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HISTOPATHOLOGICAL DIAGNOSIS OF EOSINOPHILIC OESOPHAGITIS: KEY FEATURES, BIOPSY INTERPRETATION, AND THE ROLE OF EOE-HSS

Cord Langner, MD
Diagnostic & Research Institute of Pathology
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Topics that will be addressed

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- The different histological features of eosinophilic oesophagitis and their application in the diagnostic setting
- Pros and cons of scoring systems and potential for future developments in the field

Review

Breaking down the complex pathophysiology of eosinophilic esophagitis

Brynne Underwood, MD; Ty D. Troutman, PhD; Justin T. Schwartz, MD, PhD

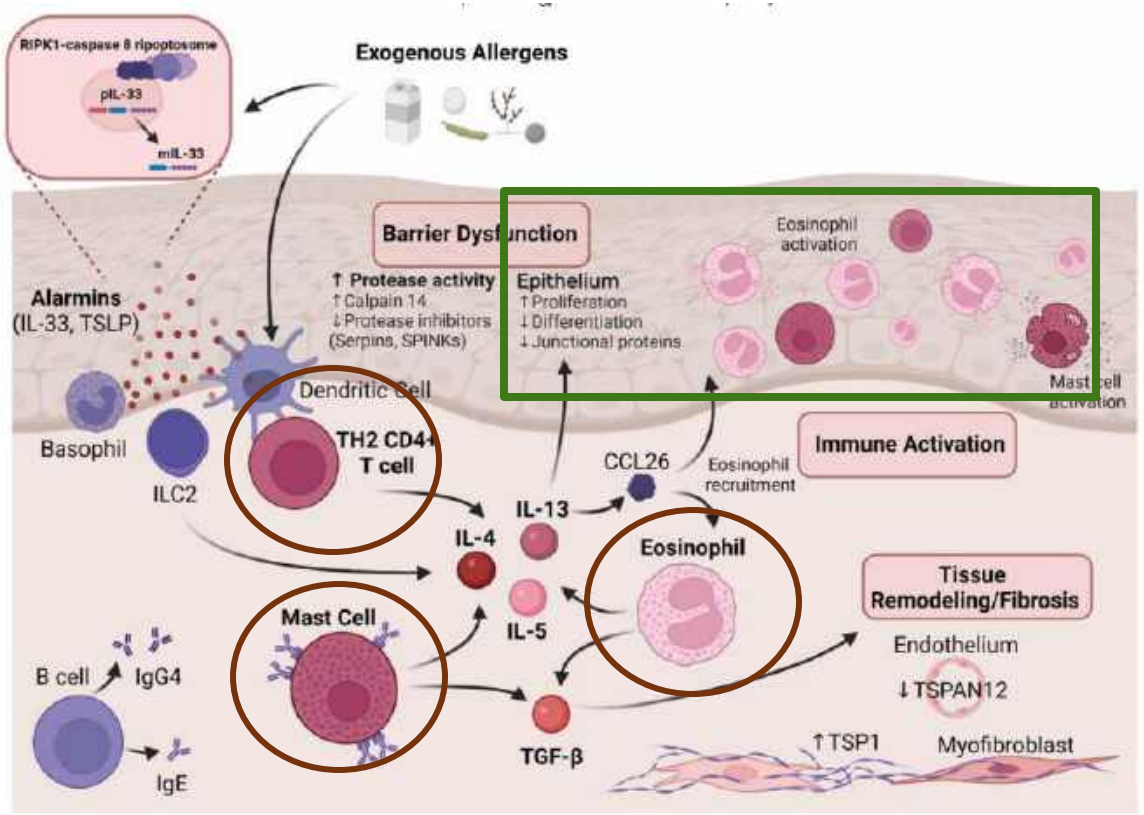


Figure 2. EoE pathophysiology model. Exogenous allergens trigger epithelial-derived cytokine TSLP and IL-33 production, the latter through activating the intracellular allergen sensor RIPK1-caspase-8 ripoptosome. An impaired mucosal barrier from dysregulated endogenous proteases and an abnormal epithelium allow translocation of food antigens to the dendritic cells, which process and present them to the CD4+ T cells. TSLP and IL-33 influence the dendritic cells to mature T_H2-biased effector T cells and stimulate ILC2s; both populations secrete cytokines IL-4, IL-5, and IL-13, which recruit and activate mast cells, eosinophils, and basophils. Mast cells and eosinophils propagate allergic inflammation through cytokine and inflammatory mediator production (eg, PGD2, leukotrienes, granule enzymes), leading to immune cell activation and epithelial changes that further impair barrier function. A feed-forward cycle develops, causing chronic inflammation that stimulates tissue remodeling/fibrosis through the cytokine TGF-β, epithelial-mesenchymal transition, and pro- and anti-fibrotic mediator (TSPAN-12, TSP1) modulation. Created with BioRender.com. EoE, eosinophilic esophagitis; IL, interleukin; ILC2, type 2 innate lymphoid cell; PGD2, prostaglandin D2; TGF-β, transforming growth factor beta; T_H2, T helper 2 cells; TSLP, thymic stromal lymphopoietin.

- EoE is an adaptive allergen-induced immune T-cell-mediated type-2 inflammatory disease characterized by prominent eosinophilic infiltration, epithelial barrier defects, and tissue remodeling/fibrosis leading to progressive oesophageal dysfunction.
- Dysregulated epithelial and immune cell responses are central to disease pathogenesis and generate a feed-forward cycle leading to (self-sustained) chronic inflammation.
- IL-4, IL-5 and IL13 represent the major drivers of the inflammatory process, in which Eotaxin-3 (encoded by the CCL26 gene, released from eosinophils and epithelial cells) is centrally involved in eosinophil recruitment and activation/degranulation.

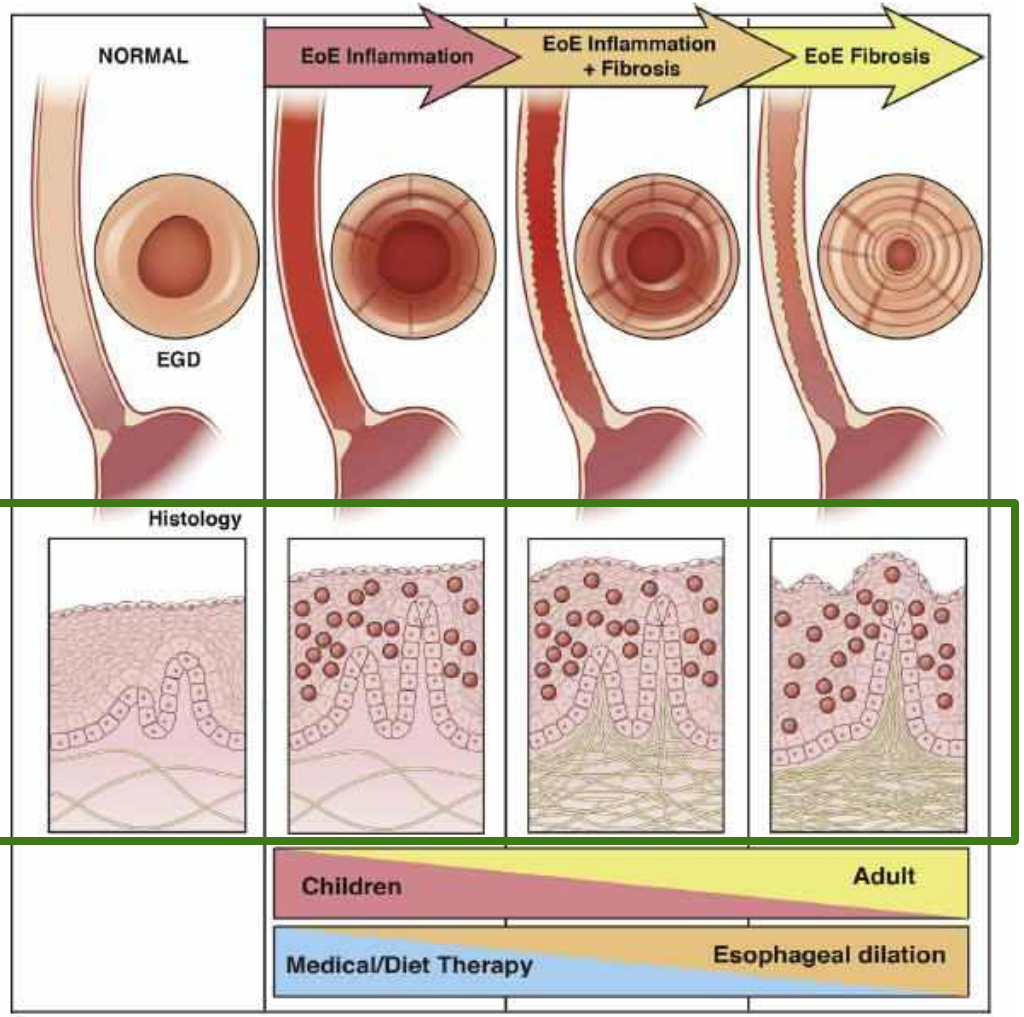
Underwood et al. Ann Allergy Asthma Immunol 2023
Ogulur et al. Cell Mol Immunol 2025
Dellon et al. Am J Gastroenterol 2025

EOSINOPHILIC ESOPHAGITIS

Epidemiology and Natural History of Eosinophilic Esophagitis

Evan S. Dellon[1]

Ikuo Hirano[2]



Inflammatory phenotype → fibrostenotic phenotype

- The diagnosis of eosinophilic oesophagitis is based on the following three requirements
  - Symptoms of oesophageal dysfunction
  - Histological proof of oesophageal eosinophilia
  - Exclusion of other diseases that may be associated with oesophageal eosinophilia (in particular GERD)
- Histology
  - Peak eosinophil count >15/HPF (>60/mm^2)
  - Additional features: degranulation ("eosinophilic dust"), surface layering (plus/minus exudate), aggregates (5-10 EOS) and abscesses (>10 EOS), basal layer hyperplasia, dilatation of intercellular spaces ("spongiosis"), eosinophils within (fibrotic) stroma

Lucendo et al. UEG Journal 2017; Dellon & Hirano. Gastroenterology 2018

EOSINOPHILIC ESOPHAGITIS

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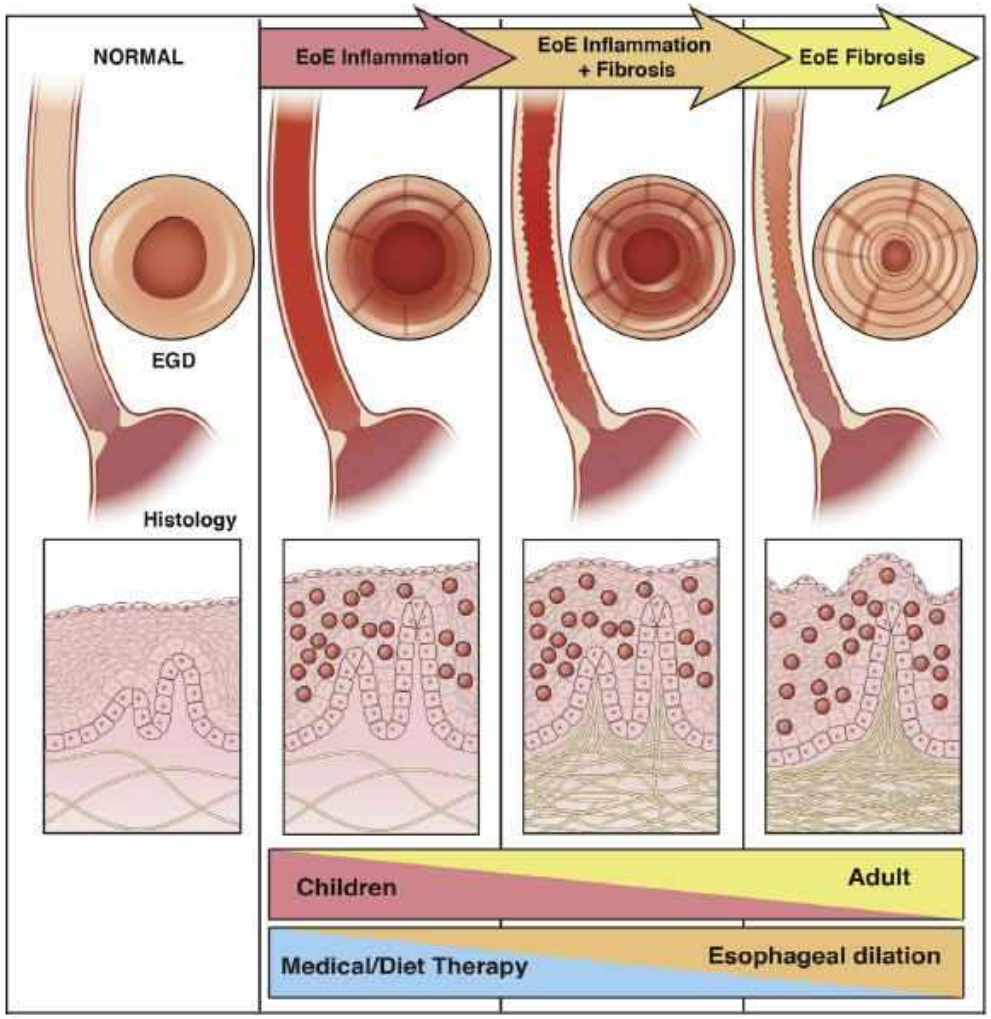
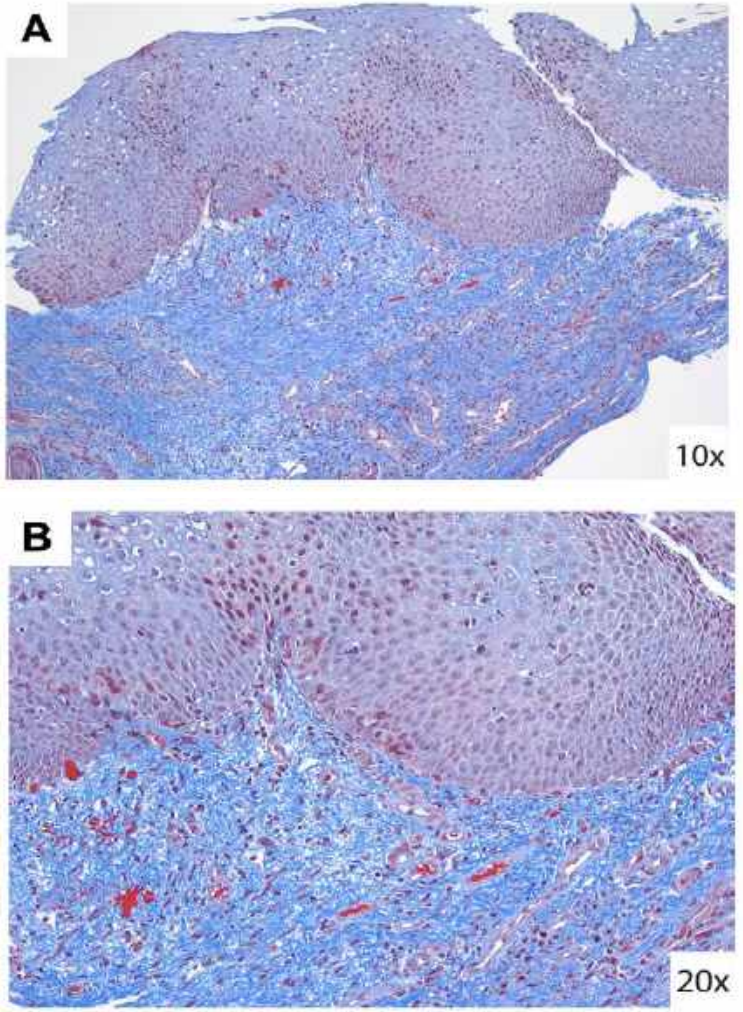
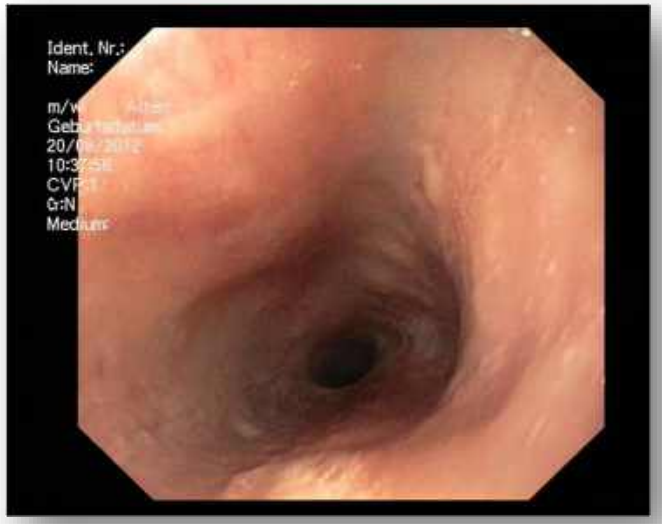
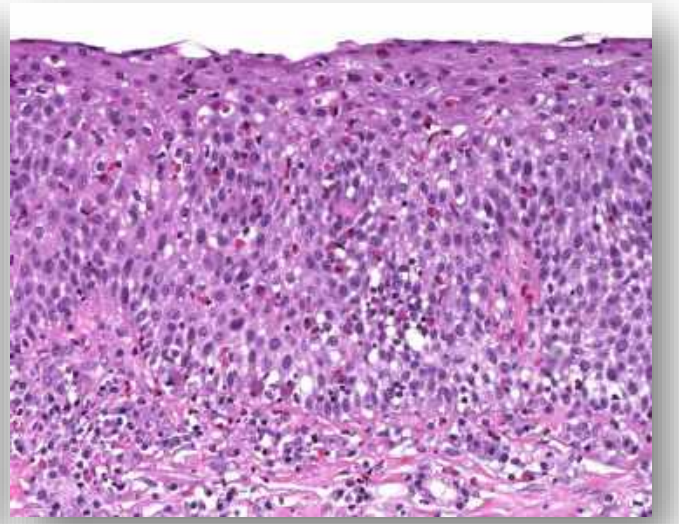


