How to measure disease activity in eosinophilic esophagitis

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SUMMARY. Activity of Eosinophilic Esophagitis (EoE) can be measured by patient reported outcomes (symptoms and quality of life) and clinician-reported outcomes (endoscopic, histologic, or biochemical alterations). Over the last years efforts have been underway to develop and validate instruments to assess EoE activity in the different domains. Such instruments are urgently needed to standardize the language of EoE activity assessment and, in so doing, to facilitate communication among various stakeholders. Such standardization will ultimately allow EoE researchers to define meaningful endpoints for use in clinical trials and observational studies, to compare the efficacy of different therapeutic modalities, and to develop algorithms in order to provide patients with the appropriate therapy. This review provides an overview of the current status of instruments that assess EoE activity in the different domains.

KEY WORDS: eosinophilic esophagitis, patient reported outcomes, quality of life, eosinophils, disease activity.

INTRODUCTION

Why is it important to measure EoE activity?

Eosinophilic esophagitis (EoE) has first been recognized as distinct disease entity in the early 1990s.^{1,2} An increasing incidence and cumulative prevalence of EoE has been noted in industrialized countries with current incidence rates of about 1 new patient in 10,000 inhabitants per year and current prevalence rates of approximately 1 patient per 2000 inhabitants.³⁻⁶ The first comprehensive definition of EoE was published in 2007.⁷ In the updated 2011 version, EoE was defined by a panel of international

experts as ‘a chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation’.⁸ Other conditions associated with esophageal eosinophilia, such as gastroesophageal reflux disease (GERD), Crohn’s disease, or achalasia, should be excluded before EoE can be diagnosed.

Given the fact that EoE has been first described a little over 20 years ago, it is not astonishing that until recently, no validated instruments to assess different aspects of EoE activity existed. The use of different, either non-EoE-specific or non-validated, instruments to assess EoE symptom severity may explain why a dissociation between EoE symptom severity and histologic activity has been documented in some,⁹⁻¹¹ but not other studies.^{12,13} In recent years, efforts have been underway to develop and validate instruments to assess EoE activity. Validated instruments are urgently needed in order to standardize the language of EoE activity assessment and, in so doing, to facilitate communication among the various EoE stakeholders, including patients, industry, physicians, and researchers. This standardization will, in turn, allow EoE researchers to define clinically meaningful end-points for use in clinical trials and observational studies, to compare the efficacy of different

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Disclaimers: The authors are among the copyright holders of the Eosinophilic Esophagitis Activity Index (EEsAI) Patient Reported Outcomes Instrument that is copyrighted by University of Bern, Switzerland. Please contact the corresponding author for questions regarding the use of the EEsAI PRO instrument for clinical trials.

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Fig. 1 Capturing all facets of the disease for activity assessment.

therapeutic modalities, and to develop therapeutic algorithms in order to provide patients with the appropriate therapy.

EoE activity assessment: capturing the multiple facets of the disease

EoE diagnosis is based on two pillars: symptoms and histology. This duality needed for establishing EoE diagnosis points to the fact that overall EoE activity should be assessed by taking into account various patient reported outcomes (PRO) and clinician-reported outcome (ClinRO) measures (Fig. 1).

PRO measures in EoE include those that assess symptom severity, quality of life, and behavioral adaptations to living with dysphagia. Our group has recently shown that EoE patients frequently avoid dense foods, modify the food to ease the swallowing, or take longer to eat a meal.¹⁴ Evaluating the extent to which patients practice these behaviors represents an integral part of EoE activity assessment. It is important to point out that patients should report their symptoms, behavioral adaptations to living with dysphagia, and quality of life without any help from physicians in order to avoid potential physician-inherent biasing.^{15,16} ClinRO measures in EoE include assessment of endoscopic, histologic, and laboratory findings, as well as assessment of other aspects of gastrointestinal physiology.

