

CLINICALLY MEANINGFUL ENDPOINTS IN EoE

North American Society of Pediatric
Gastroenterology, Hepatology and Nutrition
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Eosinophilic Esophagitis Symptom Activity Index (EEsAI)

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Goals

**1. Understand Challenges To Develop Meaningful
Endpoints**

**2. Recognize Current Endpoints For EoE Clinical
Trials And The Rationale For their use**

If you cannot measure it, you cannot change it
Robert Sandler

Cross-sector sponsorship of research in eosinophilic esophagitis: A collaborative model for rational drug development in rare diseases

Robert Fiorentino, MD,* Gumei Liu, MD, PhD,[†] Anne R. Pariser, MD,[‡] and **Andrew E. Mulberg, MD*** Silver Spring, Md

We believe that the collaborative model for EoE research, as outlined here, demonstrates that this progress is possible when disease problems are addressed concertedly from multiple directions. We hope that this model will be of encouragement to other collaborations to combat rare disease.

	Define Disease	Assess Natural History	Identify Assessment Tools
Rare Diseases	Determine Target Population	Collaborate Among Stakeholders	Develop Clinical Outcome Assessment (COA)
	Include criteria to define clinical trial population	Survey available resources	Develop patient/clinician/parent reported outcome measures
	Recognize Stakeholders	Plan for longitudinal study	Select clinical endpoints
	Initiate Collaboration	Standardize Data Entry	Evaluate Biomarkers
	Identify Impeding Factors	Use disease specific terminology	
	Address gaps in knowledge	Describe Full Disease Spectrum	
		Distinguish disease subtypes	
		Identify patient subpopulations	
	Define EoE	Assess EoE Natural History	Identify EoE Assessment Tools
EoE	Unify Diagnostic Criteria	FDA and Academia Collaboration	Address the Importance of EoE-Specific COAs
	Use symptomatic and histological criteria	Pool multiple patient registries	Raise questions on using general terms, such as dysphagia
	Invite All Stakeholders	Standardize Data Entry	Identify the need for different COAs for pediatric and adult patients
	Discuss overall plan	Interpret data from different sources	Evaluate Intraepithelial Mucosal Eosinophilia as a Biomarker
	Identify Key Issues	Recognize EoE Subpopulation	
	Lack of well-defined and reliable COA	Define differences between pediatric and adult patients	

Workshop summary

Workshop report from the National Institutes of Health Taskforce on the Research Needs of Eosinophil-Associated Diseases (TREAD)

Bruce S. Bochner, MD,¹ Wendy Book, MD,² William W. Busse, MD,³ Joseph Butterfield, MD,⁴ Glenn T. Furuta, MD,⁵ Gerard J. Gleich, MD,⁶ Amy D. Klon, MD,⁷ James J. Lee, PhD,⁸ Kristin M. Leflerman, MD,⁹ Michael Minniccozzi, PhD,¹ Redwan Morjeh, PhD, FRCPath,¹ Marc E. Rothenberg, MD, PhD,¹ Lawrence B. Schwartz, MD, PhD,¹ Hans-Uwe Simon, MD, PhD,¹⁰ Michael E. Wechsler, MD,¹¹ and Peter F. Weller, MD¹² *Baltimore and Bethesda, Md; Atlanta, Ga; Madison, Wis; Rochester, Minn; Aurora, Colo; Salt Lake City, Utah; Scottsdale, Ariz; Winnipeg, Manitoba, Canada; Cincinnati, Ohio; Richmond, Va; Bern, Switzerland; and Boston, Mass*

TABLE III. Organ/disease-specific unmet needs for eosinophil-associated diseases

Disease entity	Unmet need to be addressed
EGID	1. Identify best method for diagnosis, including exclusion of esophageal acid/retroacid disease as the cause of symptoms. 5. Define optimal frequency and validate the need of endoscopic follow-up. 6. Understand the cause of breakdown in oral food tolerance. 7. Understand the mechanisms and prevent tissue remodeling, stricture formation, and other disease complications. 8. Develop noninvasive and invasive diagnostic tests for assessing diagnosis and disease activity. 9. Understand genetic underpinning and its interaction with the environment (eg, food).