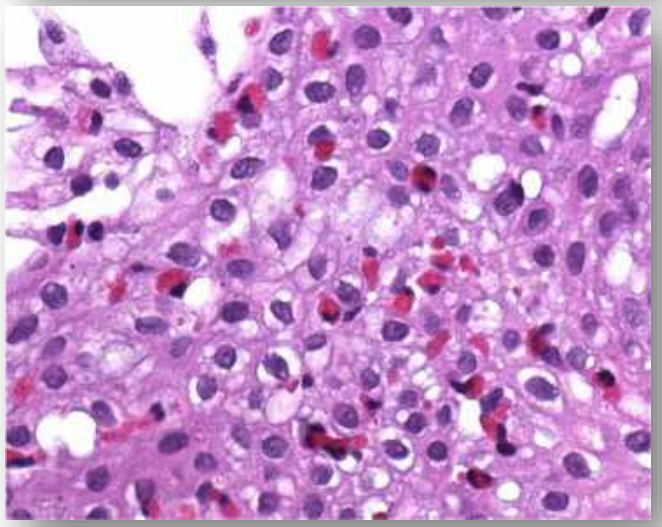


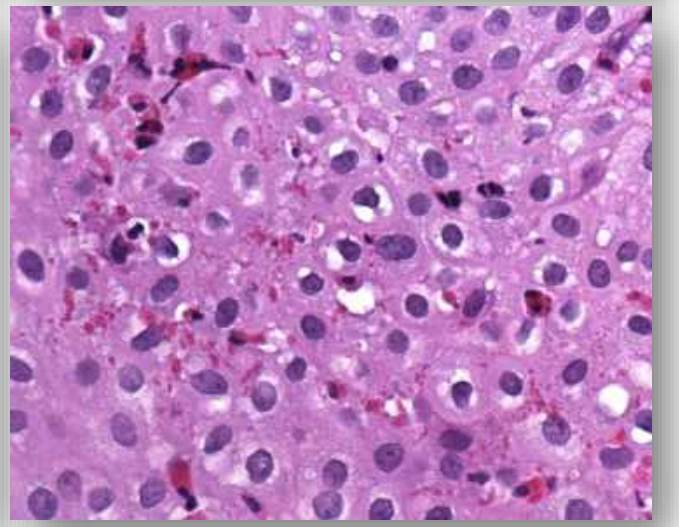
Dellon & Hirano. Gastroenterology 2018; Cheng et al. Am J Physiol Gastrointest Liver Physiol 2012

Eosinophilic oesophagitis









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ENGIP Case of the Month 1/2013

Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy

Evan S Dellon[1,2], Olga Speck[3], Kimberly Woodward[3], Shannon Covey[3], Spencer Rusin[3], Nicholas J Shaheen[1,2] and John T Woosley[3]

Medical University of Graz

Table 1 Characteristics of the study population

	Total population (n = 213)
Age (mean ± s.d.)	49.2 ± 15.4
Male (*n*, %)	102 (48)
White (*n*, %)	173 (81)
Symptoms/upper endoscopy indication (n, %)	
Dysphagia	165 (77)
Heartburn	30 (14)
Abdominal pain	23 (11)
Nausea/vomiting	6 (3)
Upper endoscopy findings (n, %)	
Normal	37 (17)
Rings	74 (35)
Stricture	47 (22)
Narrowing	27 (13)
Furrows	61 (29)
Crêpe-paper	4 (2)
White plaques/exudates	35 (16)
Decreased vascularity	17 (8)
Erosive esophagitis	34 (16)
Schatzki's ring	17 (8)
Hiatal hernia	58 (27)
Dilation performed	68 (32)
Proton pump inhibitor use at the time of endoscopy (*n*, %)[a]	168 (79)
Diagnoses (n, %)	
Eosinophilic esophagitis	41 (19)
Proton pump inhibitor-responsive esophageal eosinophilia	24 (11)
Control	148 (70)

Table 2 Histologic features analyzed by patient, by biopsy, and by high-power field

	Per patient (n = 213)	*Per biopsy (n = 923)*	*Per hpf (n = 4588)*
≥ 15 eos/hpf (*n*, %)	48 (23)	165 (18)	449 (10)
Max eosinophil count (mean eos/hpf ± s.d., range)	24.6 ± 64.9 (0–466)	13.2 ± 40.9 (0–466)	6.6 ± 25.9 (0–466)
Max eosinophil count (median eos/hpf, IQR)	1.5 (0–14)	0 (0–6.2)	0 (0–1.4)
Degranulation (*n*, %)	71 (33)	218 (24)	645 (14)
Microabscess (*n*, %)	27 (13)	60 (7)	136 (3)
Basal layer evaluable (*n*, %)	212 (99)	876 (95)	—
Basal hyperplasia (*n*, %)	48 (23)	102 (12)	—
25–50% high	25 (12)	55 (6)	
50–75% high	23 (11)	47 (5)	
Spongiosis (*n*, %)	60 (28)	153 (17)	—
Subepithelial stroma present (*n*, %)	81 (38)	151 (16)	—
Lamina prop fibrosis (*n*, %)	16 (8)	26 (3)	—
Mucosal distribution (*n*, %)[a]	—		—
Basal		39 (14)	
Superficial		50 (19)	
Diffuse		181 (67)	
Biopsy distribution (*n*, %)[a]	—		—
Patchy		216 (67)	
Diffuse		109 (33)	

[a]Percentages are calculated for those biopsies where there are eosinophils present and the distribution of eosinophils can be assessed.

- This study aimed to determine the distribution of oesophageal eosinophilia and the utility of histologic cut-points for eosinophilic oesophagitis diagnosis in subjects undergoing endoscopy. Incident cases of eosinophilic oesophagitis were diagnosed per consensus guidelines.
- There were 213 patients, yielding 923 oesophageal biopsies with 4588 HPFs. Overall, 48 patients (23%), 165 biopsy fragments (18%), and 449 HPFs (10%) had ≥15 EOS/HPF; most subjects had no or low levels of eosinophils.

Dellon et al. Mod Pathol 2015

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Medical University of Graz

Table 3 Histologic features of eosinophilic esophagitis cases stratified by esophageal level and analyzed by biopsy and by high-power field

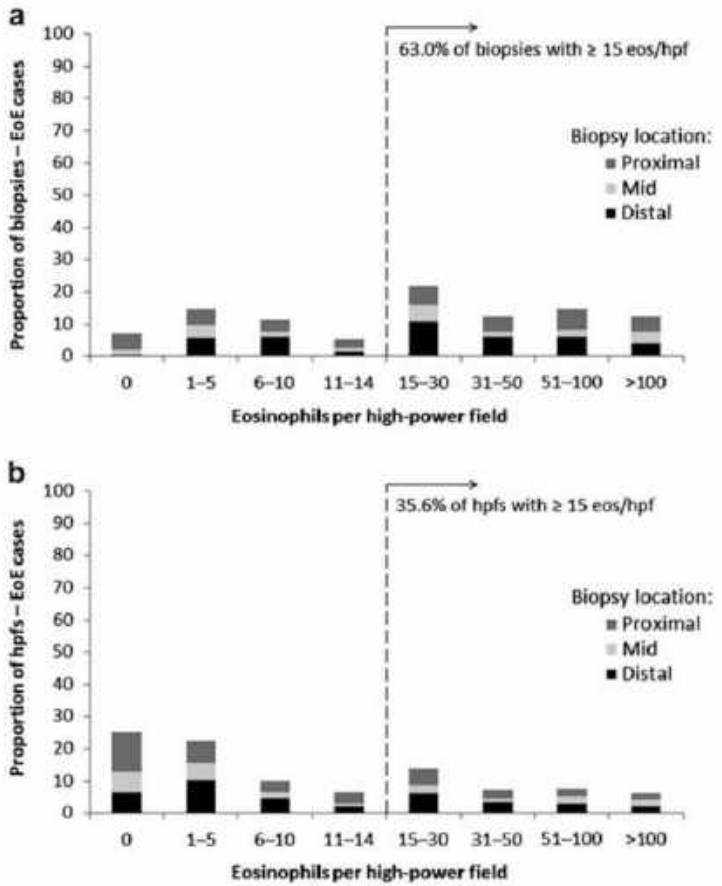
	Per-biopsy analysis (n = 189)			*Per-hpf analysis (n = 932)*		
	Distal (n = 75)	*Mid (n = 40)*	*Proximal (n = 74)*	*Distal (n = 370)*	*Mid (n = 198)*	*Proximal (n = 364)*
≥15 eos/hpf (*n*, %)	53 (75)	24 (60)	42 (57)	144 (39)	65 (33)	123 (34)
Max eosinophil count (mean eos/hpf ± s.d.)	48.8 ± 73.3	56.9 ± 93.4	44.9 ± 65.5	26.8 ± 53.6	26.5 ± 54.4	22.8 ± 42.9
Max eosinophil count (median eos/hpf, IQR)	24.1 (9.0–58.2)	18.5 (4.5–70.8)	21.1 (4.7–57.2)	8.7 (2.5–26)	4.1 (0–23)	6.7 (0–26)
Degranulation (*n*, %)	57 (76)	28 (70)	49 (66)	194 (52)	87 (44)	153 (42)
Microabscess (*n*, %)	21 (28)	12 (30)	25 (32)	48 (13)	24 (12)	57 (16)
Basal layer evaluable (*n*, %)	72 (96)	39 (98)	70 (95)	—	—	—
Basal hyperplasia (*n*, %)				—	—	—
25–50% high	12 (22)	7 (22)	9 (16)			
50–75% high	13 (24)	8 (25)	12 (21)			
Spongiosis (*n*, %)	43 (57)	20 (51)	33 (45)	—	—	—
Subepit						
Lamina						
Mucosa						
Basal						
Super						
Diffus						
Biopsy						
Patch						
Diffus						

[a]Percent

Table 4 Operating characteristics of the eosinophil counts and histologic features for diagnosis of eosinophilic esophagitis

	≥15 eos/hpf	*≥10 eos/hpf*	*≥20 eos/hpf*	*Degranulation*	*Microabscesses*	*Lamina propria fibrosis*
Sensitivity	100	100	90	93	56	27
Specificity	96[a]	87	97	81	98	97
Positive predictive value	85	35	86	54	89	69
Negative predictive value	100	100	98	98	91	85

[a]Of the seven patients who had ≥15 eos/hpf not attributable to either eosinophilic esophagitis or proton pump inhibitor-responsive esophageal eosinophilia, reflux was the cause in six, and esophageal dysmotility leading to stasis esophagitis was the cause in one.



Dellon et al. Mod Pathol 2015

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: *Global Perspectives and Novel Technologies for Esophageal Diseases*

Commentary

Inflammatory conditions of the esophagus: an update

Mikhail Lisovsky

Department of Pathology, Dartmouth-Hitchcock Medical Center and Geisel Medical School at Dartmouth, Lebanon, New Hampshire

Medical University of Graz

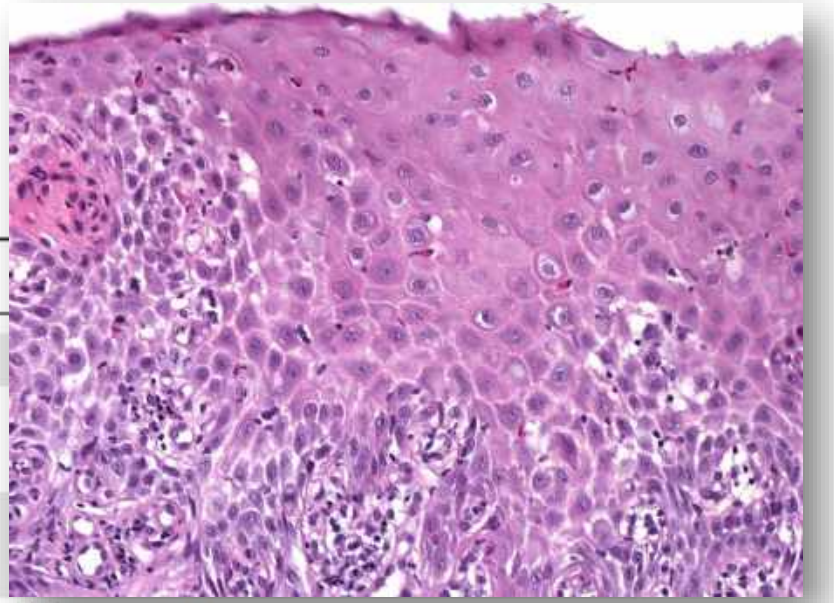


Table 1. Histologic features of eosinophilic esophagitis and reflux esophagitis[a]

	Eosinophilic esophagitis	
≥15 eosinophils/HPF	Very frequent	
Distribution of eosinophils	Equally involves proximal, mid-, and distal esophagus	
Eosinophil microabscesses	Frequent	
Surface layering of eosinophils	Frequent	Uncommon
Eosinophil degranulation	Frequent	Uncommon
Marked basal cell hyperplasia (>50%)	Frequent	Uncommon
Balooned epithelial cells	Not a feature	Characteristic feature, when present

[a]Adapted from Yantiss.[17]

Lisovsky et al. Ann NY Acad Sci 2020

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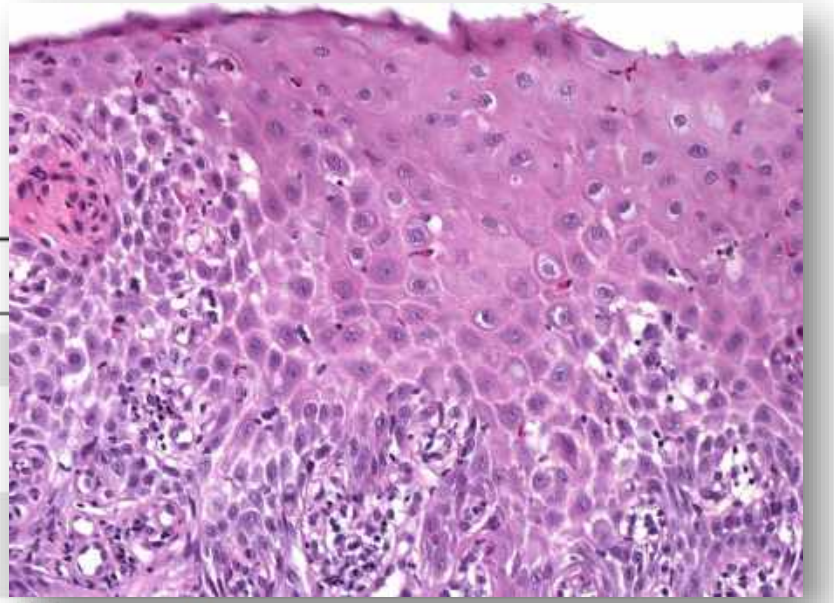

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Balooned ep		en present

[a]Adapted fr

The likelihood of EoE rather than GERD increases as the number of eosinophils increases; and: neutrophils and erosion/ulceration are uncommon in EoE

Lisovsky et al. Ann NY Acad Sci 2020

Gastroenterology 2018;155:1022–1033

CLINICAL—ALIMENTARY TRACT

Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference

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Table 2. EoE Diagnostic Criteria

- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion for EoE.
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion for EoE.
- ≥15 eos/hpf (~60 eos/mm^2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus.
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

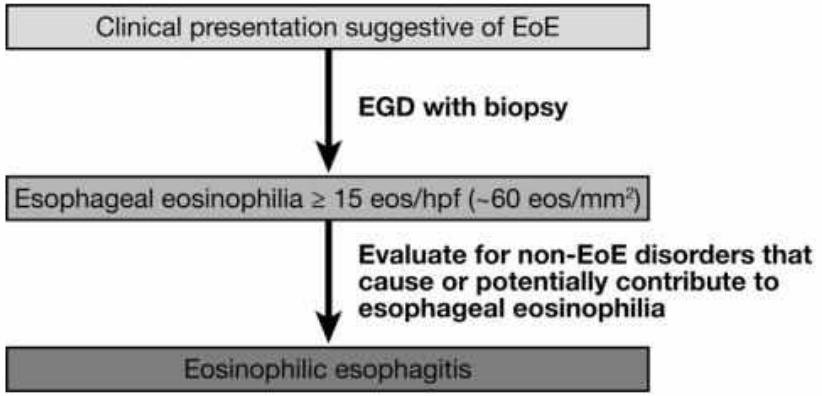

Figure 1. Updated EoE diagnostic algorithm.