In general, the utility of PRO and ClinRO measures in overall disease activity assessment strongly depends on the impact of the disease-inherent alterations on the PRO measures and availability of suitable biologic measures (e.g. biomarkers) that can be used as indicators of disease severity. We have recently described this concept elsewhere.¹⁷ In our opinion, both PRO and ClinRO measures contribute in an important way to overall EoE activity. When EoE is untreated, ongoing eosinophil-predominant

inflammation results in development of esophageal remodeling and fibrosis. It is well documented that these underlying changes are associated with EoE-associated endoscopic findings, such as stricture(s) and luminal narrowing.^{18–22} Esophageal strictures, in turn, are associated with dysphagia episodes and represent the main risk factor for food bolus impactions and a potential risk for impaction-associated esophageal perforations.^{23,24} Given the fact that in EoE severity of inflammation and stricture formation are associated with symptom severity, both PRO and ClinRO should be used to assess disease activity.^{17,25}

Defining end-points for clinical trials

To date, no EoE-specific pharmacologic therapy has been approved by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA). Nonetheless, several clinical trials that evaluate the efficacy of medications in EoE patients are currently ongoing. The sponsors of these trials face numerous challenges, and, among them, the lack of EoE-specific instruments that have been deemed by US FDA as qualified for use as end-points in exploratory studies. The US FDA has played an active role in fostering collaborations among different stakeholders in order to develop clinical outcome assessment tools to support drug development and to establish meaningful endpoints to be used in clinical trials, and observational studies.^{15,16} These concerted efforts should ultimately provide EoE patients with much needed therapies.

Challenges in clinical EoE activity assessment

PRO measures can be separated into instruments that assess symptoms, behavioral modifications, and quality of life. Given the fact that challenges in assessing EoE symptoms and developing PRO instruments are numerous, *our discussion is limited to a few aspects that we feel merit particular attention.* First, EoE symptom presentation varies with age.^{1,2,26} Infants and toddlers typically present with feeding difficulties and failure to thrive, whereas school-aged children often present with vomiting and abdominal pain.^{1,2,26} Adolescent and adult EoE patients mostly suffer from dysphagia and food impactions.^{1,2,26} This age-dependent symptom presentation should be taken into account when developing instruments to assess clinical EoE activity. For pediatric patients specifically, different PRO instruments should be developed for patients of different ages: instruments that can be completed by older children themselves, and instruments that should be completed by someone other than the patient (a parent, caregiver, or someone, who observes the patient in daily life) for children that are too young to complete the instrument on their own. Second, a distinct time period

Fig. 2 Factors influencing patient's perception of dysphagia.

has to be defined for patients to recall their symptoms. For clinical trials, regulatory authorities favor the use of a daily electronic diary. However, daily diaries may not be practical for use in settings other than *pharmaceutical company-sponsored clinical trials*. Third, measuring the severity of the key EoE symptom, dysphagia, strongly depends on the consistency of the ingested food. In practical terms, when asked by a physician, 'Do you have dysphagia?', the patient consuming a diet consisting of mostly soft foods, such as yoghurt and soup, is likely to answer 'No', even in the presence of relatively severe EoE-specific biologic alterations. If such a patient would then be encouraged to eat a more dense food item, such as piece of meat or fresh bread, this patient would be much more likely to report dysphagia. Thus, dysphagia should be assessed in the context of consuming foods of various consistencies. Similarly, behavioral modifications to living with dysphagia, such as avoidance of certain foods, modification of foods to ease the swallowing, and a relatively long time required to eat certain food items, should also be taken into account and assessed in the context of eating foods of various consistencies (Fig. 2).

INSTRUMENTS THAT ASSESS PRO MEASURES IN EoE

The purpose of this section is to provide an overview of the different EoE-specific PRO instruments published to date (Table 1). Instruments are presented in order of publication from latest to oldest.