1. Identify best method for diagnosis,

Editorial

Working with the US Food and Drug Administration: Progress and timelines in understanding and treating patients with eosinophilic esophagitis

Marc E. Rothenberg, MD, PhD,¹ Seema Aceves, MD, PhD,² Peter A. Bonis, MD,³ Margaret H. Collins, MD,⁴ Nirmala Gonsalves, MD,⁵ Sandeep K. Gupta, MD,⁶ Ikuo Hirano, MD,⁷ Chris A. Liacouras, MD,⁸ Phil E. Putnam, MD,⁹ Jonathan M. Spergel, MD, PhD,¹⁰ Alex Straumann, MD,¹¹ Barry K. Wershil, MD,¹² and Glenn T. Furuta, MD¹³ *Cincinnati, Ohio; San Diego, Calif; Boston, Mass; Indianapolis, Ind; Philadelphia, Pa; Basel, Switzerland; Chicago, Ill; and Aurora, Colo*

TABLE I. Progress in EoE

Topic	Progress		
	Low	Medium	High
Molecular understanding			X
Genetics		X	
Preclinical modeling		X	
Controlled clinical trials		X	
Assessment tools			
Histology		X	
Endoscopic assessment	X		
Clinical outcome tools	X		
Molecular markers		X	
FDA-approved drugs	X		
FDA-approved dietary treatment	X		

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT Workshop)
Eosinophilic Esophagitis Workshop

Holiday Inn-College Park, The Ballroom
10000 Baltimore Ave, College Park, Maryland
September 19, 2012

AGENDA

The goal of the workshop day dedicated to eosinophilic esophagitis (EoE) is to discuss its natural history, development of clinical outcome assessments (COAs), and biomarkers that might be used to study new treatments for both children and adults.

8:15 a.m. Opening Remarks and Introduction **A. Mulberg**

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended but not required.

Feel

Form

Function

EoE-PRO or biologic markers or both?

PRO

Migraine
Lower back pain
EoE-dysphagia

Biologic feature

Asthma
EoE
Crohn's disease
Ulcerative colitis

Arterial hypertension
Hyperlipidemia
EoE-eosinophil

Schoepfer A, Safroneeva E. Dig Dis 2014

Diseases of the Esophagus (2015) 17, 111–117
DOI: 10.1111/doe.12291

**DISEASES OF THE
ESOPHAGUS**

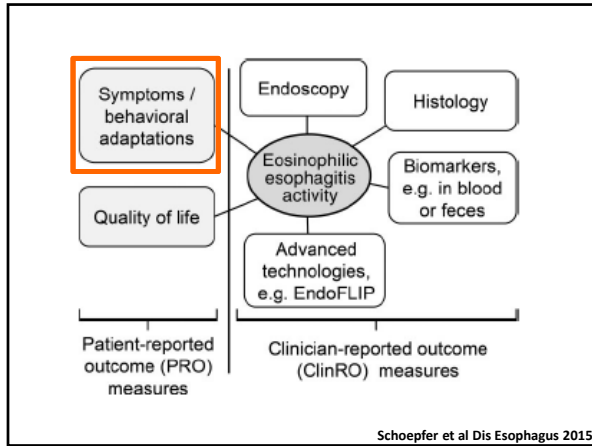
ISDE

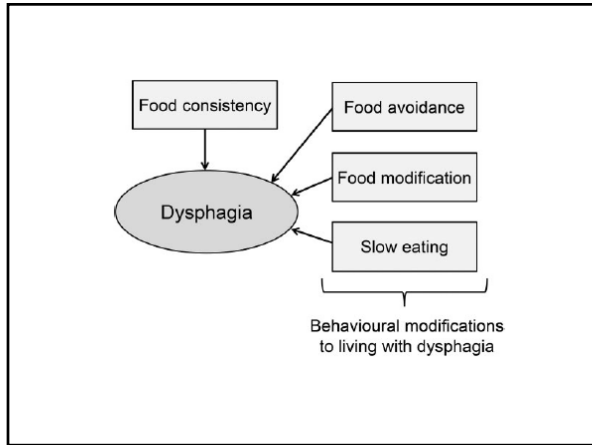
Review article

How to measure disease activity in eosinophilic esophagitis

A. Schoepfer,¹ E. Safroneeva,² A. Straumann³

¹Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois (University Hospital Lausanne), Lausanne, ²Institute of Social and Preventive Medicine, University of Bern, Bern, and ³Praxis Rönnerhof, Swiss EoE Clinic, Olten, Switzerland





Symptoms in Adults

Name of the instrument	Characteristics	Languages	References
EoE Activity Index (EEsAI) PRO instrument	<ul style="list-style-type: none"> Developed using patient input Score evaluated on 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 et al. 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	Devron et al.
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 et al. ¹⁵
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 et al. ²⁰ and McElhinney et al. ²⁶

Schoepfer et al Dis Esophagus 2015

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
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	






Symptoms in Children

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> ²⁰
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> ¹³
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> ²²