Table 3. Conditions Associated With Esophageal Eosinophilia

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- Achalasia and other disorders of esophageal dysmotility
- Hypereosinophilic syndrome
- Crohn's disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement (ie, pemphigus)
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft vs host disease
- Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, *PTEN* hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

Lucendo et al. UEG Journal 2017; Dellon et al. Gastroenterology 2018

Eosinophilic oesophagitis is a patchy disease

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Endoscopic appearance and location dictate diagnostic yield of biopsies in eosinophilic oesophagitis

J. Salek*, F. Clayton†, L. Vinson*, H. Saffari‡, L. F. Pease III*,‡,§, K. Boynton*, J. Fang*, K. Cox* & K. A. Peterson*

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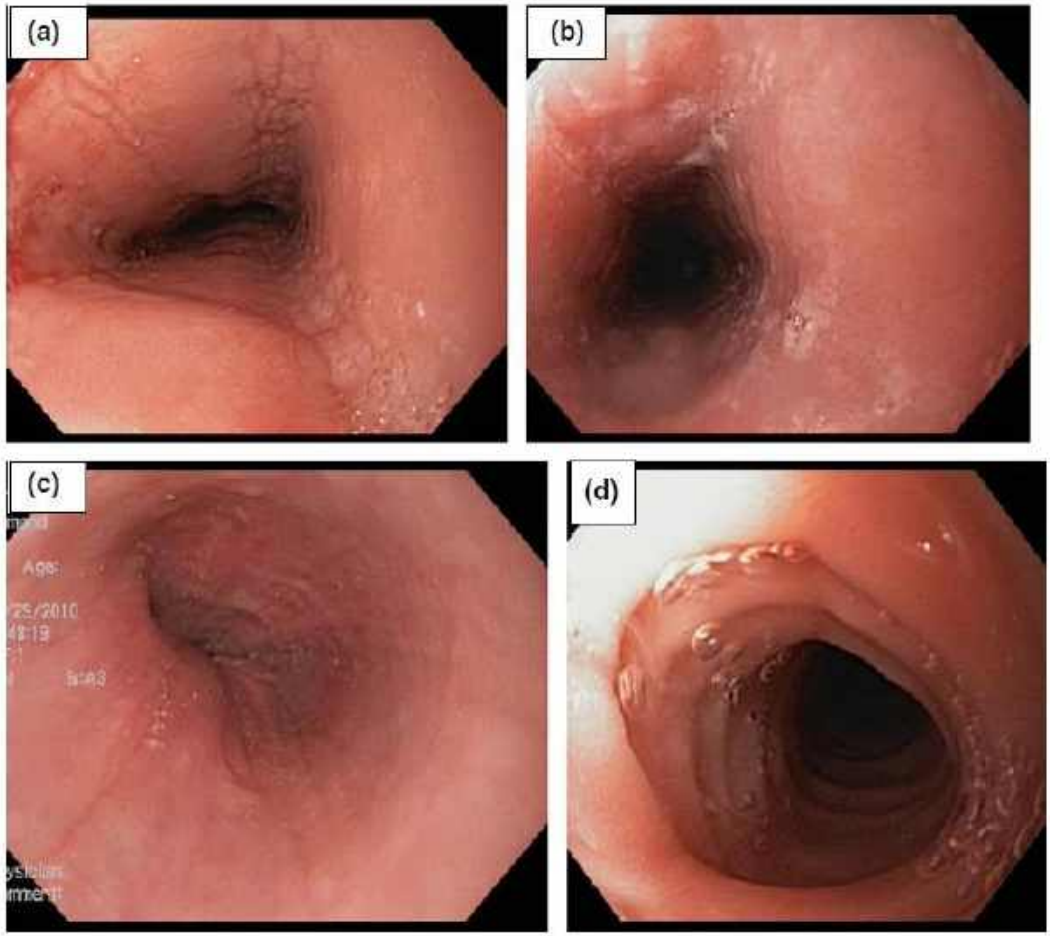


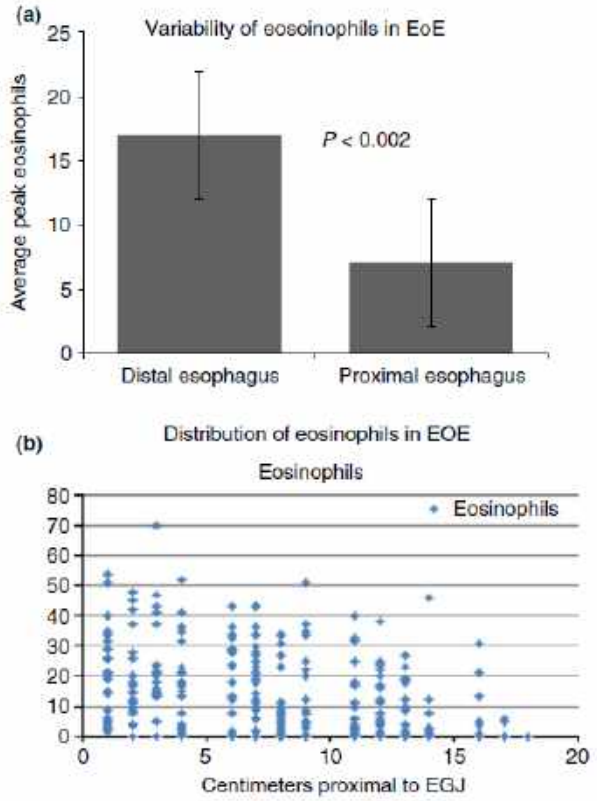


Figure 5 | (a) Eosinophil peak counts (with s.d.) as averaged over distal 10 cm of the oesophagus vs. those taken proximally. Distal biopsies reported greater numbers of eosinophils in EoE. (b) Scatter plots demonstrating the increased density of eosinophils in the distal oesophagus.

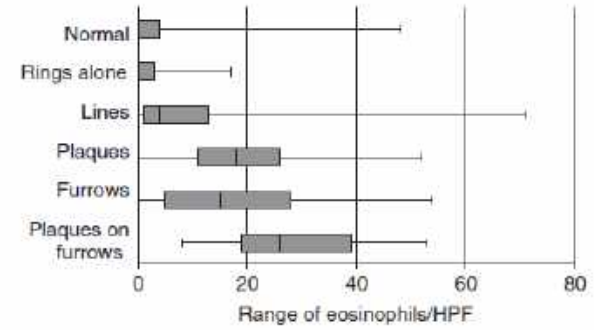


Figure 6 | Eosinophil peak counts as seen within areas of specific endoscopic changes. Furrows and plaques seen on exam reflect higher average eosinophil numbers than lines or a normal-appearing oesophagus. ANOVA analysis confirmed that counts varied significantly according to the oesophageal manifestations seen on endoscopy ($P < 0.001$). Individual comparisons to normal-appearing tissue revealed significant differences in eosinophil counts in plaques/furrows, plaques alone, furrows alone (*$P < 0.0001$ for all) with a trend for significance with lines ($P < 0.04$).

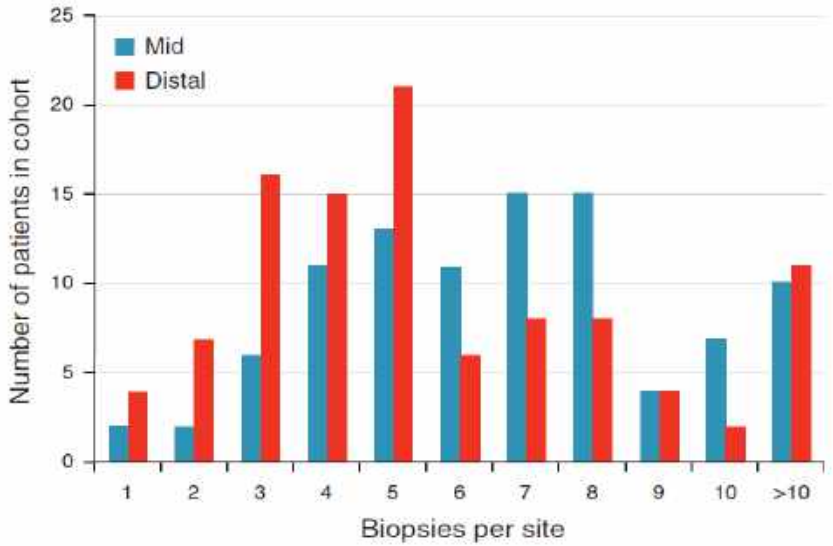
Endoscopy can be normal in 10-20% of cases, need for biopsy („microscopic oesophagitis“)

Salek et al. Aliment Pharmacol Ther 2015

The Optimal Number of Biopsy Fragments to Establish a Morphologic Diagnosis of Eosinophilic Esophagitis

Jennifer A. Nielsen, BA[1], Donna J. Lager, MD[2], Matthew Lewin, MD[2], Gabriel Rendon, MD[3] and Cory A. Roberts, MD[2]

Medical University of Graz



- There was no significant difference between the mean number of EOS/HPF from the mid (26) and lower (25) oesophagus The probability of one, four, five, and six biopsy fragments containing >15 EOS/HPF was 0.63, 0.98, 0.99, and >0.99, respectively.
- We recommend that between 4 and 6 biopsies be taken from oesophagus to rule out EoE in cohorts with unknown PPI trial therapy status.

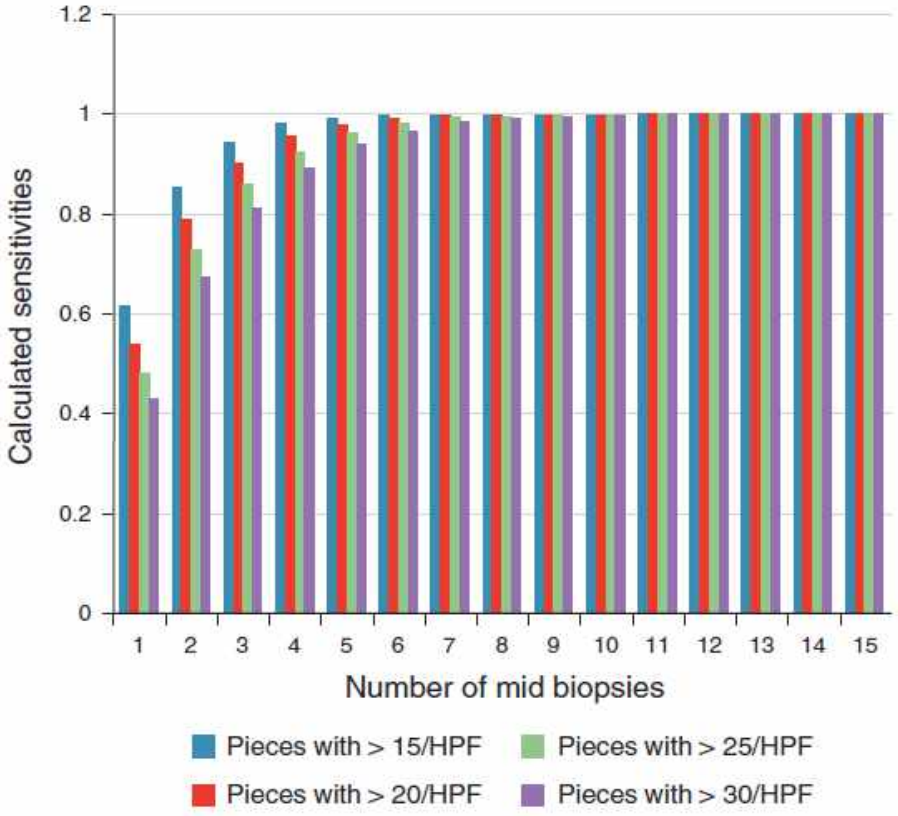


Figure 3. The calculated sensitivities of the number of biopsies taken from the mid esophagus at diagnostic thresholds of >15, >20, >25, and >30 number of eosinophils per high power field (EOS/HPF).

Nielsen et al. Am J Gastroenterol 2014

Presentation of a case: oesophageal biopsies from a 26 year-old male

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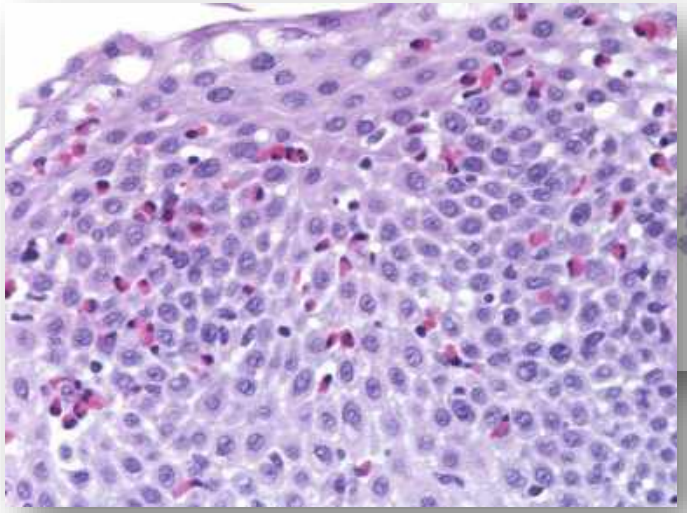

