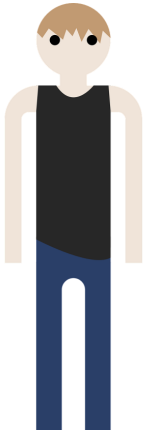
INSELGRUPPE

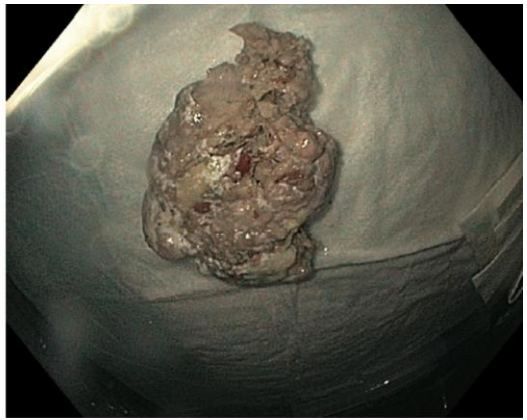
Eosinophilic Esophagitis (EoE)

Bible Class 21.05.2025 – Jonas Brunner & Roy Frei

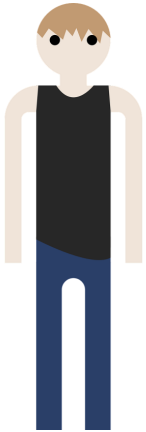
Clinical Case



- 20yo patient
- Food impactation, complete aphagia
- Recurrent chest pain while eating, always been a «slow eater»
- PA: Asthma bronchiale



Clinical Case



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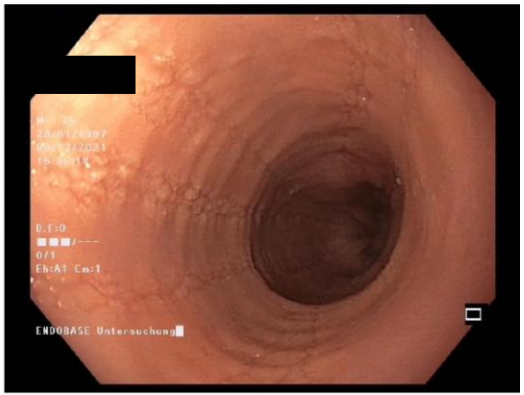
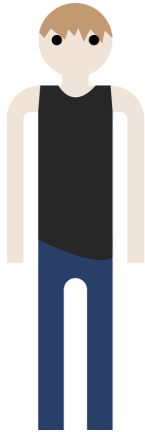
Proximaler Ösophagus



Distaler Ösophagus


PLEASE DONT FORGET

Clinical Case



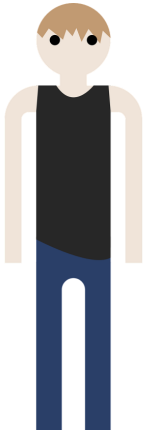
- 20yo patient
- Food impactation, complete aphagia
- Recurrent chest pain while eating, always been a «slow eater»
- PA: Asthma bronchiale

Diagnose:
B2021.45551
1: Biopsien, Ösophagus distal:
Plattenepitheliale Schleimhaut mit signifikanter Vermehrung intraepithelialer eosinophiler Granulozyten (>100 eosinophiler Granulozyten/HPF), im Sinne einer eosinophilen Esophagitis.
Kein Nachweis von Pilzelementen in der PAS Färbung. Angrenzend gastrisch glanduläre Schleimhaut, keine intestinale Metaplasie, kein Nachweis von Helicobacter pylori.
Keine Dysplasie. Keine Malignität.

2: Biopsien, Ösophagus proximal:
Plattenepitheliale Schleimhaut mit signifikanter Vermehrung intraepithelialer eosinophiler Granulozyten (87 eosinophiler Granulozyten/HPF), im Sinne einer eosinophilen Esophagitis.
Kein Nachweis von Pilzelementen in der PAS Färbung.
Keine Dysplasie. Keine Malignität.

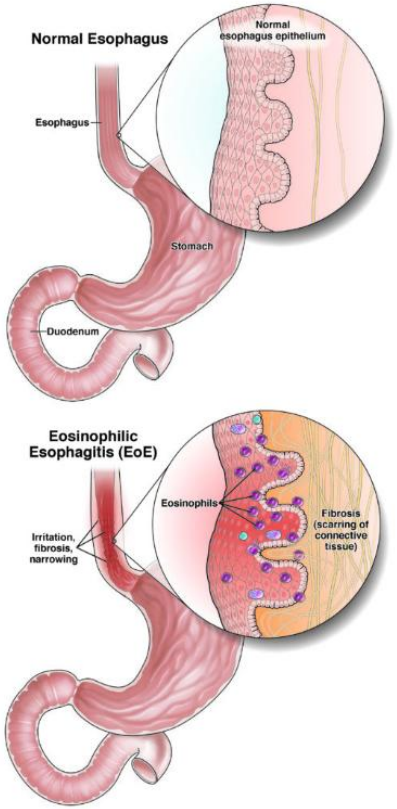
Clinical Case

- Further workup – apart from ineffective motility - negative (pH-metry, manometry)
- Diagnosis of eosinophilic esophagitis
- Treatment with high dose PPI



Definition of EoE

EoE is a chronic, **Th2-mediated** allergic disease with pathological **eosinophilic infiltration** of the oesophagus and symptoms of **oesophageal dysfunction**



AgA GI patient center

History of EoE

- First description of a case in 1970, misinterpreted as motility disorder
- Recognition as a disease in the early 90ies
- Alex Straumann et al, Switzerland (Spital Olten). Published 1994 in SMW