Instruments for assessment of clinical activity in adult EoE patients

EoE Activity Index (EEsAI) PRO instrument

In 2014, the international EEsAI study group published a study on development and validation of the EEsAI PRO instrument.¹⁴ In the process of the development and validation of the instrument, the group followed recommendations of the US FDA.¹⁵ Patient

($n = 186$) input on EoE symptoms was sought using a mixed methods approach, consisting of surveys, cognitive individual patient interviews, and focus groups that were guided by a psychologist. The newly created instrument (in paper form) containing items assessing various EoE symptoms was completed by 153 adult EoE patients. The patient global assessment of EoE symptom severity recalled over three distinct periods (24 hours, 7 days, and 30 days) was also collected. Multivariable linear regression analysis and analysis of variance with patient global assessment as an outcome and items of the instrument as predictors was used to obtain an equation for constructing a PRO score by quantifying the extent to which included items explained the variability in patient global assessment. Items addressing various characteristics of dysphagia, behavioral adaptations to living with dysphagia, and pain while swallowing were included in a preliminary version of the score. This score for a 24-hour and 7-day recall period was validated in a second independent group of 120 patients recruited in Switzerland (German and French) and the United States (English). The final score ranges from 0 to 100 points and includes seven items that assess frequency and duration of dysphagia episodes, severity of dysphagia caused by eating foods of eight different consistencies, and behavioral adaptations to living with dysphagia also assessed in the context of eating foods of eight different consistencies. Practicality and content validity were assessed by conducting cognitive debriefings. Patients took a median of 8 minutes (interquartile range 7–9, range 4–10 minutes) to complete the EEsAI PRO instrument and judged the instrument to be easy to complete.¹⁴ Furthermore, patients considered the EEsAI PRO instrument as adequate in assessing relevant EoE-related complaints (content validity).¹⁴ The EEsAI PRO instrument, which is copyrighted by the University of Bern, Switzerland, is currently being used in different clinical trials.

Dysphagia Symptom Questionnaire (DSQ)

In 2013, Dellon *et al.* published the study on development of the DSQ, a three-item electronic diary.²⁷ The diary was developed in collaboration with the Meritage Pharma, Inc. (the copyright holder). In the first phase, 10 adolescent and 10 adult EoE patients were enrolled into face-to-face concept elicitation and cognitive interview sessions in order to create the diary. Adolescent and adult patients with symptoms of dysphagia were enrolled. At the time of the study, esophageal biopsies of these patients had at least 15 eosinophils per high-power field. Solid-food-avoidance days, dysphagia days, and actions taken to get dysphagia relief were recorded. The consistency of solid food was not specified. The scoring algorithm was expert-based and was constructed by giving each item response a discrete value, which were then

Table 1 Overview of the instruments that assess symptoms and quality of life in adult and pediatric EoE patients

	Name of the instrument	Characteristics	Languages	References
Clinical activity in adult EoE patients	EoE Activity Index (EEsAI) PRO instrument	<ul style="list-style-type: none"> Developed using patient input Score evaluated in 153 patients and validated in 120 patients – based on patient global assessment Recall period: 7 days and 24 hours Completion time: 8 minutes Content valid 	English German French	Schoepfer <i>et al.</i> ¹⁴
	Dysphagia Symptom Questionnaire (DSQ)	<ul style="list-style-type: none"> Developed using patient input Field-tested in 35 adolescent and adult patients Expert-based scoring algorithm Recall period: 24 hours (daily electronic diary) Content valid 	English	Dellon <i>et al.</i> ²⁷
	Straumann Dysphagia Index (SDI)	<ul style="list-style-type: none"> Developed using physician input Expert-based scoring algorithm Recall period: 7 days Evaluated in a RPCT in 36 patients 	English German	Straumann <i>et al.</i> ¹²
	Mayo Dysphagia Questionnaire (MDQ)	<ul style="list-style-type: none"> Developed and validated to assess dysphagia in adults with different esophageal diseases (physician input was used for item generation) Recall period: 14 days and 30 days Completion time: 10 minutes Content valid Evaluated in a RPCT in 42 adults with EoE 	English	Grudell <i>et al.</i> ²⁸ and McElhiney <i>et al.</i> ²⁹
Clinical activity in pediatric EoE patients	Clinical symptom score (CSS)	<ul style="list-style-type: none"> Developed using physician input Evaluated in a RPCT in 71 pediatric patients aged 2–18 years Expert-based scoring algorithm Recall period: 14 days 	English	Gupta <i>et al.</i> ¹¹
	Pediatric EoE symptom score (PEESS, Version 2.0)	<ul style="list-style-type: none"> Developed using patient and parent input (children 2–18 years of age) Only qualitative methods have been published expert-based scoring algorithm Recall period: 30 days 	English	Franciosi <i>et al.</i> ³⁰
	Symptom scoring tool (SST)	<ul style="list-style-type: none"> Developed using physician input Field tested in 35 EoE patients, 27 GERD patients and 38 controls Completed by children and parents Expert-based scoring algorithm Evaluated in a RPCT in 24 pediatric patients 	English	Aceves <i>et al.</i> ³¹
	Pediatric EoE symptom instruments by Flood <i>et al.</i>	<ul style="list-style-type: none"> Questionnaires for parents of EoE patients 2–7 years of age and patients 8–17 years of age Recall period: 24 hours Expert-based scoring algorithm Content valid Score not validated 	English	Flood <i>et al.</i> ³²
Quality of life	Adult EoE quality of life instrument (EoO-QOL-A)	<ul style="list-style-type: none"> Developed using patient input Validated in adult EoE patients 18–70 years of age Good internal consistency and test–retest reliability Recall period: 7 days 	English Spanish	Taft <i>et al.</i> ³³
	PedsQL module	<ul style="list-style-type: none"> Developed using patient input Validated in pediatric EoE patients 5–18 years of age Good feasibility, reliability, test–retest reliability Recall period: 30 days is described in the study, but 7-day recall is also available 	English	Franciosi <i>et al.</i> ³⁴