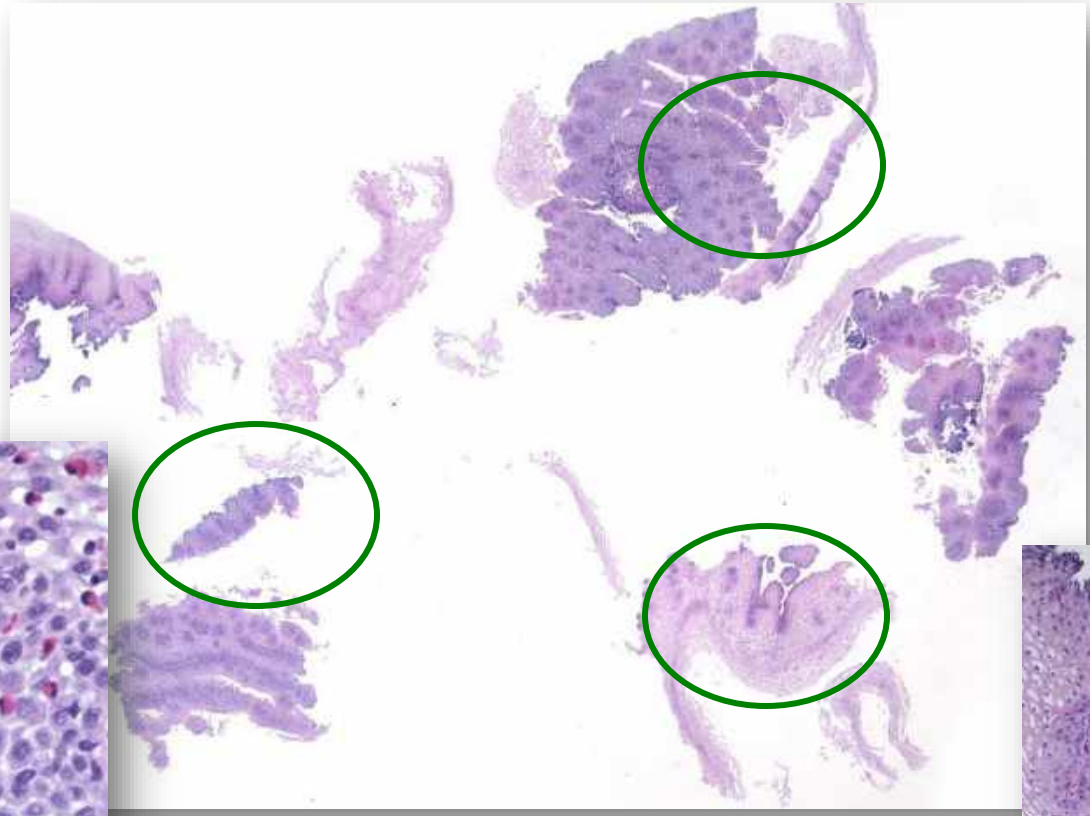

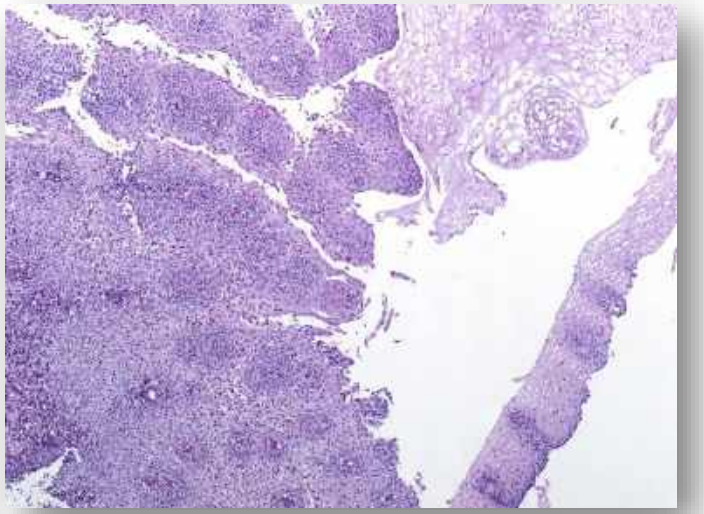

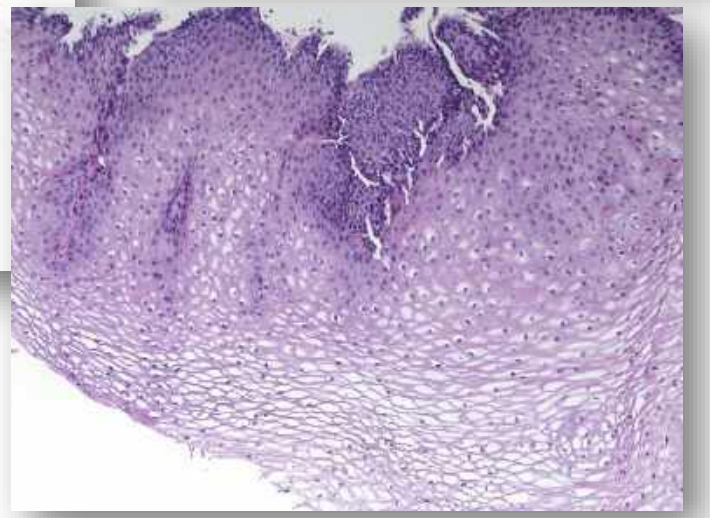

It is the peak count that matters (obtained from at least six biopsy specimens!)

Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults

2017, Vol: 5(3) 335–358
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DOI: 10.1177/2050640616689525
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Alfredo J Lucendo[1,2], Javier Molina-Infante[2,3], Ángel Arias[2,4], Ulrike von Arnim[5], Albert J Bredenoord[6], Christian Bussmann[7], Jorge Amil Dias[8], Mogens Bove[9], Jesús González-Cervera[2,10], Helen Larsson[9], Stephan Miehlke[11], Alexandra Papadopoulou[12], Joaquín Rodríguez-Sánchez[13], Alberto Ravelli[14], Jukka Ronkainen[15], Cecilio Santander[2,16], Alain M Schoepfer[17], Martin A Storr[18], Ingrid Terreehorst[19], Alex Straumann[20] and Stephen E Attwood[21]

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Statements	Level of evidence	Strength of recommendation
Al least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities.	Moderate	Strongly in favor
The accepted threshold for eosinophil density for the diagnosis of EoE is 15 eosinophils per high andard size of ~0.3 mm^2) in ucosa, taken as the peak concen- pecimens examined.	Moderate	Strongly in favor
n staining is sufficient for histo- nent of EoE in routine clinical	Low	Weakly against
inophil count, additional histo- s may include eosinophil micro- al zone hyperplasia, dilated aces, eosinophil surface layering, gation, and lamina propria	Moderate	Weakly in favor

What is the current definition of EoE?. **Statement 1:** EoE represents a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and local causes of esophageal eosinophilia should be excluded. Clinical manifestations or pathologic data should not be interpreted in isolation.

LE: NA; **Agreement**: 100%, votes: strongly agree (100%).

Lucendo et al. UEG Journal 2017

CME

ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis

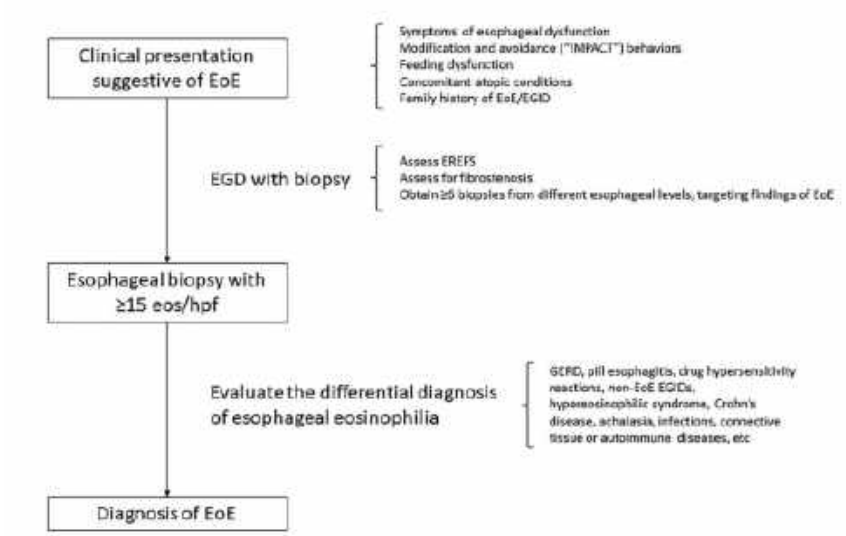
Evan S. Dellon, MD, MPH, FACG[1], Amanda B. Muir, MD[2,3,4], David A. Katzka, MD, FACG[5], Shailja C. Shah, MD, MPH[6,7], Bryan G. Sauer, MD, MSc, FACG[8], Seema S. Aceves, MD, PhD[9,10], Glenn T. Furuta, MD[11,12], Nirmala Gonsalves, MD, FACG[13,*] and Ikuo Hirano, MD, FACG[13,*†]

1. We recommend that EoE is diagnosed based on the presence of symptoms of esophageal dysfunction and at least 15 eosinophils per high-power field (eos/hpf) on esophageal biopsy, after evaluating for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia (quality of evidence: low; strength of recommendation: strong).

3. We recommend obtaining at least 6 esophageal biopsies from at least 2 esophageal levels (e.g., proximal/mid and distal), targeting EoE endoscopic findings, if possible, to assess for histologic features consistent with EoE (quality of evidence: low; strength of recommendation: strong).

4. We recommend that eosinophil counts be quantified on esophageal biopsies from every endoscopy performed for EoE (quality of evidence: low; strength of recommendation: strong).

17. We recommend evaluating response to treatment of EoE with assessment of symptomatic and endoscopic and histologic outcomes (quality of evidence: low; strength of recommendation: strong).



- More detail than a histological diagnosis “>15 EOS/HPF” (>60 EOS/mm2) is needed for subsequent patient management (monitoring), with <15 EOS/HPF being a “reasonable goal” for most patients (indicating remission under treatment)
- Beyond eosinophils other inflammatory cells are seen (T cells of several subtypes, mast cells, basophils etc) as well as changes of squamous epithelium and stroma

Dellon et al. Am J Gastroenterol 2025

Atypical (variant) forms of EoE: fact or fiction?

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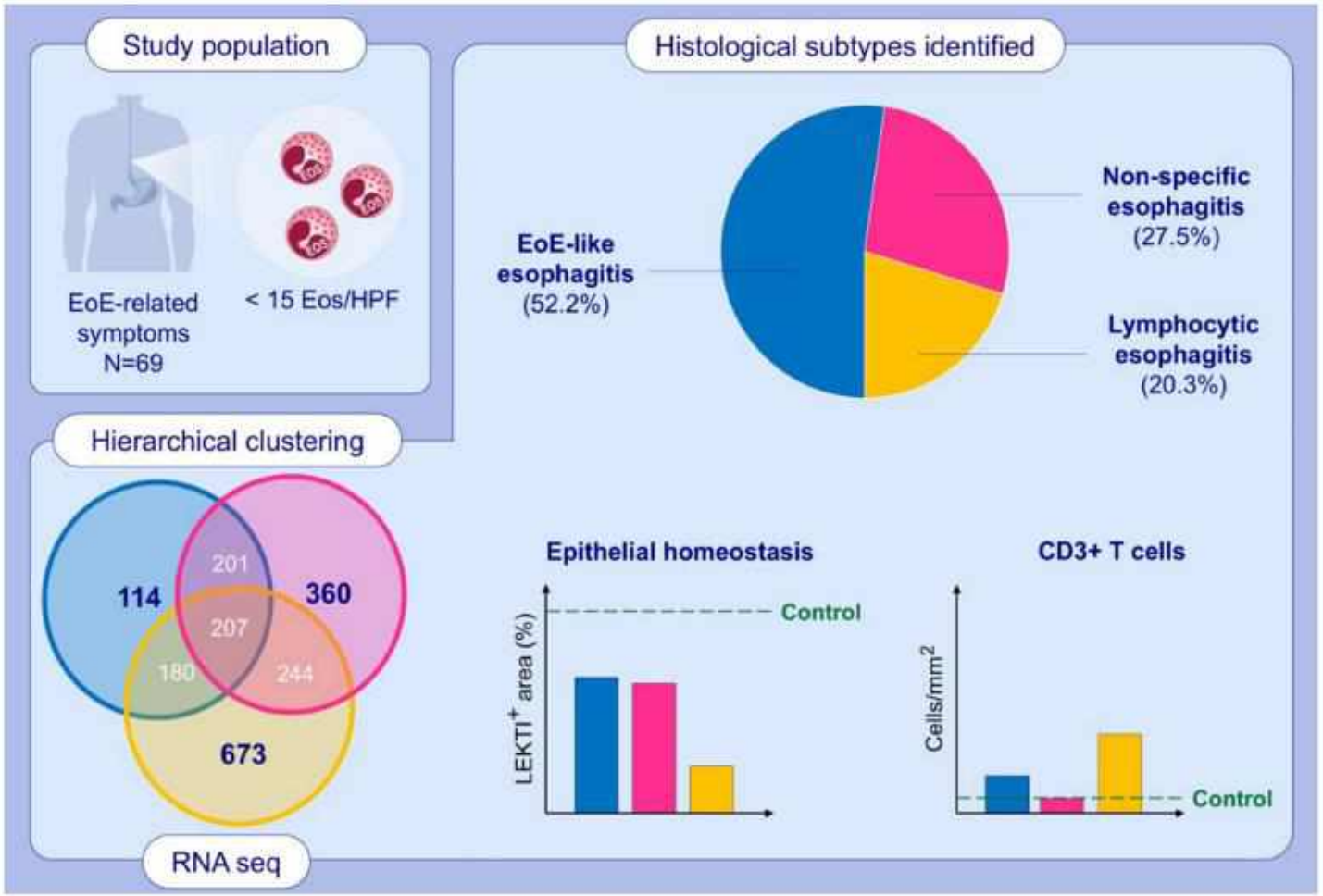
ORIGINAL ARTICLE
Food Allergy and Gastrointestinal Disease

Allergy EAACI WILEY

Characterization of eosinophilic esophagitis variants by clinical, histological, and molecular analyses: A cross-sectional multi-center study



- Patients (n=69) with symptoms of oesophageal dysfunction, but peak eosinophil counts <15/HPF in oesophageal biopsies with GERD excluded
- Three histological subtypes:
  - EoE-like oesophagitis (36/69; 52%)
  - Lymphocytic oesophagitis (14/69; 20%)
  - Non-specific oesophagitis (19/69; 28%)
- Hierarchical sample clustering of RNA sequencing data confirmed the presence of an EoE-like (characterized by Eotaxin-3 expression), non-specific, and lymphocytic variant clusters (characterized by CD3 cells and TSLP expression)

Greuter et al. Allergy 2022

Eosinophilic Esophagitis beyond Eosinophils – an Emerging Phenomenon Overlapping with Eosinophilic Esophagitis: Collegium Internationale Allergologicum (CIA) Update 2023

Vanessa Sofia Salvador Nunes[a] Alex Straumann[b] Luis Salvador Nunes[c]
Alain M. Schoepfer[c] Thomas Greuter[b, c, d]

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Table 1. Histological definitions of EoE variants

EoE variant	Histological definition
EoE-like esophagitis	Presence of 0–59 eos/mm^2 (<15 eos/hpf), but typical histological EoE features, particularly dilated intercellular spaces and basal zone hyperplasia [30]
Lymphocytic esophagitis	Typical pattern with high number of intraepithelial lymphocytes (≥30 per hpf), gathered mainly in peripapillary fields, peripapillary spongiosis (dilated intercellular spaces) and absence of intraepithelial granulocytes [79]
Non-specific esophagitis	Histological infiltration of lymphocytes or neutrophils not fulfilling the numerical and distributional criteria of lymphocytic esophagitis [60]

- A novel entity clinically resembling EoE but without eosinophilic infiltration in the oesophagus, so-called “EoE-like disease”, has been described in 2016 in five patients from four EoE families (clinically resembling EoE but not fulfilling the histological criteria).
- EoE is a Th2- mediated disease with many more disease features than eosinophilic infiltration. In fact, EoE might be only the tip of the iceberg (and the most extreme phenotype) with several variant forms, at least three, lying on a disease spectrum.
- Progression to conventional EoE has been observed in some cases.

Salvador Nunes et al. Int Arch Allergy Immunol 2023

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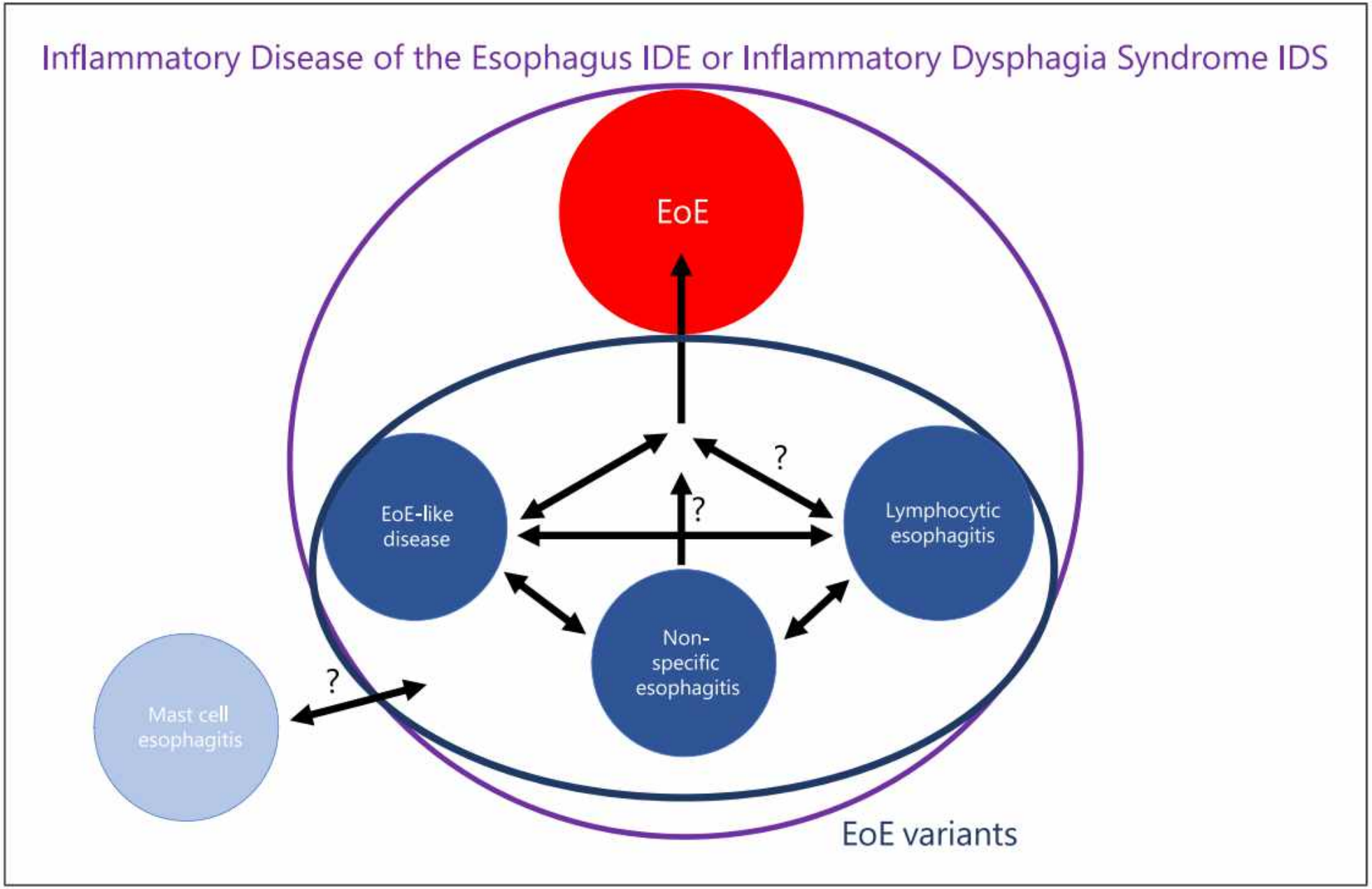