- Stephen Attwood et al, USA. Published 1993 in Digestive Disease Science
- First guidelines in 2007

Epidemiology

Prevalence

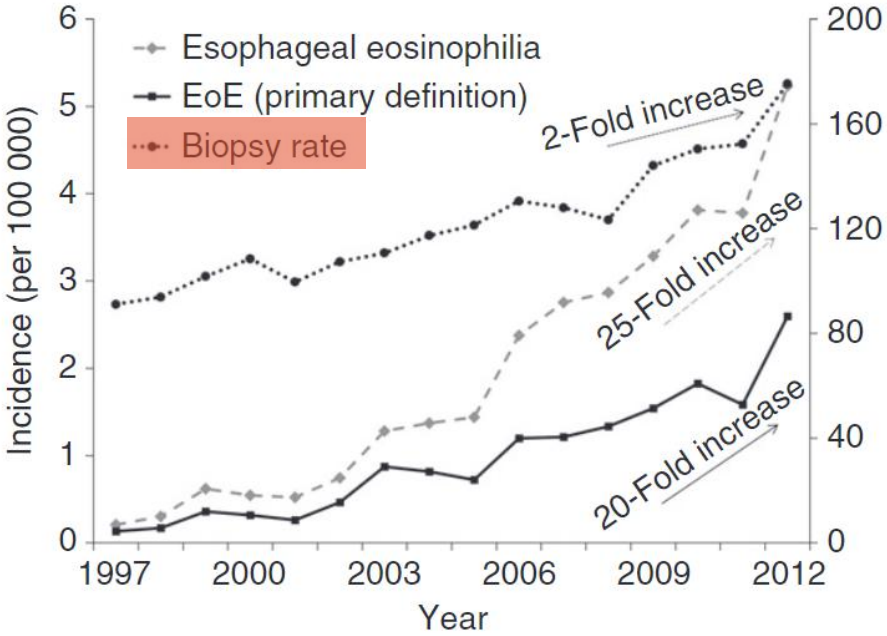
- 32.5 adult, resp. 3

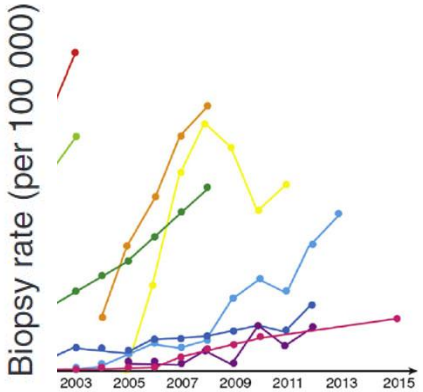
Increasing incidence

- 2007 3 cases per
- 2016 13.7 cases pe

Switzerland?

- Prevalence 24.1-4
- Incidence increas





to 2013)

Aliment Pharmacol Ther 2015; 41: 662–670
Giriens B et al. J Allergy Clin Immunol 2011
Arias A et al. APT 2016
Molina-Infante J et al. United European Gastroenterol J. 2018
Dellon E, Hirano I et al. Gastroenterology 2018

«Typical EoE Patient»

- Predominantely men (ratio 3:1)
- Median age around 30y, rarely old age
- Caucasian
- Urban-rural, north-south/west-east gradient
- History of atopy

Risk Factors

- **Atopy!** → 50-60% EoE patients are atopic and sensitized to food and aeroallergens

OR 5.09

OR 3.01

OR 2.85

González-Cervera J et al. Ann Allergy Asthma Immunol, 2017

Risk Factors

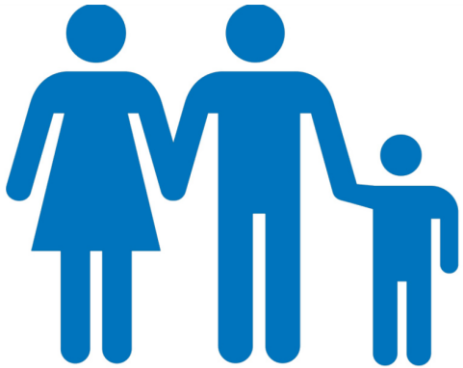
<u>Genetic risk variants</u>

- Overexpression of Thymic stromal lymphopoetin (TSLP) -> Th2 differentiation
- CCL26 -> Production of eotaxin-3 (chemoattractant for eosinophils)
- CAPN14 -> IL-13 induced cystein proteinase, esophagus specific
- Shared genetics with IBD and MS

<u>Familial clustering/Genetic inheritance</u>

- Relative risk 10 to 64x increased

(higher in male relatives, esp. brothers)

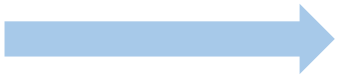


Collins MH. Gastroenterol Clin North Am. 2014
Alexander ES et al. J Allergy Clin Immunol 2014
Peterson K et al. Am J Gastroenterol. 2016

