | 33.3 | 47 | 30.7 | 36 | 23.5 | 9 | 5.9 | 8 | 5.2 |

NOTE. The 8 food consistencies and examples of foods to illustrate those are as follows: (1) solid meat (steak, chicken, turkey, and lamb), (2) soft foods (pudding, jelly, and apple sauce), (3) dry rice or sticky Asian rice, (4) ground meat (hamburger and meatloaf), (5) fresh white untoasted bread or similar foods (doughnuts, muffins, and cake), (6) grits, porridge (oatmeal), or rice pudding, (7) raw fibrous foods (apple, carrots, and celery), and (8) French fries. The sample calculation of the visual dysphagia question, and food avoidance, modification, and slow eating scores are provided in Appendix 3.




**Supplementary Figure 6.** The relationship between the PatGA of EoE severity and the PRO components that were chosen for the construction of the PRO score. The data for the 7-day recall period are shown. TS, trouble swallowing.