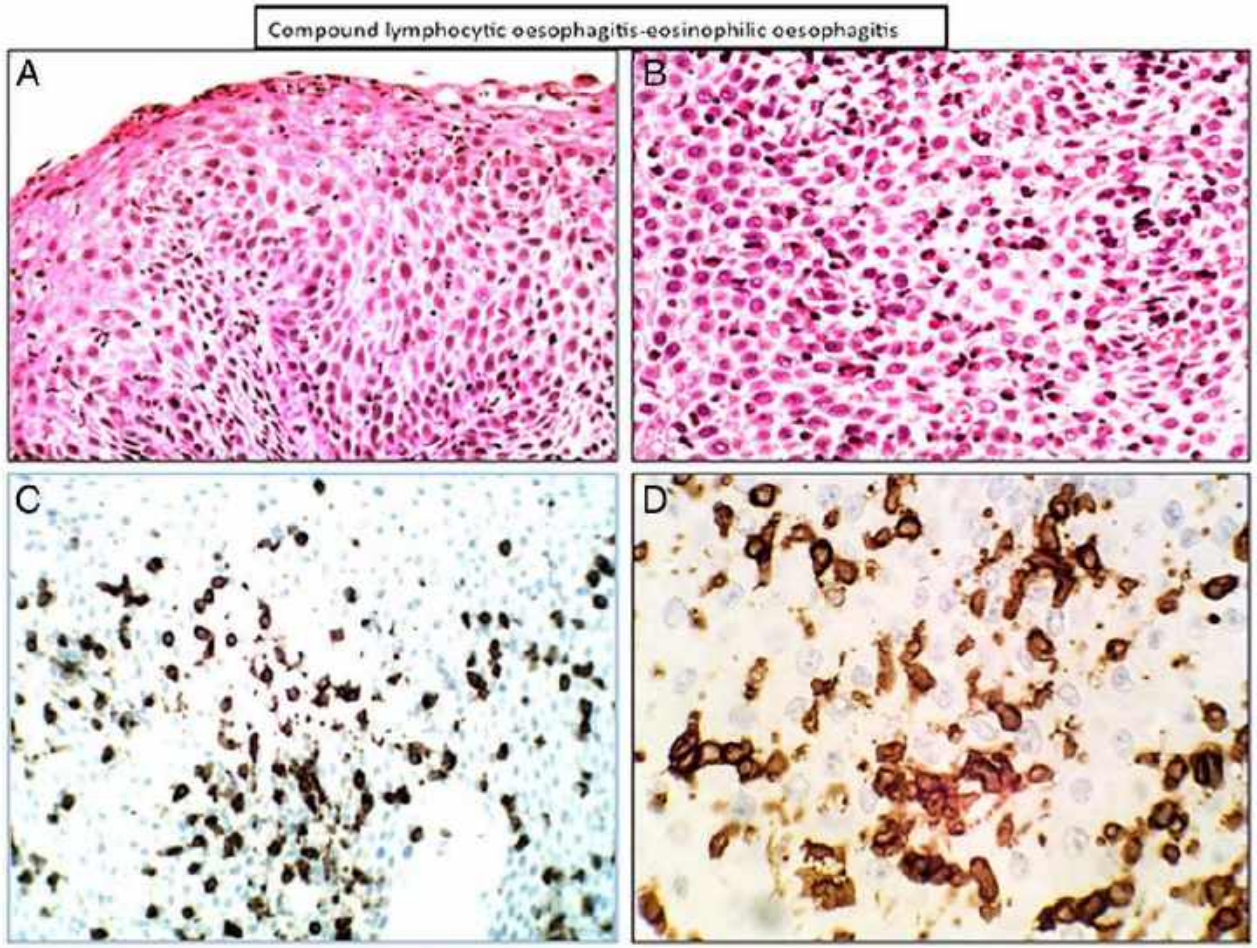
Salvador Nunes et al. Int Arch Allergy Immunol 2023

Lymphocytic oesophagitis, eosinophilic oesophagitis and compound lymphocytic–eosinophilic oesophagitis I: histological and immunohistochemical findings

C A Rubio,[1] T Ichiya,[2] P T Schmidt[2]

Medical University of Graz

- Oesophageal biopsies from 311 patients were stained with H&E and with CD3
- Four histological–immunohistochemical oesophagitis phenotypes were recorded:
  - Lymphocytic oesophagitis (LyE, ≥40 CD3+ lymphocytes/HPF)
  - Eosinophilic oesophagitis (EoE, ≥15 eosinophils/HPF in H&E stain)
  - Lymphocytic infiltration (≤39 CD3+/HPF)
  - Compound lymphocytic oesophagitis–eosinophilic oesophagitis (Co LyE-EoE)



Rubio et al. J Clin Pathol 2017

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Table 2 H&E-CD3 oesophagitis phenotypes at index biopsy and at first follow-up biopsy in 87 patients

Index biopsies	Normal	Lym inf	LyE	EoE	Co LyE/EoE	Total
Lym inf	5	15/31 (48.4%)	9	2		31
LyE	3	4	12/24 (50.0%)	2	3	24
EoE	4	11	1	6/22 (27.3%)		22
Co LyE/EoE	1	4	1		4/10 (40.0%)	10
Total	13	34	23	10	7	87

Co LyE/EoE, compound lymphocytic oesophagitis/eosinophilic oesophagitis; EoE, eosinophilic oesophagitis (≥15/HPF) with lymphocytic infiltration; LyE, lymphocytic oesophagitis (≥40/HPF) with or without eosinophilic infiltration; Lym inf, lymphocytic infiltration (≤39/HPF) with or without eosinophilic infiltration (≤14/HPF).

Table 3 H&E-CD3oesophagitis phenotypes at index biopsy and at second follow-up biopsy in 61 patients

	Second follow-up biopsy					
Index biopsies	Normal	Lym inf	LyE	EoE-lym inf	Co LyE/EoE	Total
Lym inf	8	12/32 (37.5%)	8	4		32
LyE					1	13
EoE					3	12
Co LyE/EoE					2/4 (50.0%)	4
Total					6	61

Co LyE/EoE, c… HPF) with or … …ocytic infiltration; LyE, lymphocytic oesophagitis (≥40/… (≤14/HPF).

A persistent oesophagitis phenotype was found in 42.5% (37/87) in the first follow-up biopsy and in 34.4% (21/61) in the second follow-up biopsy

Rubio et al. J Clin Pathol 2017

Please don't forget, the most common cause of lymphocyte-rich inflammation in the oesophagus is Candida

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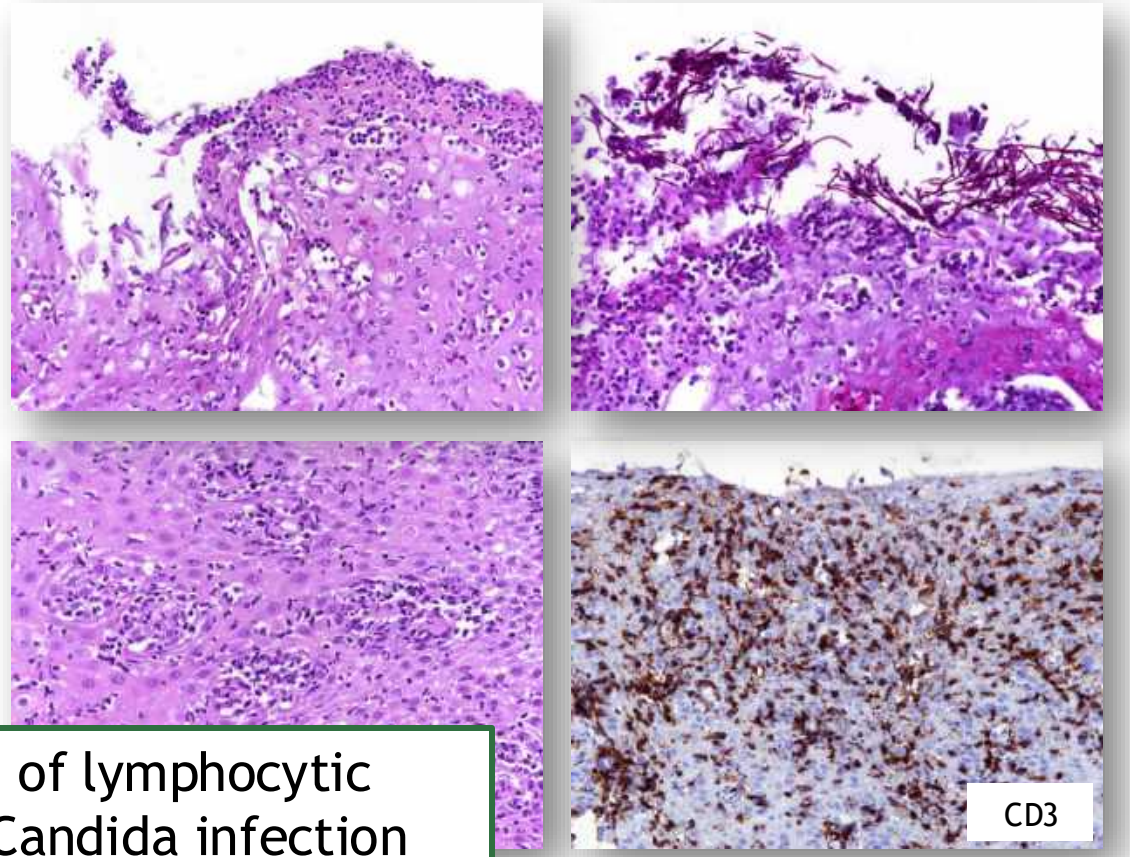
	Candida esophagitis, % ($n = 88$)	Reflux esophagitis, % ($n = 64$)	*P*-value
Basal hyperplasia	73	95	.0007
Elongated papillae	52	81	.0003
Intraepithelial neutrophils			
		22	<.0001
		14	<.0001
		8	.0342
		19 (12/64)	<.0001
		17 (2/12)	.0011
		83 (10/12)	.0011
		17 (2/12)	.005
		2	<.0001
		0	<.0001
		0	<.0001
		2	<.0001
and increased lymphocytes			
Intraepithelial eosinophils			
No	66		
Rare	20		
Multiple	14		
Erosion/ulcer	0		



First step in diagnosis of lymphocytic oesophagitis: rule out Candida infection (cytology > histology)

Martin et al. Mod Pathol 2018

Do we need a histological scoring system for EoE diagnosis?

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Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring

M. H. Collins,[1] L. J. Martin,[2] E. S. Alexander,[3,6] J. Todd Boyd,[1] R. Sheridan,[1] H. He,[2] S. Pentiuk,[4] P. E. Putnam,[4] J. P. Abonia,[5] V. A. Mukkada,[4] J. P. Franciosi,[4] M. E. Rothenberg[5]

Medical University of Graz

- A histology scoring system (HSS) for biopsies from suspected EOE patients that evaluates **eight** features: eosinophil density (EI), basal zone hyperplasia (BZH), eosinophil abscesses (EA), eosinophil surface layering (SL), dilated intercellular spaces (DIS), surface epithelial alteration (SEA), dyskeratotic epithelial cells (DEC), and lamina propria fibrosis (LPF).

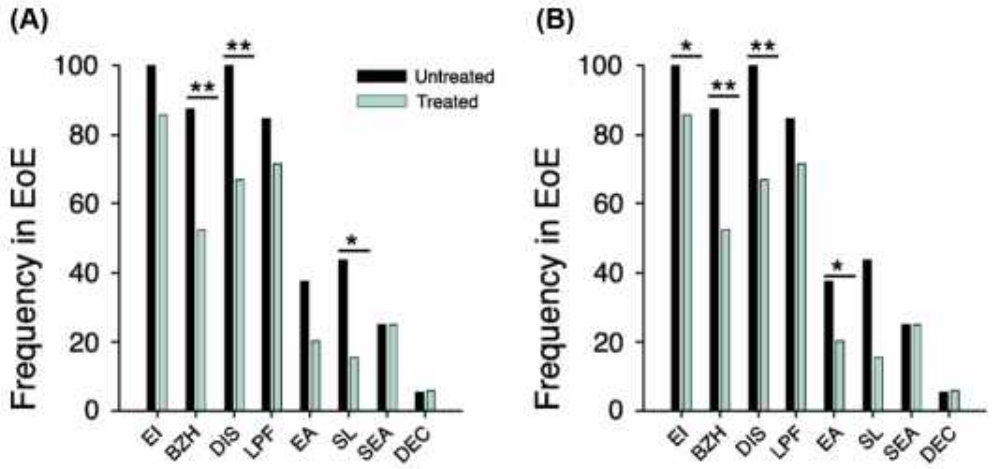

Fig. 2 EoEHSS feature frequency. Frequency of histologic abnormalities in untreated (black bars) and treated (gray bars) in distal (A) and proximal (EoE) biopsies (B). $*P \leq 0.05$, $**P \leq 0.0063$ (Bonferroni multiple testing threshold).

Collins et al. Dis Esophagus 2017; Hiremath et al. Clin Gastroenterol Hepatol 2023

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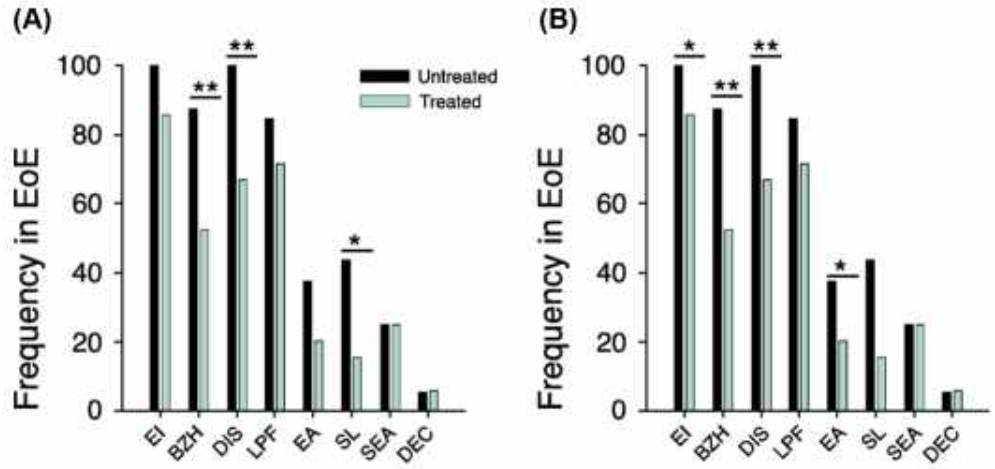
- Severity (grade) and extent (stage) of abnormalities were scored using a 4-point scale (0 normal; 3 maximum change).



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"This system has been validated in pediatric and adult EoE patients and has excellent interobserver and intraobserver reliability. It also performs better than PEC alone in assessing treatment response."

Collins et al. Dis Esophagus 2017; Hiremath et al. Clin Gastroenterol Hepatol 2023

Table 1 EoEHSS grade scores[a] and PEC

	Distal			Proximal		
	Untreated	Treated	*P*	Untreated	Treated	*P*
EI	3 (2–3)	2 (1–3)	0.0035	3 (2–3)	1 (0–2)	0.0002
BZH	2 (1–3)	1 (0–2)	0.024	2 (1–3)	0 (0–1)	<0.0001
DIS	3 (3–3)	2 (0–3)	0.0051	3 (3–3)	2 (0–3)	0.0002
LPF	2 (2–3)	2 (0–2.5)	0.20	2 (0.75–2.25)	1 (0–2)	0.26
EA	0 (0–1)	0 (0–0)	0.14	0 (0–1)	0 (0–0)	
SL	0 (0–2)	0 (0–0)	0.012	0 (0–1)	0 (0–0)	
SEA	0 (0–0.75)	0 (0–0.75)	0.90	0 (0–0.25)	0 (0–0)	
DEC	0 (0–0)	0 (0–0)	0.19	0 (0–0)	0 (0–0)	
Non-PEC feature mean	0.47 (0.28–0.57)	0.29 (0.08–0.47)	0.0062	0.44 (0.28–0.51)	0.14 (0.05–0.38)	
PEC	131.5 (24.3–175)	26 (3–93)	0.008	69 (30.3–113.8)	3 (0–44)	

[a] Median (IQR). Groups were compared using Wilcoxon rank sum analyses.