Risk Factors

Developmental/environmental

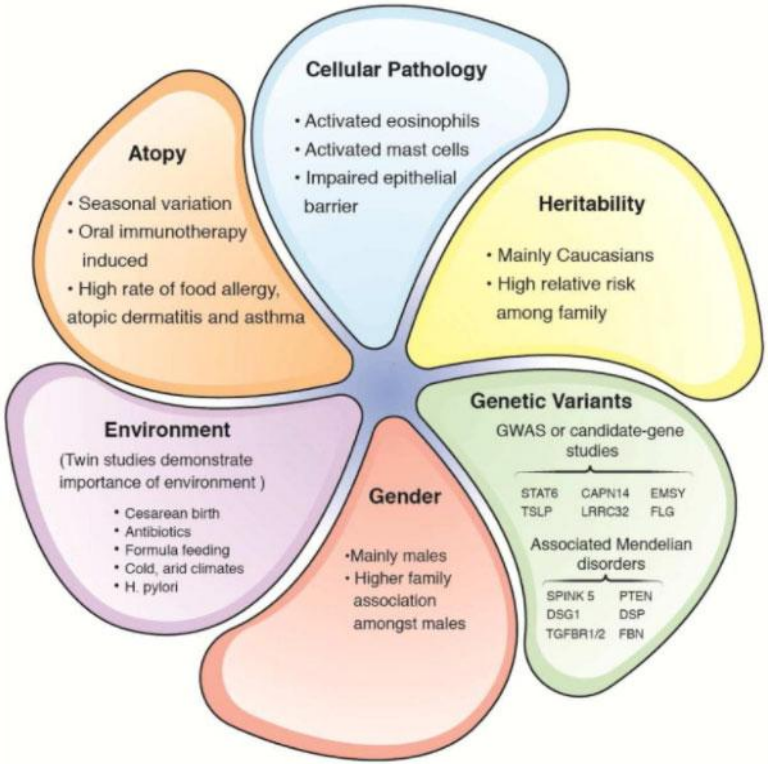
- C-section
- Premature birth
- Antibiotics and PPI in childhood
- No breastfeeding/formula
- Cold and dry climate
- H.pylori (Inversely proportional!)



Modulation of microbiota

- Firmicutes ↑
- Proteobacteriae ↑
- Streptococci ↓

Benitez AJ et al. Microbiome 2015



O'Shea KM. Gastroenterology. 2018 Jan

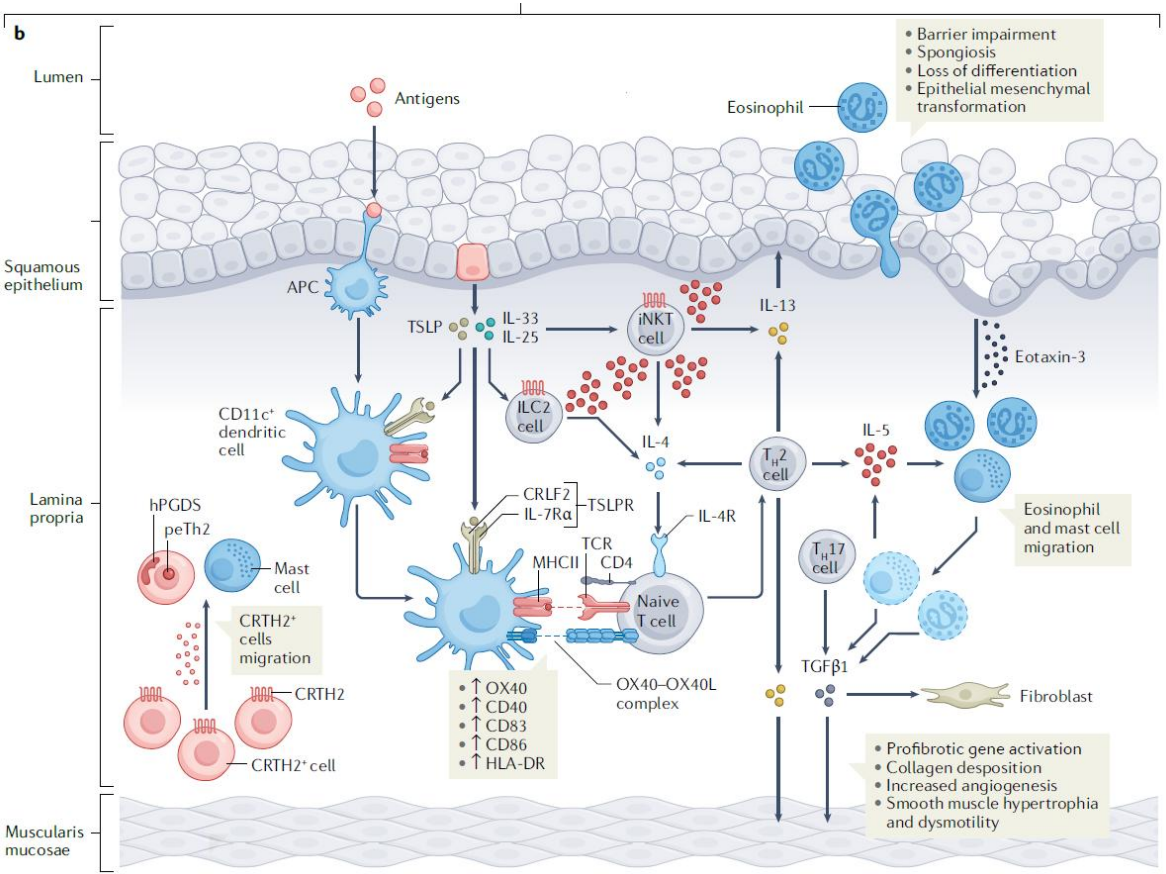
Pathophysiology

Penetration of antigens as primary driving factor

Impaired expression of barrier proteins is crucial factor

Polarization of T-cells to a T helper 2 cell pattern

Activated immune response promotes fibrosis and stricture formation in the long term



Symptoms in children

- Reflux/regurgitation
- Refusal or avoidance of food
- Reduced growth
- Nausea and vomiting
- Abdominal pain
- Diarrhea