Instruments are listed according to the year of publication, with the most recent listed first. RPCT, randomized, placebo-controlled trial.

totalled for each week. This total was divided by the number of days the DSQ was completed. The DSQ score ranges from 0 to 5. A total 18 adults and 17 adolescents completed the field trial. The DSQ score strongly correlated with the number of dysphagia days ($R = 0.96$, $P < 0.001$) and showed to be content valid. The DSQ is currently being used in a clinical trial (E Dellon, pers. comm. 2015).

Straumann Dysphagia Index (SDI) instrument

SDI is a non-validated PRO instrument that was first evaluated in a natural history study by Straumann

et al. (published in 2003) and subsequently used, in a modified form, in a randomized, placebo-controlled trial by Straumann *et al.* (published in 2010) evaluating the efficacy of swallowed topical budesonide in 36 adult EoE patients.^{12,35} The instrument was developed using physician input, and the scoring algorithm for this instrument is expert-based. The SDI assesses the following EoE symptoms: (i) frequency of dysphagia events and (ii) intensity of dysphagia events. The SDI score ranges from 0 to 9 points. Treatment with swallowed topical budesonide significantly reduced esophageal peak eosinophil counts, and the SDI was

responsive.³⁵ A clinical response was defined as a ≥ 3 -point decrease from the SDI score baseline value. The SDI does not assess dysphagia caused by eating foods of different consistencies and does not take into account behavioral adaptations to living with dysphagia.

Mayo Dysphagia Questionnaire (MDQ)

The MDQ has been developed and validated by Grudell *et al.*²⁸ The MDQ consists of a total of 28 items. Of these, 17 items assess frequency and severity of dysphagia, 3 items assess the presence of concomitant allergies, 3 items assess the use of acid-suppressive medication, 2 items evaluate the presence of esophageal surgery, 1 item assesses the presence of GERD, 1 item evaluates esophageal dilations, and 1 item evaluates the overall duration of trouble swallowing. Assessment of dysphagia severity is carried out in the context of consuming foods of different consistencies. In addition, patients are also questioned about food modification and time to eat a regular meal. The MDQ aims to evaluate dysphagia in adult patients with different esophageal disorders and has not specifically been developed and validated for adult EoE patients. The reliability and validity of the MDQ, 30-day version (MDQ-30), has been documented in a large population of patients suffering from dysphagia.²⁹ The MDQ-30 takes an average of 10 minutes to complete. The MDQ-30 is copyrighted by Mayo Clinics. The MDQ 2-week version, has been used in a double-blind, randomized, placebo-controlled trial evaluating efficacy of fluticasone in 42 adults with a new EoE diagnosis.⁹ The treatment with aerosolized, swallowed fluticasone led to histologic but not symptom response, with response defined as either complete lack of trouble swallowing or decrease in frequency or severity of this symptom.