Table 2 EoEHSS stage scores[a]

	Distal			Proximal		
	Untreated	Treated	*P*	Untreated	Treated	
EI	2.5 (1–3)	1 (0–2)	0.0049	2 (1–3)	0 (0–2)	
BZH	2.5 (2–3)	1 (0–3)	0.0070	3 (1–3)	0 (0–2)	
DIS	3 (3–3)	1.5 (0–3)	0.0002	2.5 (2–3)	1 (0–3)	
LPF	3 (2.5–3)	3 (0–3)	0.12	3 (0.75–3)	2.5 (0–3)	
EA	0 (0–1)	0 (0–0)	0.18	0 (0–1)	0 (0–0)	
SL	0 (0–1)	0 (0–0)	0.011	0 (0–1)	0 (0–0)	
SEA	0 (0–0.75)	0 (0–0.75)	0.98	0 (0–0.25)	0 (0–0)	
DEC	0 (0–0)	0 (0–0)	0.19	0 (0–0)	0 (0–0)	0.94
Non-PEC feature mean	0.5 (0.31–0.54)	0.21 (0.04–0.43)	0.0024	0.46 (0.24–0.52)	0.13 (0–0.38)	0.0003

[a] Median (IQR). Groups were compared using Wilcoxon rank sum analyses.

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The EoEHSS discriminates treated from untreated patients, uses features commonly found in such biopsies, and is utilizable by pathologists ***after minimal training***. These data provide rationales and a method to evaluate oesophageal biopsies for features in addition to PEC.

Collins et al. Dis Esophagus 2017

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- The maximum possible grade or stage score for each biopsy is 24.
- The final score is the ratio of the sum of the assigned scores for each feature evaluated divided by the maximum possible score for that biopsy: For example, if all 8 features have maximum grade and stage scores of 3, the final score for both grade and stage would be 24/24 = 1.
- If a feature is not evaluated, the maximum possible score is reduced by 3. Most maximum possible score reductions occur because lamina propria is not present; if all other features are evaluable, the maximum possible score for a biopsy lacking lamina propria is reduced from 24 to 21 because 7 instead of 8 features are evaluated.

Collins et al. Dis Esophagus 2017

Reliability of histologic assessment in patients with eosinophilic oesophagitis

M. J. Warners[1] | C. A. Ambarus[1] | A. J. Bredenoord[1] | J. Verheij[1] | G. Y. Lauwers[2] | J. C. Walsh[3] | D. A. Katzka[4] | S. Nelson[3] | T. van Viegen[3] | G. T. Furuta[5] | S. K. Gupta[6] | L. Stitt[3] | G. Zou[3] | C. E. Parker[3] | L. M. Shackelton[3] | G. R. D`Haens[1,3] | W. J. Sandborn[3,7] | E. S. Dellon[8] | B. G. Feagan[3] | M. H. Collins[9] | V. Jairath[3] | R. K. Pai[10]

EOEHSS	Grade score	Stage score
Eosinophilic inflammation: Intra-epithelial eosinophils are not normally found in oesophageal biopsies; therefore any intra-epithelial eosinophils were considered abnormal. (Figure 1a)	Grade score for eosinophilic inflammation was based on the quantity of eosinophils in the most inflamed high power field (HPF) (peak eosinophil count, PEC). 0 = intra-epithelial eosinophils not present 1 = PEC <15/HPF 2 = PEC 15-59/HPF 3 = PEC >60/HPF	Stage score for EI was based on the amount of the biopsy that exhibited the threshold value for EoE diagnosis: 0 = intra-epithelial eosinophils 0-14/HPF 1 = PEC ≥15/HPF in <33% of HPFs 2 = PEC ≥15/HPF in 33%-66% of HPFs 3 = PEC ≥15/HPF in >66% of HPFs
Epithelial basal zone: The basal zone of oesophageal squamous epithelium is composed of closely packed small cells and normally occupies ≤15% of the total epithelial thickness. The upper limit of the basal zone was defined as the level at which basal epithelial cell nuclei were separated by a distance equal to or greater than the diameter of a basal cell nucleus (Figure 1a)	Grade score for basal zone hyperplasia (BZH) was based on the amount of total epithelial thickness occupied by the basal zone (Figure 1a): 0 = BZH not present 1 = basal zone occupies >15% but <33% of total epithelial thickness 2 = basal zone occupies 33%-66% of total epithelial thickness 3 = basal zone occupies >66% of total epithelial thickness OR *Cannot be scored*	Stage score for BZH was based on the amount of the biopsy that exhibited any BZH: 0 = BZH not present 1 = BZH (any grade >0) in <33% of epithelium 2 = BZH (any grade >0) in 33%-66% of epithelium 3 = BZH (any grade >0) in >66% of epithelium OR *Cannot be scored*

Warners et al. Aliment Pharmacol Ther 2018

Eosinophil abscess (EA): intra-epithelial eosinophil group or aggregate in which eosinophils form solid masses and the epithelial architecture is disrupted, so that adjacent eosinophils are not separated by intervening epithelial tissue (Figure 1b)	Grade score for EA was based on the density of eosinophils forming an abscess: 0 = groups or aggregates of eosinophils not present 1 = group of 4-9 eosinophils 2 = group of 10-20 eosinophils 3 = group of >20 eosinophils	Stage score for EA was based on the amount of the biopsy that exhibited EA: 0 = groups or aggregates of eosinophils not present 1 = EA (any grade >0) in <33% of epithelium 2 = EA (any grade >0) in 33%-66% of epithelium 3 = EA (any grade >0) in >66% of epithelium
Eosinophil surface layering (SL): linear alignment of at least 3 eosinophils in the upper third of the epithelium parallel to the lumen (Figure 1b)	Grade score for SL was based on the number of eosinophils forming the layer: 0 = absent SL (fewer than 3 aligned eosinophils) 1 = SL of 3-4 eosinophils 2 = SL of 5-10 eosinophils 3 = SL of >10 eosinophils	Stage score for eosinophil surface layering was based on the amount of the biopsy that exhibited any eosinophil surface layering: 0 = absent SL 1 = SL (any grade >0) in <33% of epithelium 2 = SL (any grade >0) in 33%-66% of epithelium 3 = SL (any grade >0) in >66% of epithelium
Dilated intercellular spaces (DIS): circumferential paracellular spaces in oesophageal squamous epithelium that exhibit intercellular bridges. (Figure 1b)	Grade score of DIS was based on the degree of magnification required to see intercellular bridges: 0 = DIS not seen at any magnification 1 = intercellular bridges in DIS visible at 400× magnification only 2 = intercellular bridges in DIS visible at 200× magnification 3 = intercellular bridges in DIS visible at 100× magnification or lower	Stage score for intercellular spaces was based on the amount of the biopsy that exhibited intercellular bridges: 0 = DIS not seen at any magnification 1 = DIS (any grade >0) in <33% of epithelium 2 = DIS (any grade >0) in 33%-66% of epithelium 3 = DIS (any grade >0) in >66% of epithelium

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Surface epithelial alteration (SEA): altered tinctorial properties of surface epithelium that manifest as increased (darker red) staining of surface epithelial cells, with or without associated eosinophil infiltrate	Grade score for SEA was based on the amount of eosinophil infiltration in altered surface epithelium: 0 = SEA not present 1 = SEA without eosinophils 2 = SEA with any eosinophils 3 = shed altered surface epithelium admixed with numerous eosinophils consistent with exudate	Stage score for SEA was based on the amount of the biopsy that exhibited any surface epithelial alteration: 0 = SEA not present 1 = SEA (any grade >0) in <33% of epithelium 2 = SEA (any grade >0) in 33%-66% of epithelium 3 = SEA (any grade >0) in >66% of epithelium
Dyskeratotic epithelial cells (DEC): individual cells (*potentially apoptotic*) with deeply eosinophilic cytoplasm and round small hyperchromatic nuclei (Figure S1b)	Grade score for DEC was based on the quantity of dyskeratotic cells: 0 = DEC not present 1 = 1 DEC/HPF 2 = 2-5 DEC/HPF 3 = >5 DEC/HPF	Stage score for DEC was based on the amount of the biopsy that exhibited any dyskeratotic epithelial cells: 0 = DEC not present 1 = DEC (any grade >0) in <33% of epithelium 2 = DEC (any grade >0) in 33%-66% of epithelium 3 = DEC (any grade >0) in >66% of epithelium
Lamina propria fibrosis (LPF): thickened connective tissue fibres in the lamina propria (Figure 1a). Lamina propria fibres that were arranged singly and had a diameter smaller than a basal layer nucleus were considered normal, fibres that were cohesive without increased diameter were considered abnormal, as were fibres with a diameter equal to or greater than a basal layer cell nucleus (Figure 1c)	Grade score for lamina propria fibrosis was based on the degree of fibre thickening: 0 = LPF not present 1 = fibres are cohesive and interfibre spaces cannot be demarcated 2 = fibre diameter equals the diameter of a basal cell nucleus 3 = fibre diameter exceeds the diameter of a basal cell nucleus	Stage score for LPF was based on the amount of lamina propria that showed any fibrosis: 0 = LPF not present 1 = LPF (any grade >0) in <33% of lamina propria 2 = LPF (any grade >0) in 33%-66% of lamina propria 3 = LPF (any grade >0) in >66% of lamina propria

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TABLE 3 Reliability of the EoEHSS and exploratory histologic items and correlation of the items with the VAS global rating of histopathologic disease severity

	Reliability ICC (95% CI)		Correlation with VAS r (95% CI)
	Intra-rater	Inter-rater	
EoE HSS—Grade	0.92 (0.87, 0.95)	0.84 (0.76, 0.89)	.24 (0.72, 0.86)
EoE HSS—Stage	0.92 (0.88, 0.95)	0.88 (0.82, 0.91)	.85 (0.78, 0.89)
Eosinophilic inflammation			
Grade	0.92 (0.86, 0.95)	0.87 (0.80, 0.90)	.84 (0.78, 0.87)
Stage	0.93 (0.87, 0.96)	0.87 (0.77, 0.93)	.82 (0.74, 0.88)
Epithelial basal zone			
Grade	0.83 (0.73, 0.90)	0.67 (0.52, 0.78)	.77 (0.66, 0.85)
Stage	0.91 (0.84, 0.95)	0.76 (0.58, 0.86)	.80 (0.70, 0.87)
Eosinophil abscess			
Grade	0.80 (0.64, 0.88)	0.66 (0.39, 0.80)	.62 (0.50, 0.71)
Stage	0.77 (0.60, 0.85)	0.56 (0.35, 0.69)	.63 (0.51, 0.72)
Eosinophil surface layering			
Grade	0.78 (0.65, 0.85)	0.66 (0.47, 0.78)	.56 (0.40, 0.67)
Stage	0.76 (0.63, 0.85)	0.63 (0.46, 0.73)	.57 (0.42, 0.68)
Dilated intercellular spaces			
Grade	0.80 (0.68, 0.88)	0.60 (0.40, 0.74)	.54 (0.40, 0.64)
Stage	0.80 (0.70, 0.87)	0.74 (0.63, 0.81)	.80 (0.59, 0.77)
Surface epithelial alteration			
Grade	0.74 (0.62 (0.84)	0.39 (0.24, 0.52)	.54 (0.33, 0.61)
Stage	0.68 (0.58, 0.76)	0.37 (0.21, 0.51)	.80 (0.24, 0.54)
Dyskeratotic epithelial cells			
Grade	0.28 (0.14, 0.49)	0.03 (0.00, 0.07)	.06 (−0.02, 0.14)
Stage	0.23 (0.12, 0.41)	0.02 (0.00, 0.06)	.08 (0.00, 0.17)
Lamina propria fibrosis			
Grade	0.82 (0.73, 0.89)	0.58 (0.44, 0.69)	.24 (0.02, 0.44)
Stage	0.78 (0.65, 0.88)	0.61 (0.46, 0.73)	.25 (0.03, 0.47)

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- Almost perfect **intra-rater reliability** was observed for the composite EoEHSS scores and the VAS.
- **Inter-rater reliability** was also almost perfect for the composite EoEHSS scores and substantial for the VAS.
- Of the **EoEHSS items**, eosinophilic inflammation was associated with the highest ICC estimates and consistent with almost perfect intra- and inter-rater reliability. With the exception of dyskeratotic epithelial cells and surface epithelial alteration, ICC estimates for the remaining EoEHSS items were above the benchmarks for substantial intra-rater, and moderate inter-rater reliability.

Warners et al. Aliment Pharmacol Ther 2018

Problems with the EoEHSS

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- The EoEHSS means a huge work load for the pathologist (eight parameters – **why so many?**): Will clinicians in the routine setting take notice of this effort and make therapy decisions on the scoring result or should the EoEHSS better be reserved for clinical trials?
- The eight parameters are not independent (**why these eight?**): For instance, there is a strong correlation between eosinophil density (EI), eosinophil abscesses (EA), and eosinophil surface layering (SL); likewise, basal zone hyperplasia (BZH) and dilated intercellular spaces (DIS) usually occur jointly.
- Lamina propria is often not sampled in “reasonable” amounts (approximately 50% of cases), moreover, lamina propria evaluation is significantly affected by technical issues, such as the thickness of the slide: Do we need a special stain for evaluation?

Development and Validation of Web-Based Tool to Predict Lamina Propria Fibrosis in Eosinophilic Esophagitis

Girish Hiremath, MD, MPH[1], Lili Sun, PhD[2], Hernan Correa, MD[3], Sari Acra, MD, MPH[1], Margaret H. Collins, MD[4], Peter Bonis, MD[5], Nicoleta C. Arva, MD, PhD[6], Kelley E. Capocelli, MD[7], Gary W. Falk, MD, MS[8], Eileen King, PhD[9], Nirmala Gonsalves, MD[10], Sandeep K. Gupta, MD[11], Ikuo Hirano, MD[10], Vincent A. Mukkada, MD[12], Lisa J. Martin, PhD[12], Philip E. Putnam, MD[12], Jonathan M. Spergel, MD, PhD[13], Joshua B. Wechsler, MD, MS[1], Guang-Yu Yang, MD, PhD[14], Seema S. Aceves, MD, PhD[15], Glenn T. Furuta, MD[1], Marc. E. Rothenberg, MD, PhD[16], Tatsuki Koyama, PhD[2] and Evan S. Dellon, MD, MPH[17]

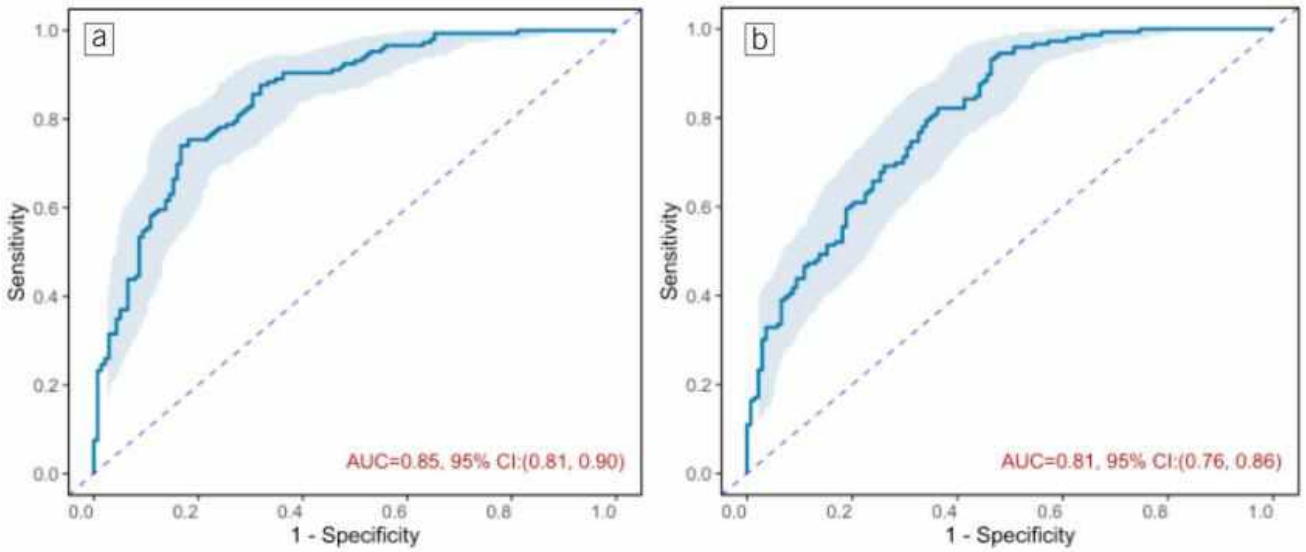

Figure 2. Area under the curve of prediction models: (**a**) grade and (**b**) stage of lamina propria fibrosis. AUC, area under the receiver operating characteristic curve; CI, confidence interval.