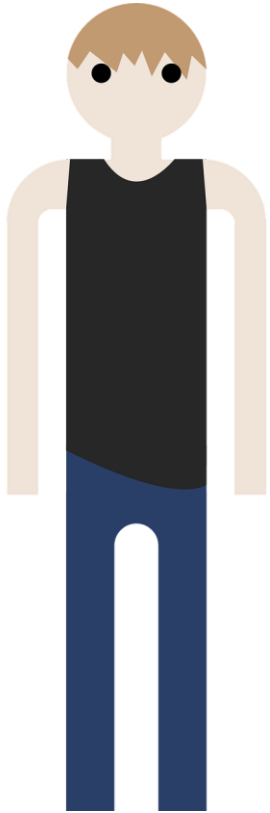
Symptoms in adults

- Dysphagia (75%)
- Impactions (33-54%)
- Retrosternal pain or burning (>50%)
- Regurgitations

- **Often underestimated due to compensation mechanisms (slow eating/chewing, fluid intake, avoidance of eliciting food)**

- **Symptom burden does not correlate to histological extent of inflammation**

- **Median Diagnostic delay 5 years!**



Diagnostic approach

→ **Symptoms**

→ **Endoscopy**

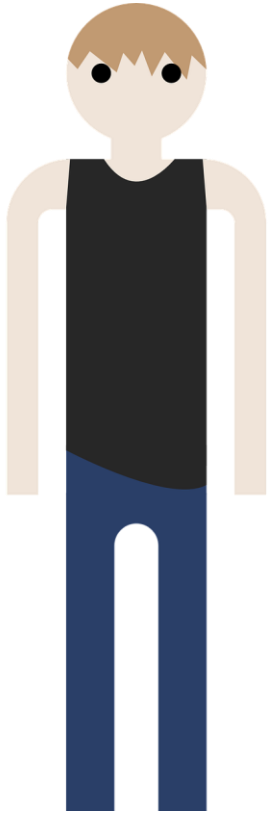
→ **Histology**

Taking a medical history in an EoE patient

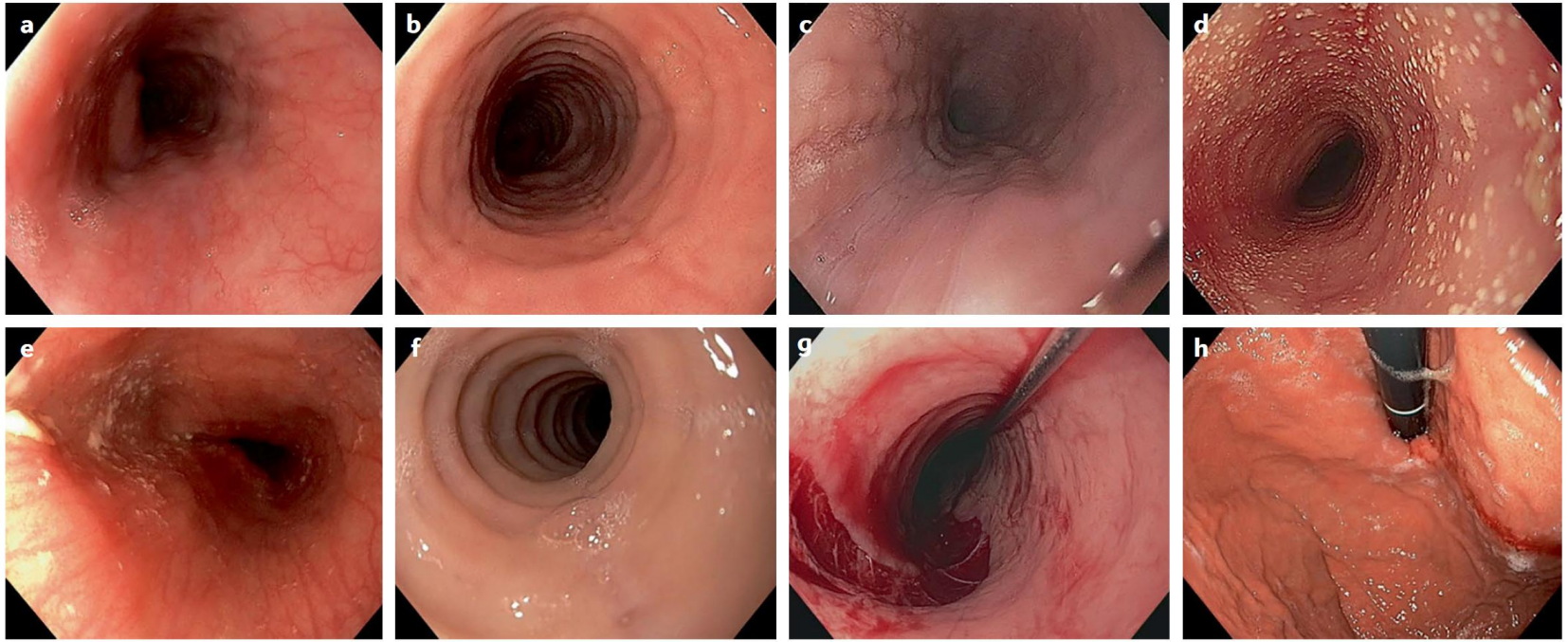
Table 4. "IMPACT" behaviors to assess while taking a dysphagia history

Behavior	Description
Imbibe fluids	Drinking a lot of liquids to help get each bite down smoothly
Modify foods	Cutting foods into small pieces or pureeing foods
Prolong meal times	Eating slowly and being the "last one at the table"
Avoid hard texture foods	Meats, crusty breads, and foods with sticky consistencies are often removed from the diet to minimize symptoms
Chew excessively	Thorough chewing to achieve a mush-like consistency to allow easier swallowing
Turn away tablets/pills	Pill dysphagia is a subtle symptom of EoE and may be the only indication of swallowing dysfunction

EoE, eosinophilic esophagitis.
Adapted from Hirano and Furuta. Gastroenterology. 2020;158(4):840–51 (81).