Instruments for assessment of clinical activity in pediatric EoE patients

Clinical symptom score (CSS)

Gupta *et al.* evaluated the CSS when conducting a randomized, placebo-controlled trial on efficacy of 12-week oral budesonide suspension treatment in a group of 71 pediatric EoE patients between the ages 2 and 18 years old.¹¹ The CSS is a newly developed, non-validated symptom score adapted from a previously published symptom scoring tool (SST).³⁶ It is based on the physician assessment of the frequency and disruptiveness of multiple symptoms including heartburn, abdominal pain, nocturnal awakening with various symptoms, nausea, regurgitation or vomiting, anorexia or early satiety, dysphagia, odynophagia or food impaction, and the use and disruptiveness of coping behaviors, as determined by questioning the patient and/or caregiver. The CSS

does not assess symptoms in the context of eating foods of different consistencies. Each symptom category is scored by the experts on a scale from 0 to 3 points. In order to be scored, the symptom must have been present in the period of the last 14 days before the assessment. The total CSS ranges from 0 to 18 points. A clinical response was defined as a $\geq 50\%$ reduction in the CSS. Given the fact that a large percentage of placebo-treated patients demonstrated symptom improvement, there was no significant difference in clinical response between oral budesonide suspension treatment groups and the placebo group.¹¹

Pediatric EoE symptom score (PEESS)

In 2011, Franciosi *et al.* published the study on the qualitative methodology used for the development of the PEESS, version 2.0.³⁰ Authors followed the FDA guidelines for PRO development.¹⁵ The authors conducted a total of 75 interviews with children (ages 8–12 and 13–18 years) and parents (caregivers) (ages 2–4, 5–7, 8–12, and 13–18 years) to construct the PRO instrument. Domains assessing frequency and severity of various symptoms were developed, and open-ended questions were used to generate specific items during the individual focus interviews. This was followed by cognitive interviews for face and content validation. Later on, the instrument construct, instructions, timeframe, scoring, and specific items were reviewed with a separate EoE patient group and their parents during the cognitive interviews. Each item was scored on a scale from 0 to 4. The symptoms were recalled over a period of 30 days. Results of the field-testing process (evaluation phase) and the validation phase have not yet been published.

Symptom scoring tool

Aceves *et al.* developed and prospectively evaluated a PRO instrument, the so-called SST, to discriminate pediatric patients with EoE from those with GERD or other atopic and non-atopic conditions.³¹ This symptom score is a modified version of the score developed for children with acid-peptic disease.³⁷ The instrument was tested in 35 EoE patients (not receiving anti-eosinophil therapies), 27 GERD patients (not undergoing acid suppression), and 38 control patients. The overall symptom score was higher in patients with EoE and GERD when compared with control patients. The SST assesses the frequency and severity of the following groups of symptoms: heartburn/regurgitation, abdominal pain, nausea/vomiting, anorexia/early satiety, dysphagia, symptom-induced nocturnal awakening, and gastrointestinal bleeding. For each of the seven groups of symptoms, a maximum of 2 points can be given for a most severe for of a symptom. The score ranges from 0 to 14 points. The SST has been developed using physician input and is completed by parents and

children. The SST does not assess dysphagia caused by eating foods of different consistencies. Authors showed that only dysphagia and anorexia/early satiety could discriminate EoE patients from GERD patients. Dysphagia and anorexia/early satiety also correlated with the severity of EoE-associated histologic and endoscopic findings ($P < 0.05$).³¹ In a randomized, placebo-controlled trial evaluating the efficacy of oral viscous budesonide treatment in pediatric patients with histologically and clinically active EoE, the authors found that the SST score decreased in the treatment group when compared with placebo ($P = 0.031$) over a 12-week treatment period.³⁸

Pediatric EoE symptom instrument by Flood et al.