- This study aimed to develop and validate a web-based tool to predict LPF in oesophageal biopsies with inadequate lamina propria
- **Age of the patient, basal zone hyperplasia, dyskeratotic epithelial cells, and surface epithelial alteration were associated with presence of LPF**
- Our grade model had 82% accuracy in predicting the presence of LPF in an external validation data set

Study Highlights

WHAT IS KNOWN

- ✓ In eosinophilic esophagitis (EoE), lamina propria fibrosis (LPF) is central to esophageal remodeling and fibrostenotic complications.
- ✓ However, almost half of esophageal mucosal biopsies do not contain adequate lamina propria, thereby making it impossible to ascertain LPF.
- ✓ Developing an easy and widely applicable approach to predict LPF in esophageal biopsies with inadequate lamina propria sampling can contribute toward improving clinical outcomes in EoE.

WHAT IS NEW HERE

- ✓ Using patient characteristics and the peak grade and stage score for each of the features of the EoE histology scoring system, we developed parsimonious models to predict the presence of LPF (grade and stage) in esophageal biopsies with inadequate lamina propria.
- ✓ The area under the receiver operating characteristic curve of our model to predict of LPF (grade) was 0.84 (95% confidence interval [CI]: 0.80–0.89) and that for the LPF (stage) was 0.79 (95% CI: 0.74–0.84).
- ✓ Our grade model predicted presence of LPF with 82% accuracy in an independent data set (external validation).
- ✓ The prediction model is made available as a web-based tool: https://ls2021.shinyapps.io/pre_lpf/.

Hiremath et al. Am J Gastroenterol 2021

Development and Validation of Web-Based Tool to Predict Lamina Propria Fibrosis in Eosinophilic Esophagitis

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Medical University of Graz

Model to Predict Lamina Propria Fibrosis (LPF) in Eosinophilic Esophagitis

Please select if you would like to estimate the 'Grade' or 'Stage' of lamina propria fibrosis for your sample

(●) Grade ( ) Stage

Note:

1. Please select the highest score for each of the epithelial features.
2. If score for a particular feature is missing then you may assume it to be "0".

Age in years:

60

Basal zone hyperplasia (BZH)

( ) 0 ( ) 1 (●) 2 ( ) 3

Surface epithelial alteration (SEA)

( ) 0 ( ) 1 (●) 2 ( ) 3

Dyskeratotic epithelial cells (DEC)

( ) 0 ( ) 1 (●) 2 ( ) 3

Submit Reset

Status/Output

Predicted probability of LPF (Grade)	95% confidence interval
0.95	[0.83, 0.99]

Hiremath et al. Am J Gastroenterol 2021

Additional problems with the EoEHSS

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- **Can the same histological markers be used for grading and staging** (compare grading and staging in chronic gastritis and chronic hepatitis)?
- EoE is known as a patchy disease: Does the proposed “EoEHSS stage” (reflecting the **extent** of inflammatory features across the biopsy specimens) really indicate the stage of disease or is the proposed “EoEHSS stage” only a marker of increased inflammatory activity and **should better be used for grading?**
- Considering other systems (e.g. chronic gastritis and chronic hepatitis), shouldn't the result of chronic oesophageal injury, which is fibrosis (and its clinical consequences), be regarded as the only marker of disease stage (or perhaps even better clinical parameters such as narrowing/stenosis of the oesophageal lumen and/or reduced wall distensibility)?

Should we go for an alternative EoE score?

Medical University of Graz

- The EoEHSS is currently the only “validated” score and is thus pushed by some clinicians who are “searching for histological objectivity” (e.g. more informative diagnoses with reduced interobserver variation)

A Clinical Severity Index for Eosinophilic Esophagitis: Development, Consensus, and Future Directions

Table 1. Eosinophilic Esophagitis Severity Index

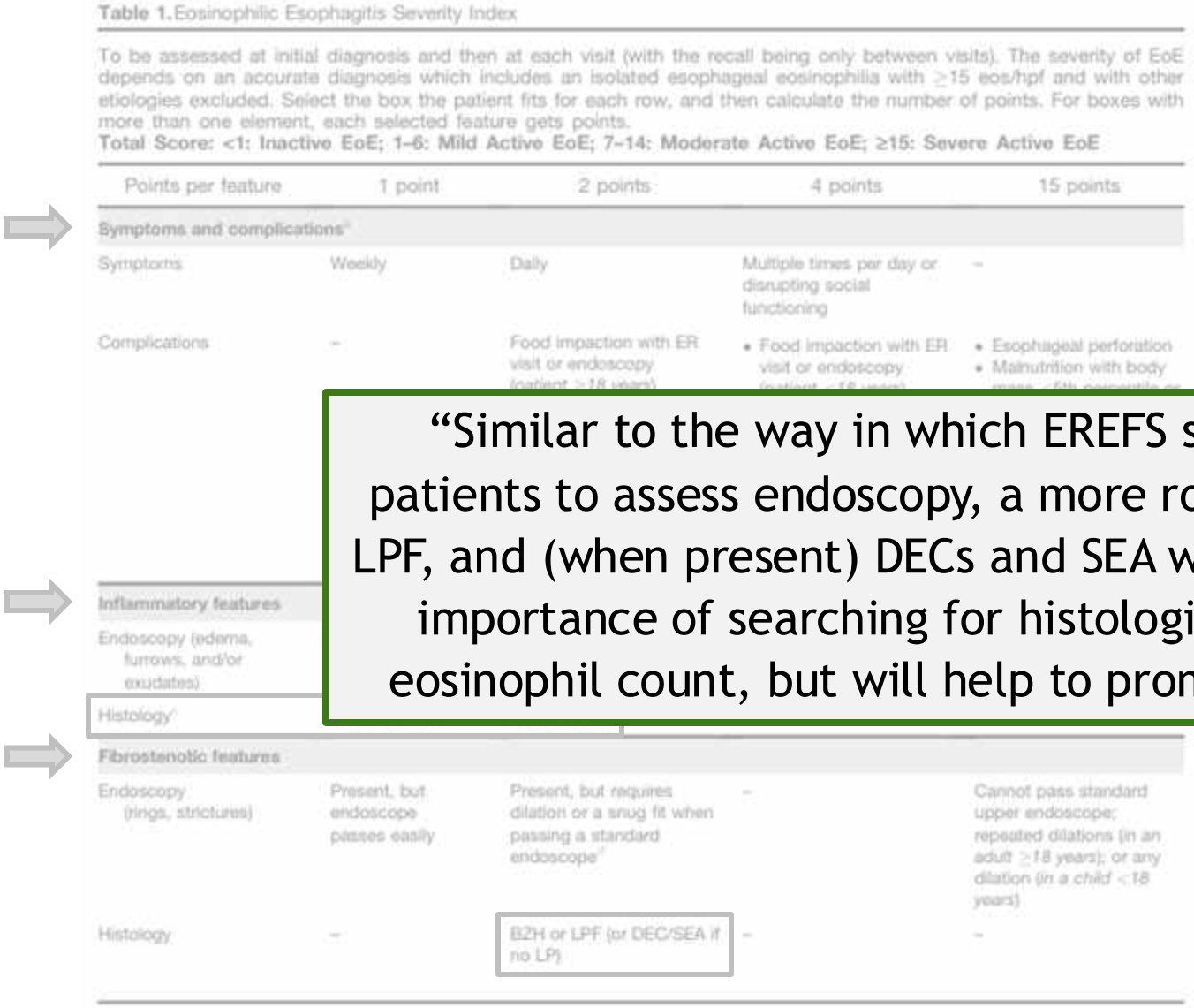
To be assessed at initial diagnosis and then at each visit (with the recall being only between visits). The severity of EoE depends on an accurate diagnosis which includes an isolated esophageal eosinophilia with ≥15 eos/hpf and with other etiologies excluded. Select the box the patient fits for each row, and then calculate the number of points. For boxes with more than one element, each selected feature gets points.
Total Score: <1: Inactive EoE; 1–6: Mild Active EoE; 7–14: Moderate Active EoE; ≥15: Severe Active EoE

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy (*patient ≥18 years*)	• Food impaction with ER visit or endoscopy (*patient <18 years*) • Hospitalization due to EoE	• Esophageal perforation • Malnutrition with body mass <5th percentile or decreased growth trajectory • Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15–60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations (*in an adult ≥18 years*); or any dilation (*in a child <18 years*)
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

- Symptom features and complications and inflammatory and fibrostenotic features on both endoscopic and histologic examination were collated into a simplified scoring system—the Index of Severity for Eosinophilic Esophagitis (I-SEE).
- Although many oesophageal biopsies do not contain evaluable lamina propria, the presence of surface epithelial alteration (SEA) and dyskeratotic epithelial cells (DECs) may predict the presence, but not severity, of fibrosis in these biopsies.
- The peak eosinophil count should be quantified in all cases for both diagnosis and to allow monitoring of eosinophil counts; additional histologic features should be assessed, particularly BZH, LPF, DEC, and SEA; if LP is not present, DEC/SEA can be used to predict LPF.

Dellon et al. Gastroenterology 2022

A Clinical Severity Index for Eosinophilic Esophagitis: Development, Consensus, and Future Directions



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Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
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Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)				
Histology				
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope	–	Cannot pass standard upper endoscope; repeated dilations (in an adult ≥18 years); or any dilation (in a child <18 years)
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

> "Similar to the way in which EREFS should be used for all patients to assess endoscopy, a more routine reporting of BZH, LPF, and (when present) DECs and SEA will not only highlight the importance of searching for histologic findings beyond the eosinophil count, but will help to prompt use of the EoEHSS"

- Symptom features and complications and inflammatory and fibrostenotic features on both endoscopic and histologic examination were collated into a simplified scoring system—the Index of Severity for Eosinophilic Esophagitis (I-SEE)
- Although many esophageal biopsies do not pria, the presence n (SEA) and DECs) may predict y, of fibrosis in
- ould be quantified in all cases for both diagnosis and to allow monitoring of eosinophil counts; additional histologic features should be assessed, particularly BZH, LPF, DEC, and SEA; if LP is not present, DEC/SEA can be used to predict LPF

Dellon et al. Gastroenterology 2022

Lessons that we may learn from IBD…

Medical University of Graz

Systematic review: Histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative

R.V. Bryant [a], S. Winer [b], SPLTravis [a], R.H. Riddell [b,*]

Medical University of Graz

Table 1 Histological Scoring Systems in Inflammatory Bowel Disease.

IBD	Author, year	Key features of score	Comments
Ulcerative colitis	Truelove & Richards, (1956)[39]	3 grade scale: 1) no inflammation 2) mild to moderate inflammation 3) severe inflammation	Partially validated. Extensive use in clinical trials and RCT's.
	Matts et al. (1961)[51]	5 grade scale: 1) normal to 5) ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all of its layers	No validated. Extensive use in clinical trials and RCT's.
	Watts et al. (1966)[40]	4 grade scale: 0) normal to 3) severe inflamematory change	Not validated
	Korelitz et al. (1976)[52]	Mucosal cell counting in addition to histologic features	Not validated Cell counting labor intensive
	Powell-Tuck et al. (1982)[53]	3 grade scale: 1) no inflammation 2) mild inflammation 3) moderate/severe inflammation	Not validated
	Keren et al. (1984)[42]	Dichotomized: active versus inactive inflammation	Not validated
	Friedman et al. (1986)[41]	4 grade scale: 0) normal 1) lamina propria inflammation 2) crypt injury 3) ulceration	Not validated. Subsequent use in clinical trials.
	Gomes et al. (1986)[31]	5 grade scale 0) normal, to 4) severe inflammation and active ulceration	Not validated Subsequent use in clinical trials
	Saverymuttu et al. (1986)[43]	4 histological features: 1) enterocyte damage 2) crypt abnormalities 3) lamina propria involvement 4) acute inflammatory infiltrate in the lamina propria. Each graded from 0) normal to 3) severe.	Not validated Extensive clinical trials and RCT's.
	Floren et al. (1987)[45]	5 grade scale: 0) normal, to 5) severe inflammation and ulceration	Not validated. Extensive clinical trials and RCT's.
	Riley et al. (1991)[38]	6 histological features assessed; each graded on a 4 point scale	Partially validated. Prognosticates time to relapse. Extensive clinical trials and RCT's.
	Hanauer et al. (1993)[32]	4 grade scale: 0) normal colonic mucosa to 3) high grade active inflammatory bowel disease (combines histologic and endoscopic appearances)	Not validated. Central reference pathologist
	Sandborn et al. (1992)[44]	4 grade scale: 0) inactive chronic colitis to 3) severely active chronic colitis	Not validated.
	Geboes et al. (2000)[30]	7 histological features graded Scoring from 0 to 5.4	Partially validated. Subsequent clinical studies.
	Harpaz Score	Harpaz Score: 4 grade scale: 0) no cryptitis,	Partially validated.
	Fiel et al. (2003)[47]	1) cryptitis < 50% crypts, 2) cryptitis >50% crypts 4) ulcerations or erosions.	Subsequent clinical studies.
	Rutter et al. (2004)[37]	5 grade scale: 0) normal to 4) severe active inflammation	Not validated.
	Rubin et al. (2007)[33]	6 grade scale: 0) normal to 5) crypt abscesses in >50% of crypts or erosion/ulceration	Not validated. Case control prospective grading by two pathologists to validate internally
	Baars et al. (2012)[34]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.
Crohn's Disease	D'Haens et al. (1998)[57]	16 point grading system 8 histological and distribution features	Subsequently called the CGHAS and IGHAS in clinical trials[4]
	Nichols et al. (1994)[60]	4 grades: 1) worse 2) no change, 3) improvement, 4) resolution of inflammation	Subjective. Not validated.
	Breese et al. (1995)[58]	5 histological features (ulceration, acute and chronic inflammation, crypt distortion, goblet cell depletion and villous atrophy), 4 grades: 0) normal to 3) severely inflamed.	Not validated.
	Baars et al. (2012)[34]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.

Key: RCT, randomized controlled trial; CGHAS, Colonic Global Histologic Disease Activity Score; IGHAS, Ileal Global Histologic Disease Activity Score.

Table 3 Prognostic value of histopathology in IBD.

IBD type	Author, date	Patient number/ follow up period	Scoring system	Disease-related outcome and histological predictor
Ulcerative colitis	Wright and Truelove (1966)[22]	n = 77 12 months	Truelove and Richards Score (see Table 1)	*Clinical relapse rate* Predicted by histological disease activity.
	Riley et al. (1991)[38]	n = 82 12 months	Riley Score (see Table 1)	*Clinical relapse rate* 33% clinical relapse. Predicted by acute inflammation 52 vs. 25% (p 0.02); Crypt abscesses: 78 vs. 27% (p < 0.005); Mucin depletion: 56 vs. 26% (p < 0.02); Surface epithelium breach: 75 vs. 31% (p = 0.1).
	Bitton et al. (2001)[24]	n = 74 12 months	Normal or abnormal. If abnormal: active colitis, chronic colitis, Paneth cell metaplasia, basal lymphoid aggregates and plasmacytosis.	*Clinical and endoscopic relapse rate* 36.5% relapse rate. Predicted by basal plasmacytosis (HR 4.3 1.7–11.0, p = 0.003).
	Azad et al. (2011)[35]	n = 26 12 months	Geboes Score (see Table 1)	*Clinical relapse rate* 57.7% clinical relapse. Predicted by eosinophils & neutrophils in lamina propria (p = 0.01).
	Helfi et al. (2009)[25]	n = 561 21.4 years	Harpaz Index (see Table 1)	*Colectomy rate* 17.3% colectomy rate; 26% of these for dysplasia. Mean mucosal inflammation predictive of colectomy overall. (p < 0.001).
	Rubin et al. (2007)[33]	n = 106	Rubin et al. Score (see Table 1)	*Colectomy and hospitalisation rates* Correlated with increased histological inflammation (HR 1.9, 95% CI 1.02–3.51, p 0.042; HR 1.52 95% CI 0.9–2.61, p 0.121 respectively; relative to a 1 point increase in inflammation).
	Burger et al. (2011)[60]	n = 91 29 months	Truelove and Richards Score (see Table 1)	*Colectomy and hospitalisation rates* Predicted by histologic activity.
	Ikeissow et al. (2012)[54]	n = 75 12 months	Geboes Score (see Table 1) Basal plasmacytosis	*Clinical relapse rate* 20% relapse rate. Predicted by basal plasmacytosis (p = 0.007), and Geboes Score ≥ 3.1 (p = 0.007)
	Gupta et al. (2007)[12]	n = 418 2168 patients years	Harpaz Score (see Table 1)	*Colorectal dysplasia and neoplasia* 1.6% advanced neoplasia. Inflammation over follow-up period (IS-mean) correlated with risk of neoplasia (HR 3.0, 95% CI 1.4–6.3)
	Rutter et al. (2004)[37]	n = 68 (136 controls with colorectal neoplasia)	Rutter et al. score (see Table 1)	*Colorectal neoplasia* 68 UC patients with colorectal neoplasia matched to controls. Histologic inflammation correlates with risk of colorectal neoplasia (OR 5.1 p < 0.001)
	Baars et al. (2012)[34]	n = 98 6.8 years	Baars Score (See Table 1)	*Relapse, surgery, mortality* No evidence of increased relapse rates, surgery, or mortality in patients with histological inflammation and normal endoscopic appearances (p > 0.05)
Crohn's disease	Baars et al. (2012)[60]	n = 46 6.8 years	Baars Score (see Table 1)	*Relapse, surgery, mortality* No evidence of increased relapse rates, surgery, or mortality in patients with histological inflammation and normal endoscopic appearances (p > 0.05)

Table 4 Histologic remission and therapy in IBD.