Endoscopy



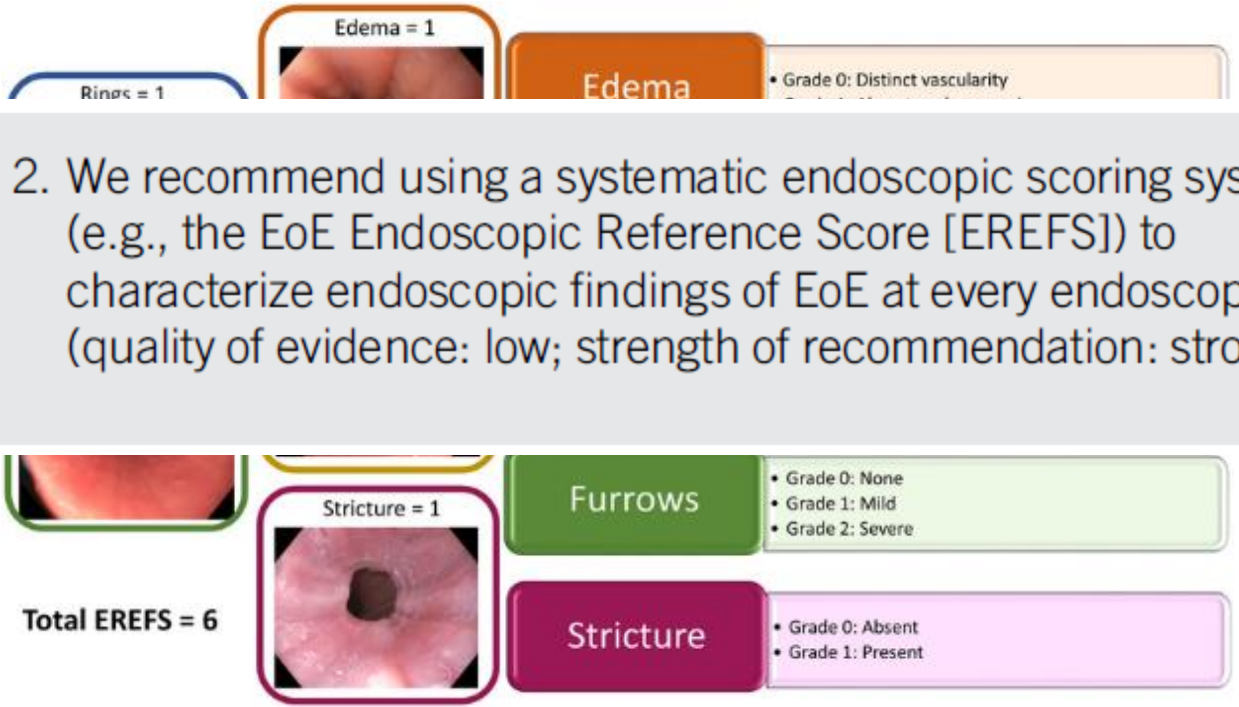
Endoscopy: EREFS-Classification

- In 2013 **Hirano** et al proposed the endoscopic reference score (EREFS) classification system as a way for **standardization** and reporting the endoscopic signs of EoE in adults

- This classification has demonstrated good interobserver and intraobserver concurrence

- Since then several studies in adults have demonstrated that this metric is highly predictive of EoE diagnosis and responsive to treatment

Endoscopy: EREFS-Classification



2. We recommend using a systematic endoscopic scoring system (e.g., the EoE Endoscopic Reference Score [EREFS]) to characterize endoscopic findings of EoE at every endoscopy (quality of evidence: low; strength of recommendation: strong).

Low, Eric & Dellon et al., Alimentary Pharmacology & Therapeutics 2013

Histology – Biopsy protocol

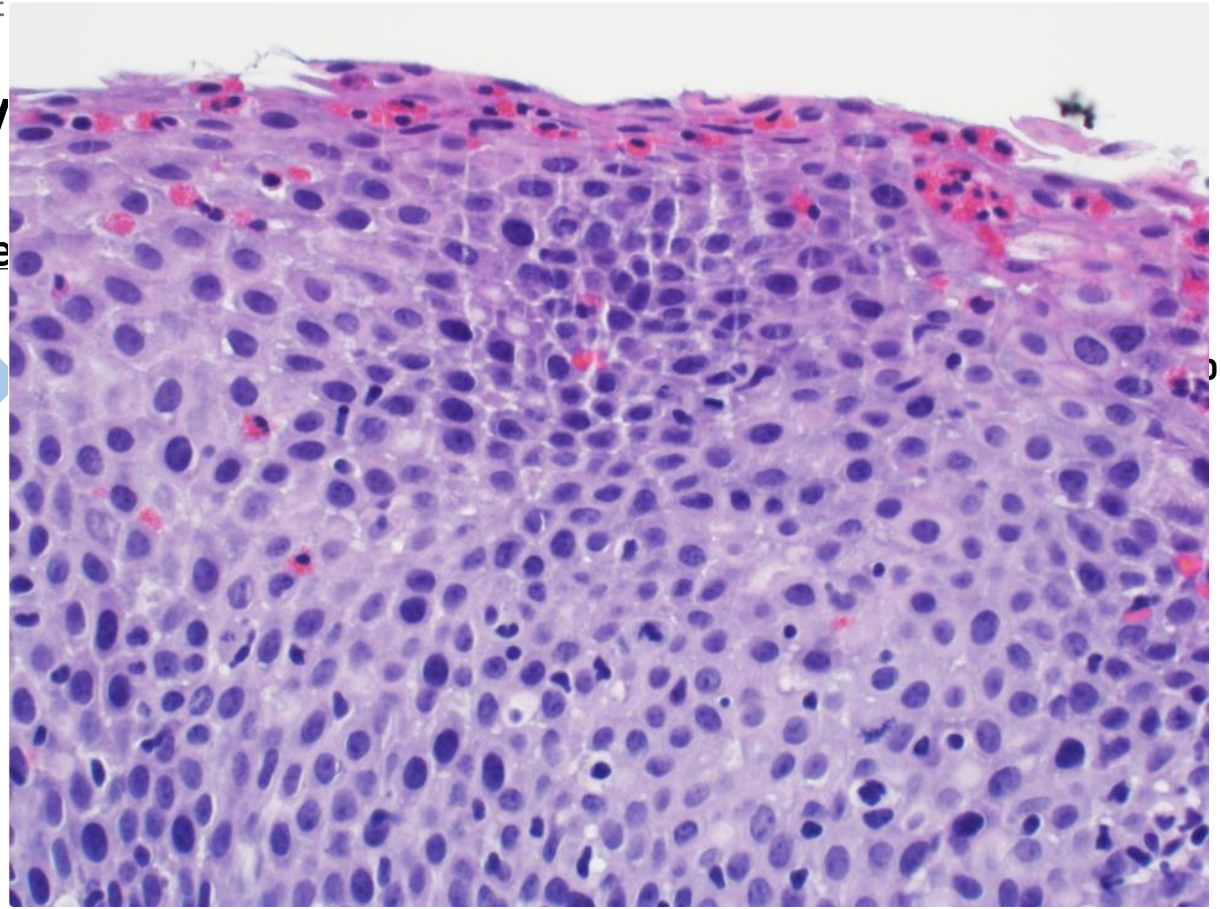
- 6-8 biopsies from different locations (proximal & distal esophagus)