In 2008, Flood *et al.* were the first to publish a study on the development of pediatric EoE symptom instruments.³² The authors developed the instruments based on a review of the literature and clinical expert consultation. Specifically, the instrument for the parent/caregiver consists of five items, including those on intensity of pain in the stomach and in the chest, frequency of vomiting, as well as trouble swallowing and pain when drinking and eating. The instrument for children and teenagers consists of six items; in addition to items assessing all the symptoms already described for the parent/caregiver instrument, an item on being bothered by a lump in the throat was included. Each item was scored on a scale from 1 to 5. They then interviewed (one-to-one interviews) parents of EoE patients aged 2–7 years ($n = 12$) and EoE patients aged 8–17 years ($n = 16$) about EoE-related symptoms and their impact on everyday life, using open-ended questions, to confirm the appropriateness of the item content of the instruments. Participants then completed the appropriate symptom instruments and were asked to provide feedback on the relevance, comprehensiveness, and clarity of each item. The symptom recall period for the caregiver and the patient instruments was 24 hours. Overall, participants thought that the instruments were clear, relevant, and appropriate for symptom assessment. The instruments did neither assess symptoms in the context of consuming foods of different consistencies nor evaluated behavioral adaptations to living with EoE-related symptoms. The scoring algorithm was based on expert input. Data on the construct validity, reliability, and responsiveness of the measures have not been published to date.

Instruments for assessment of quality of life in adult and pediatric EoE patients

Adult EoE quality of life (EoO-QOL-A) instrument

In 2011, Taft *et al.* published a study on development and validation of the first quality of life instrument for adult EoE patients, the adult EoO-QOL-A instru-

ment.³³ A total of 201 patients, between 18 and 70 years of age, participated in the study. Using qualitative methods, the authors studied the disease-specific concerns and their impact on quality of life and identified items for the five following subscales to be included into the EoO-QOL-A instrument: eating/diet impact, social impact, emotional impact, disease anxiety, and choking anxiety. The EoO-QOL-A instrument consists of 37 items. Patients not currently being treated by elimination diets are completing 32 items. A 7-day recall period was chosen to assess impact of EoE on quality of life. The EoO-QOL-A instrument demonstrated excellent internal consistency, split-half and test–retest reliability. The instrument is copyrighted by the Northwestern University (Chicago, IL, USA).

Pediatric quality of life (PedsQL) module

In 2013, Franciosi *et al.* published a study on a quality of life instrument for pediatric EoE patients, the so-called PedsQL EoE Module.³⁴ The PedsQL EoE Module was completed by 196 pediatric EoE patients and 262 parents. The 33-item PedsQL EoE Module encompasses seven scales, including two symptoms scales (assessing chest/throat/stomach pain, nausea/vomiting, and trouble swallowing), treatment scale, worry scale, communication scale, food and eating scale, and food feelings scale. The recall period for the PedsQL EoE Module utilized in the published study was 30 days. The PedsQL EoE Module scales evidenced excellent feasibility, excellent group comparison reliability across total scale scores, good reliability for the seven individual scales, and excellent test–retest reliability. PedsQL EoE Module scores were worse among patients with active histologic disease (defined as ≥ 5 eosinophils per high-power field) when compared with those in histologic remission and those treated with dietary restrictions compared with those with no restrictions.

ASSESSING BIOLOGIC MEASURES IN EoE

Endoscopic activity

EoE Endoscopic Reference Score (EREFS) grading system

Hirano *et al.* have recently published a study on a classification and grading system for endoscopic assessment of esophageal EoE features.³⁹ This system, also known as EREFS system, evaluates the severity of the following endoscopic features: exudates, rings, edema, furrows, and strictures. Endoscopic videos from 25 EoE patients and control patients were reviewed by 21 gastroenterologists. Interobserver agreement was assessed by estimating multi-rater κ and the proportion of pairwise agreement. The instrument standardizes the long-needed

common nomenclature and severity grading for the assessment of endoscopic disease activity. The EREFS grading system showed good interobserver agreement among practicing and academic gastroenterologists. The EREFS grading system is not an endoscopic score in the strict sense of the wording. Definitions regarding endoscopic remission, mild, moderate, or severe endoscopic activity have not yet been established.