IBD type	Therapy	Author, date	Patient number	Key features	Outcomes
Ulcerative colitis	Corticosteroids	Truelove et al. (1958)[39]	n = 40 Distal UC	Rectal hydrocortisone 1 week therapy Truelove and Richards score	55% shift to a mild grading. No histological 'normalization'.
		Sommers et al. (1975)	n = 215	Prednisolone (+/- mercaptopourine) for 2 weeks	Mucosal cell counts: decreased neutrophils and plasma cells.
		Ruddell et al. (1980)[40]	n = 30 Distal UC	Hydrocortisone enema vs. foam 2 weeks therapy	Significant improvement in active inflammation in enema group.
		Lee et al. (1996)[59]	n = 295 Distal UC	Randomized trial Prednisolone foam enema vs. mesalazine foam enema assessed at 4 weeks	Histologic remission in 27% mesalazine vs 21% steroid group.
		Hanauer et al. (1998)[32]	n = 233 Distal UC	Budesonide enema (dose finding) vs. placebo Modified Truelove and Richards score	Overall histologic improvement in budesonide groups (2 mg/ 100 ml, and 8 mg/100 mL).
		Gross et al. (2006)[62]	n = 449 Distal UC	Budesonide foam vs. enema Riley scoring[38]	Histological improvement in 51% foam enema and 57% liquid enema.
		Sherlock et al. (2010)[63]	3 studies	Cochrane review: oral budesonide therapy	46.9% histological remission
		Hartmann et al. (2010)[64]	n = 237 Left-sided UC	Mesalazine enema vs. budesonide enema assessed at 4 weeks	Non-significantly higher histologic remission with mesalazine (48.6%) vs budesonide (43%) (p < 0.145)
	Salicylates	Rao et al. (1989)[65]	n = 37 Distal UC	Olsalazine (2 g/day) vs. sulfasalazine (3 g/day) assessed at 4 weeks	Histologic improvement in both groups similar (44% and 46% respectively, p = NS)
		Green et al. (2002)[67]	n = 57 Active UC, variable distribution	Balsalazide (6.75 g/day) vs. sulfasalazine (3 g/day) (+steroids if needed) assessed at 12 weeks	Similar histological improvement in both groups
		Marshfield et al. (2002)[66]	n = 50 Active UC variable distribution	Balsalazide (6.75 g/day) vs. sulfasalazine (3 g/day) assessed at 12 weeks	Histological improvement overall. 34% no histological inflammation overall.
		Prantera et al. (2005)[68]	n = 79 Active Left-sided UC	Slow release mesalazine vs. topical 5ASA Florin score[49]	Histological remission in 15% of oral and 8% of enema treated groups.
		Kruis et al. (2009)[69]	n = 380 Active UC Variable distribution	Mesalazine granules 3 g/day in single or thrice daily dosing	Histological remission in 35% of single dosing and 41% of thrice daily dosing groups.
		Marshall et al. (2010)[46] (of 38 included)	Cochrane Review 6 trials	Rectal 5ASA for induction of remission in UC	Superior to placebo in inducing histologic remission (OR 6.28, p < 0.0001)
	Immunomodulator	Pardoll et al. (2002)[57]	n = 32 Active refractory UC	Azathioprine or methotrexate for 6 months Truelove and Richards score[56]	78% histological remission at 6 months
	Biological agents	Choy et al. (2007)[61]	n = 16 Active refractory UC	Infliximab Single infusion (5 mg/kg), 6/16 patients had a 2nd infusion at 5 months	Significant improvement from baseline in histologic score (p < 0.001)

Bryant et al. J Crohns Colitis 2014

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable—local excess of neutrophils in part of crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

- More than 30 scores have been developed and applied (sometimes in different ways) in inflammatory bowel disease
- The most widely applied (in clinical trials, not in the routine setting) is the **Geboes Score**
- Possible shortcomings of the Geboes Score include the following
  - The chronic inflammatory infiltrate does not specifically address “basal plasmacytosis”
  - Eosinophils are included (together with neutrophils in Grade 2), which are nowadays not regarded as indicators of active disease

Geboes et al. Gut 2000

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
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5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

A Simplified Geboes Score for Ulcerative Colitis

Aranzazu Jauregui-Amezaga,[a,b] Auke Geerits,[c] Yannick Das,[c] Bart Lemmens,[c] Xavier Sagaert,[c] Talat Bessissow,[d] Triana Lobatón,[e] Marc Ferrante,[a,b] Gert Van Assche,[a,b] Raf Bisschops,[a] Karel Geboes,[c] Gert De Hertogh,[c] Séverine Vermeire[a,b]

Table 2. The proposed Simplified Geboes Score.

Grade 0: No inflammatory activity	0.0 No abnormalities 0.1 Presence of architectural changes 0.2 Presence of architectural changes and chronic mononuclear cell infiltrate
Grade 1: Basal plasma cells	1.0 No increase 1.1 Mild increase 1.2 Marked increase
Grade 2A: Eosinophils in lamina propria	2A.0 No increase 2A.1 Mild increase 2A.2 Marked increase
Grade 2B: Neutrophils in lamina propria	2B.0 No increase 2B.1 Mild increase 2B.2 Marked increase
Grade 3: Neutrophils in epithelium	3.0 None 3.1 < 50% crypts involved 3.2 > 50% crypts involved
Grade 4: Epithelial injury [in crypt and surface epithelium]	4.0 None 4.1 Marked attenuation 4.2 Probable crypt destruction: probable erosions 4.3 Unequivocal crypt destruction: unequivocal erosion 4.4 Ulcer or granulation tissue

Jauregui-Amezaga et al. J Crohns Colitis 2017; Geboes et al. Gut 2000

Development and validation of a histological index for UC

Mahmoud H Mosli,[1,2,3] Brian G Feagan,[1,2,4] Guangyong Zou,[1,4] William J Sandborn,[1,5] Geert D'Haens,[1,6] Reena Khanna,[1,2] Lisa M Shackelton,[1] Christopher W Walker,[1] Sigrid Nelson,[1] Margaret K Vandervoort,[1] Valerie Frisbie,[1] Mark A Samaan,[1] Vipul Jairath,[1,7,8] David K Driman,[9] Karel Geboes,[10] Mark A Valasek,[11] Rish K Pai,[12] Gregory Y Lauwers,[13,14] Robert Riddell,[15] Larry W Stitt,[1,4] Barrett G Levesque[1,5]

$$\begin{aligned}\text{RHI} = {} & 1 \times \text{chronic inflammatory infiltrate level (4 levels)} \\ & + 2 \times \text{lamina propria neutrophils (4 levels)} \\ & + 3 \times \text{neutrophils in epithelium (4 levels)} \\ & + 5 \times \text{erosion or ulceration (4 levels after combining} \\ & \quad \text{Geboes 5.1 and 5.2).}\end{aligned}$$

- The total score ranges from 0 (no disease activity) to 33 (severe disease activity)
- The intra-rater and inter-rater ICCs (95% CIs) for RHI were 0.92 (0.88 to 0.94) and 0.82 (0.74 to 0.86), indicating 'almost perfect' intra-rater and inter-rater reliability

Table 3 Final regression model for Robarts Histopathology Index

Component	Coefficient (SE)	p Value
Intercept	−9.62 (2.41)	<0.001
Chronic inflammatory infiltrate		
0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	3.34 (1.27)	0.008
Lamina propria neutrophils		
0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	5.60 (1.82)	0.002
Neutrophils in epithelium		
0=None 1=<5% crypts involved 2=<50% crypts involved 3=>50% crypts involved	8.90 (1.21)	<0.001
Erosion or ulceration		
0=No erosion, ulceration or granulation tissue 1=Recovering epithelium+adjacent inflammation 1=Probable erosion—focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	14.92 (1.40)	<0.001

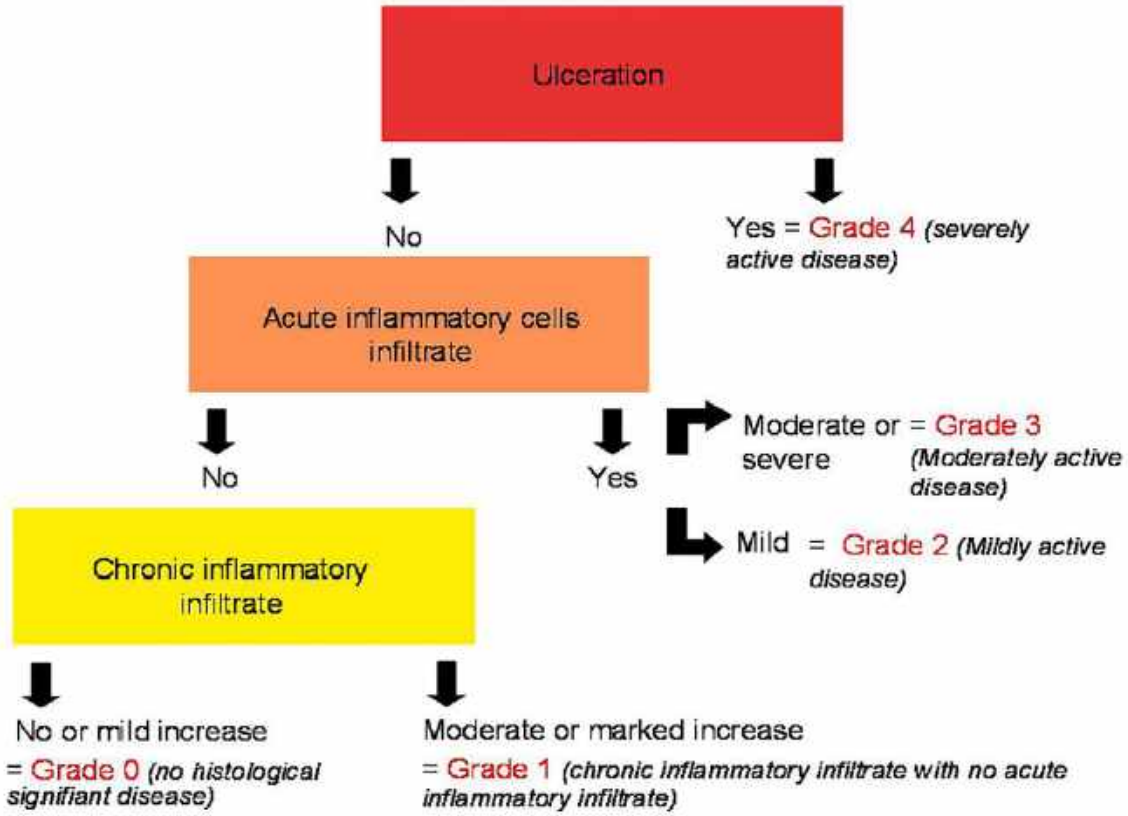
SE, standard error.

Mosli et al. Gut 2017

ORIGINAL ARTICLE

Development and validation of the Nancy histological index for UC

Aude Marchal-Bressenot,[1,2] Julia Salleron,[3] Camille Boulagnon-Rombi,[1] Claire Bastien,[4] Virginie Cahn,[5] Guillaume Cadiot,[6] Marie-Danièle Diebold,[1] Silvio Danese,[7] Walter Reinisch,[8] Stefan Schreiber,[9] Simon Travis,[10] Laurent Peyrin-Biroulet[2,11]



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- Grade 0: no histological significant disease
- Grade 1: chronic inflammatory infiltrate, no acute inflammatory infiltrate
- Grade 2: **Mildly active** disease
- Grade 3: **Moderately active** disease
- Grade 4: **Severely active** disease

Marchal-Bressenot et al. Gut 2016

Should we go for an alternative EoE score?

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- The EoEHSS is currently the only “validated” score and is thus pushed by some clinicians who are “searching for histological objectivity” (e.g. more informative diagnoses with reduced interobserver variation)
- Thus, we probably need a more simple and robust score indicating injury and consequences – perhaps a combined clinicopathological score?!
- The grade of activity should reflect eosinophilic infiltration **and** injury of the squamous epithelium (BZH and DIS are not specific for EoE, they are well established histological markers in gastro-oesophageal reflux disease)

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Table 1. Histopathology Scoring Tool

Feature	Scoring key
Epithelium: No. of eosinophils	0: 0 per hpf; 1: 1–10 per hpf; 2: 11–20 per hpf; 3: 21–40 per hpf; 4: 41–60 per hpf; and 5: ≥61 per hpf
Basal zone hyperplasia	0: <20%; 1: 21%–50%; 2: 51%–75%; and 3: >75%
Dilated intercellular spaces	0: absent; and 1: present
Epithelial desquamation	0: absent; and 1: present
Eosinophil clusters	0: absent; and 1: present
Degranulated eosinophils	0: absent; and 1: present
Lamina propria: No. of eosinophils	0: 0 per hpf; 1: 1–5 per hpf; 2: 6–20 per hpf; 3: >20 per hpf
Lamina propria fibrosis	0: absent; 1: mild; 2: moderate; and 3: severe
Total score	18 possible

Abbreviation: hpf, high-power field.

Aceves et al. Ann Allergy Asthma Immunol 2009

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- The grade o… **and** injury of the squamous ep… they are well established … disease)

Table 2. Histologic Evaluation of Esophageal Biopsy Specimens

Points assigned	Basal cell zone %	Eosinophils (#/hpf)
0	<20%	0
1	21%–35%	1–5
2	36%–75%	6–15
3	>75%	>15

NOTE. Composite biopsy score = points for basal cell zone + points for number of eos/hpf. Histologic grade was based on composite biopsy scores: 0, normal; 1–2, mild; 3–4, moderate; 5–6, severe.

Schaefer et al. Clin Gastronterol Hepatol 2008

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Table 2. Histologic Evaluation of Esophageal Biopsy Specimens

Points assigned	Basal cell zone %	Eosinophils (#/hpf)
0	<15%	0
1	15-33%	<15 per HPF
2	33-66%	15-60 per HPF
3	>66%	>60 per HPF

NOTE. Composite biopsy score = points for basal cell zone + points for number of eos/hpf. Histologic grade was based on composite biopsy scores: 0, normal; 1–2, mild; 3–4, moderate; 5–6, severe.

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- Thus, we probably need a more simple and robust score indicating injury and consequences – perhaps a combined clinicopathological score?!
- The grade of activity should reflect eosinophilic infiltration **and** acute injury of the squamous epithelium (BZH and DIS are not specific for EoE, they are well known histological markers of gastro-oesophageal reflux disease)
- The stage of disease should reflect the consequences of the inflammatory injury, which is stromal fibrosis (potentially fibrosis in deeper levels of the oesophageal wall) leading to oesophageal dysfunction

Concluding remarks

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- EGIDs are characterized by chronic GI symptoms and increased numbers and/or activation of eosinophils in the GI tract in the absence of another identifiable cause
- Diagnosis of EoE is complex and needs to consider clinical and histological findings in conjunction
- In addition to peak eosinophil count (cut-off value >15 eosinophils per HPF) several other histological findings should be taken into account, such as injury & reactive changes of the squamous epithelium
- Two questions need to be solved:
  - Do we need a score in the routine setting (or only in clinical trials)?
  - Is the EOE-HSS the score that makes us all happy – or should we go for a score that is easier to use and therefore more likely to be accepted in the routine setting?

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Thank you very much for your kind attention!

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