→ Patchy disease histologically

→ Only elevated eosinophils in distal esophagus?

Histology

Major crite

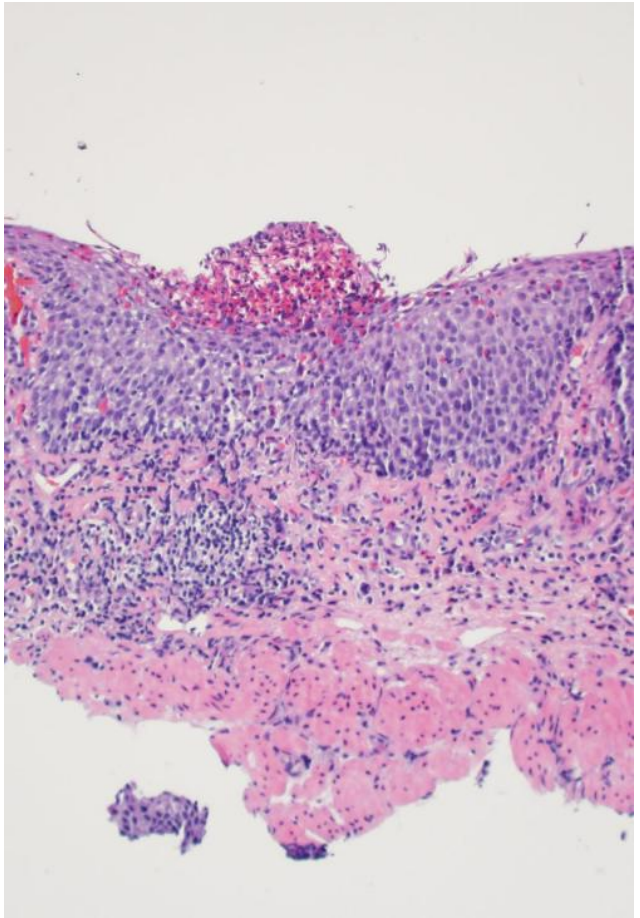


resent in the

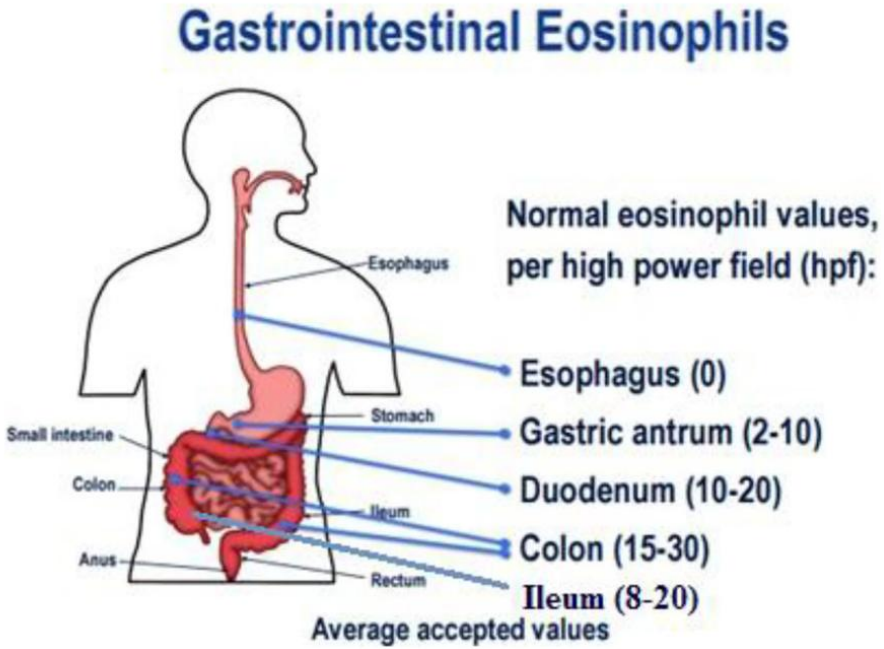
Histology

Minor criteria

- Extreme basal zone hyperplasia
- Eosinophilic microabscesses
- Eosinophil degranulation
- Lamina propria fibrosis