Frequency				
Never	Almost never	Sometimes	Often	Almost always
	(less than once a week)	(1 or more times a week)	(1 time a day)	(2 or more times a day)

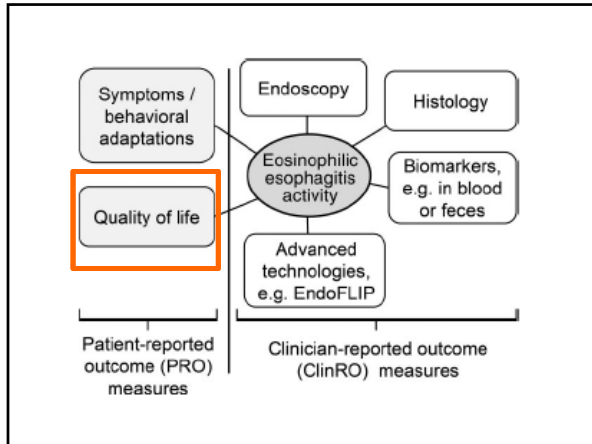
1. How often do you have chest pain, ache, or hurt?

0	1	2	3	4
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Severity				
Not bad at all	A little bad	Kind of bad	Bad	Very bad
				

2. How bad is the chest pain, ache, or hurt?

0	1	2	3	4
---	---	---	---	---



EoE QoL			
Adult EoE quality of life instrument (EoE-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> ¹⁰
Pediatric EoE quality of life instrument (EoE-QoL-P)	<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	Francisco <i>et al.</i> ²⁴

AP_{GT} Alimentary Pharmacology and Therapeutics

The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life

T. H. Taft, E. Kern, M. A. Kwiatek, I. Hirano, N. Gonsalves & L. Keefer

- Valid and reliable
- 37 items
- 5 factors
 - eating
 - social
 - emotional
 - social anxiety
 - choking anxiety

EoE QoL

1. I find EoE to be a stressful disease.

2. I have to be cautious about eating because I have EoE.

EoE QoL

<p>Adult EoE quality of life instrument (EoEQoL-A)</p>	<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 	<p>English Spanish</p>	<p>Taft <i>et al.</i>¹⁰</p>
<p>PedsQL module</p>	<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 used in validation 	<p>English</p>	<p>Franciosi <i>et al.</i>²⁴</p>

PedsQL Eosinophilic Esophagitis Module: Feasibility, Reliability, and Validity (*JPGN* 2013;57: 57-66)

James P. Franciosi,¹ Kevin A. Hommel,² Cristiane B. Bendo,³ Eileen C. King,⁴ Margaret H. Collins,⁵ Michael D. Eby,⁶ Keith Marsolo,⁷ J. Pablo Abonia,⁸ Karl F. von Tiedl,⁹ Philip E. Putnam,¹⁰ Alexandria J. Greenler,¹¹ Allison B. Greenberg,¹² Ronald A. Bryson,¹³ Carla M. Davis,¹⁴ Anthony P. Olive,¹⁵ Sandeep K. Gupta,¹⁶ Elizabeth A. Erwin,¹⁷ Mary D. Klinnert,¹⁸ Jonathan M. Spergel,¹⁹ Jolanda M. Denham,²⁰ Glenn T. Furuta,²¹ Marc E. Rothenberg, and ²²James W. Varni

Worry

I worry about having EoE*

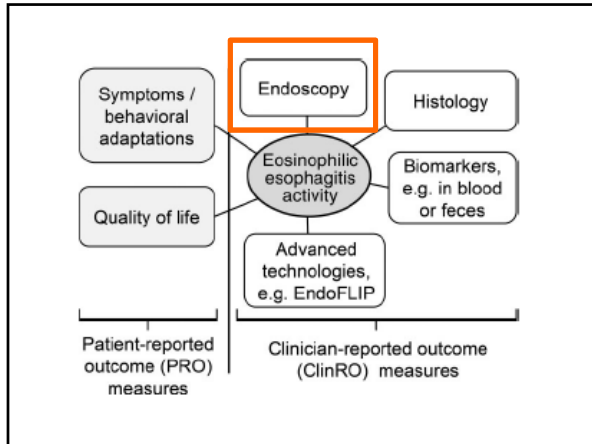
I worry about getting sick in front of other people

I worry about what other people think about me because of EoE*

I worry about going to the doctor

I worry about getting an endoscopy (scope, EGD)