Histologic activity

As of yet, no validated histology score for pediatric and adult EoE patients exists. Assessing histologic activity mainly relies on the peak eosinophil count per high-power field. Additional histologic findings, such as basal layer hyperplasia, papillary elongation, eosinophil degranulation, or subepithelial fibrosis, have also been reported as important histologic outcome parameters. In 2007, Dellon *et al.* have shown that peak eosinophil counts reported in various studies may not be necessarily comparable as different microscope types with different high power field sizes are used in different studies.⁴⁰ Reporting the observed peak eosinophil counts standardized to mm² could standardize reporting of peak eosinophils counts in different studies. Similar to the reporting of endoscopic severity, no established definitions of histologic remission, as well as mild, moderate, and severe histologic activity currently exists.

Esophageal string test and Cytosponge

In order to avoid repetitive endoscopies in EoE patients, several groups have evaluated minimally invasive biologic measures, such as the esophageal string test and the Cytosponge, in order to assess the degree of histologic inflammation.

Furuta *et al.* have recently published a study on the esophageal string test, a minimally invasive tool to assess mucosal inflammation.⁴¹ The authors demonstrated that the level of luminal eosinophil-derived proteins extracted from the esophageal string correlated with the esophageal peak eosinophil counts. As such, this test can be considered as a good measure of mucosal inflammation in children with EoE. The esophageal string test will likely be useful in pediatric EoE patients needing repeated assessment of mucosal inflammation to spare these children the burden of repeated endoscopy under general anesthesia.

Katzka *et al.* compared the accuracy, safety, and tolerability of esophageal sample collection via Cytosponge, an ingestible gelatin capsule containing compressed mesh attached to a string, with those of esophageal biopsies.⁴² Esophageal tissue samples were collected from 20 EoE patients using both Cytosponge and esophageal biopsy sampling during endoscopy. Number of eosinophils per high-power

field and levels of eosinophil-derived neurotoxin were determined; hematoxylin and eosin staining was performed. All 20 samples collected by Cytosponge were adequate for analysis. By using a cut-off value of 15 eosinophils per high-power field, analysis of samples collected by Cytosponge identified 11 of the 13 individuals with active EoE (83%); additional features, such as abscesses were also identified. Numbers of eosinophils in samples collected by Cytosponge correlated with those in esophageal biopsies ($r = 0.50$, $P = 0.025$). Analysis of tissues collected by Cytosponge identified four of the seven patients without active EoE (57% specificity), as well as three cases of active EoE not identified by analysis biopsy samples. Including information on the level of eosinophil-derived neurotoxin did not increase the diagnostic accuracy. All patients preferred to swallow Cytosponge when compared with undergoing endoscopy. The authors concluded that the Cytosponge is a safe and well-tolerated method for collecting near mucosal specimens.

Measuring esophageal compliance and diameter using endolumenal functional lumen imaging probe

Uncontrolled eosinophil-predominant esophageal inflammation that persists over time leads to remodeling with formation of strictures.²⁰⁻²⁴ These structural esophageal abnormalities may be detected by the means of endolumenal functional lumen imaging probe that helps physicians to monitor esophageal wall distensibility both to assist in diagnosis of EoE and to track the progress of patients on various treatments.⁴³

OUTLOOK

Described a little over 20 years ago, EoE is still a 'young' disease. Nevertheless, considerable progress has been achieved in this relatively short time interval in regards to our understanding of EoE's natural history, as well as its endoscopic, histologic, and molecular characterization. The common nomenclature for assessing symptoms, quality of life, endoscopic, and histologic activity is about to be standardized. Developing PRO measures in accordance with US FDA guidelines and having these newly developed instruments undergo qualification review by the US FDA remains an important target. We remain hopeful that some of the reviewed instruments will qualify as end-points to be used in clinical trials, and observational studies. This will help all the EoE stakeholders to bring much needed therapies to EoE patients.

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