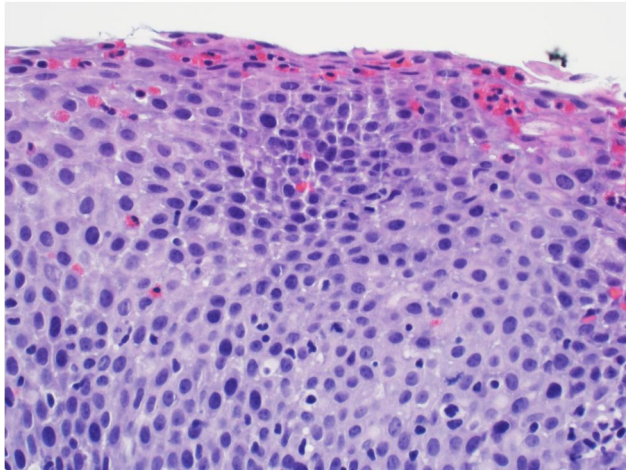


Eosinophils in the GI-Tract



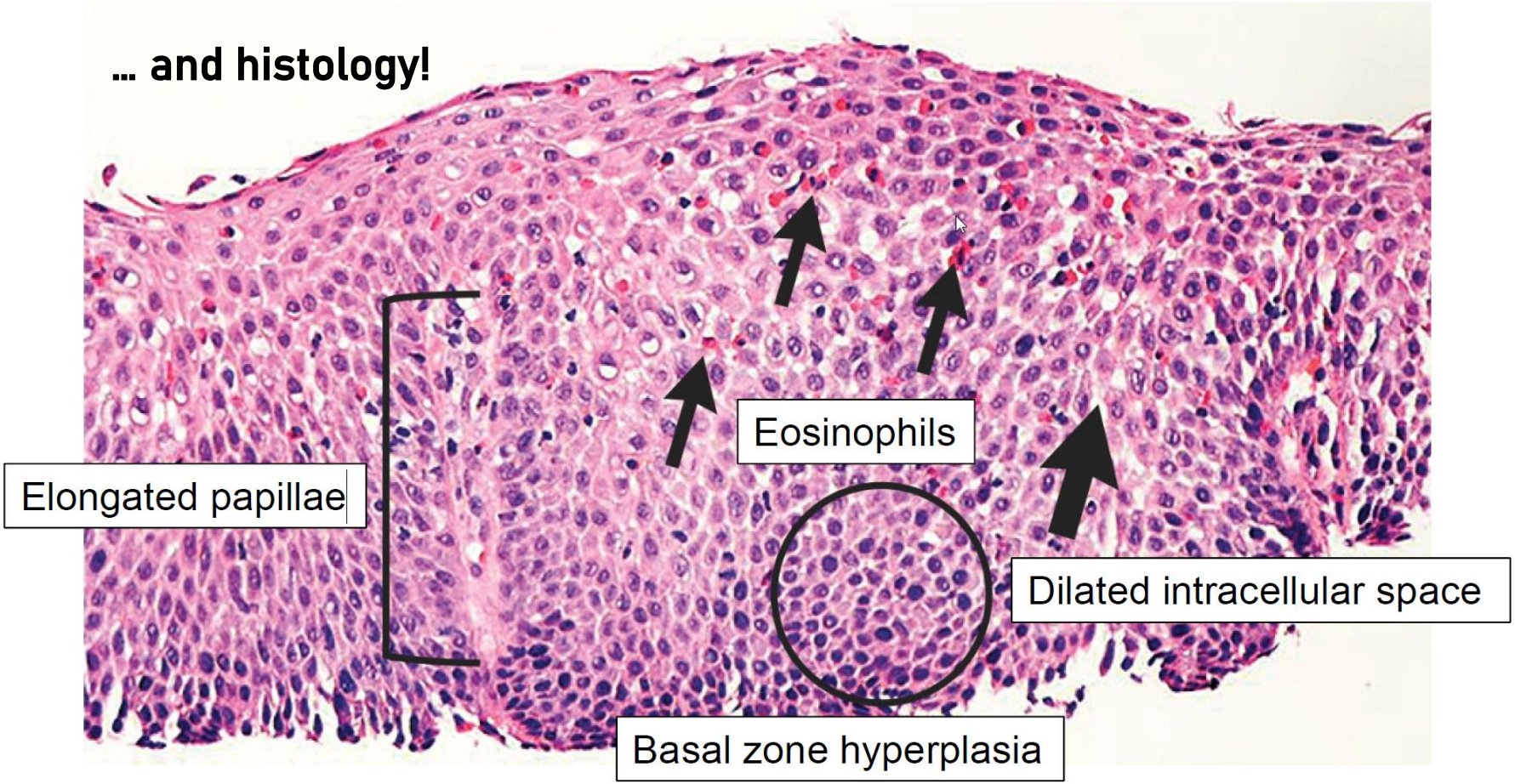
Expected physiological numbers of eosinophils in the intestinal tract DeBrosse CW et.al. Pediatr Dev Pathol. 2006;9(3):210-8.