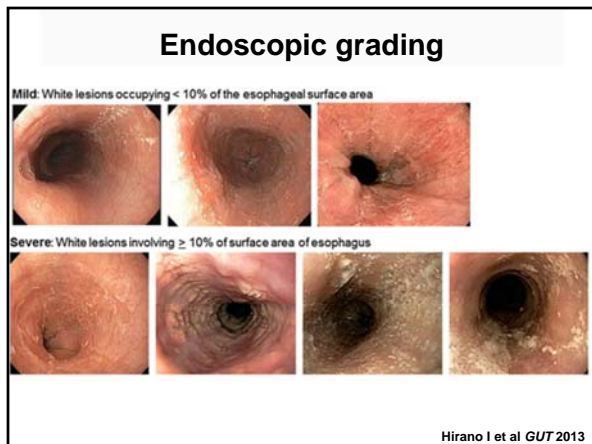
I worry about getting allergy testing

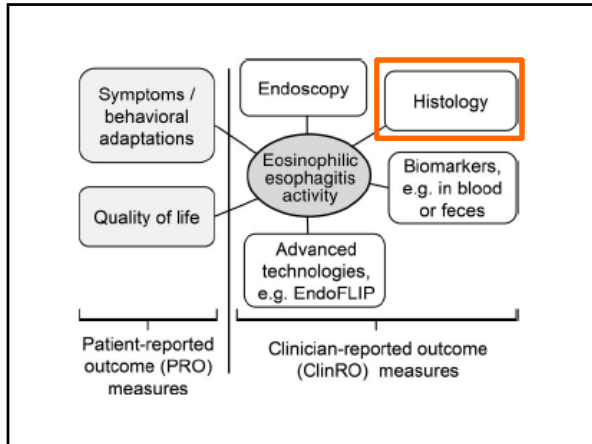


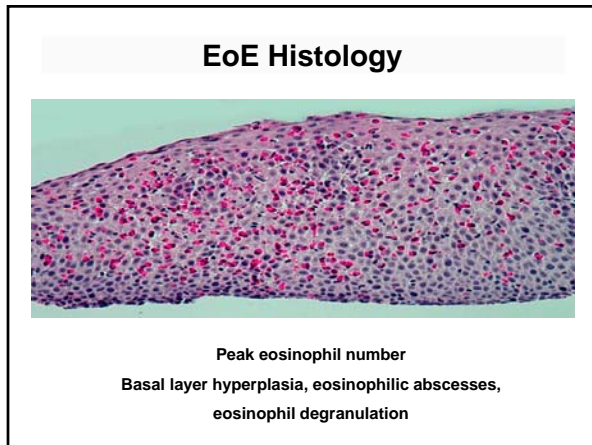
ORIGINAL ARTICLE
Endoscopic classification of eosinophilic esophagitis
 Ikuo Hirano,¹ Sami R Ache, Gonsalves,¹ Hirano I, et al. *GUT* 2013

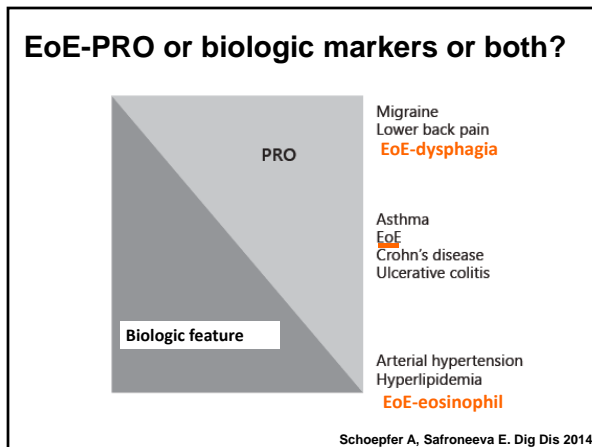
Major features

- **Fixed rings** (also referred to as concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealisation)
 - Grade 0: none
 - Grade 1: mild (subtle circumferential ridges)
 - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm))
 - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
- **Exudates** (also referred to as white spots, plaques)
 - Grade 0: none
 - Grade 1: mild (lesions involving <10% of the oesophageal surface area)
 - Grade 2: severe (lesions involving >10% of the oesophageal surface area)
- **Furrows** (also referred to as vertical lines, longitudinal furrows)
 - Grade 0: absent
 - Grade 1: mild (vertical lines present without visible depth)
 - Grade 2: severe (vertical lines with mucosal depth [indentation])
- **Oedema** (also referred to as decreased vascular pattern, mucosal pallor)
 - Grade 0: absent (distinct vascularity present)
 - Grade 1: mild (loss of clarity of vascular markings)
 - Grade 2: severe (absence of vascular markings)
- **Stricture**
 - Grade 0: absent
 - Grade 1: present









Eosinophilic Esophagitis Symptom Activity Index (EEsAI)

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