Differential diagnosis



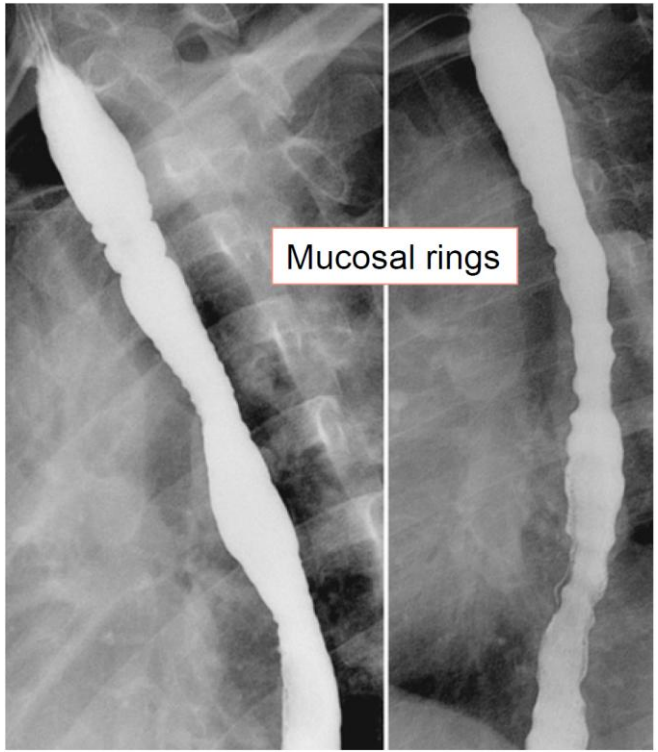
- **GERD**, Achalasia
- Eosinophilic gastroenteritis
- Crohns disease
- Drugs (NSAID, Enalaprtil, Rifampicin, Tacrolimus, Carbamazepin)
- Parasitic infection
- Celiac disease
- Pemphigus (rare!)

… and histology!



Additional diagnostic tools – barium swallow

- Not helpful in diagnosis
- Can help with stenosis (e.g. extent)
- Not in guidelines



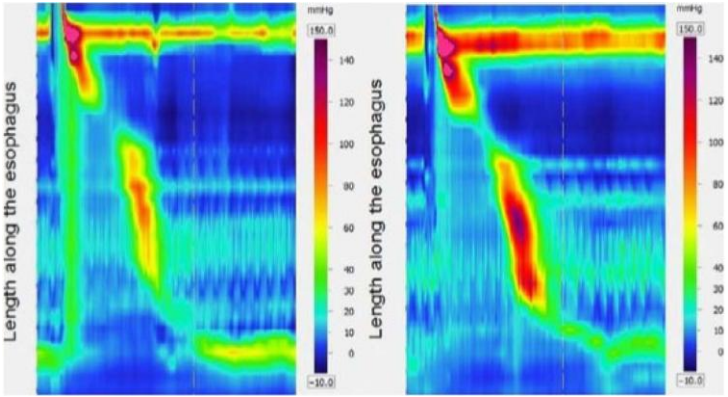
Additional diagnostic tools – HR Manometry

- 1/3 with altered motility
- 86% improve after therapy

<u>Frequent findings</u>

- Early, panesophageal increase in pressure
- Weak and insufficient peristalsis

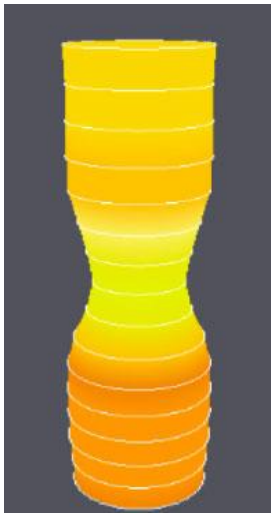
Possibility when persistent symptoms despite remission and absence of fibrosis!



Nennstiel S et al.. Neurogastroenterol Motil 2016
Roman S et al. Neurogastroenterol Motil. 2011 Mar

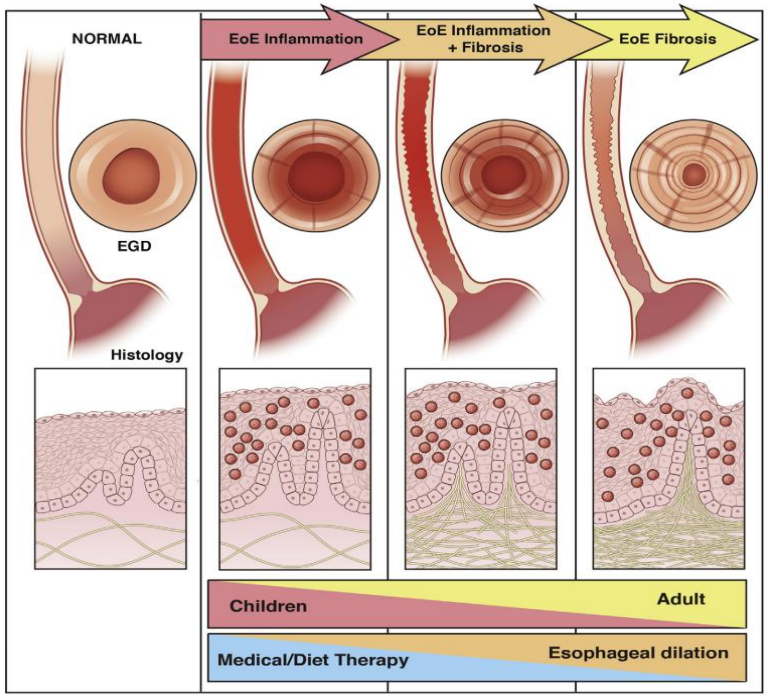
Additional diagnostic tools – EndoFLIP

- Accurate assessment of esophageal distensibility
- Monitoring of progression of fibrosis
- Monitoring of response to therapy



Kwiatek M et al. Gastroenterology 2011

Natural History of EoE

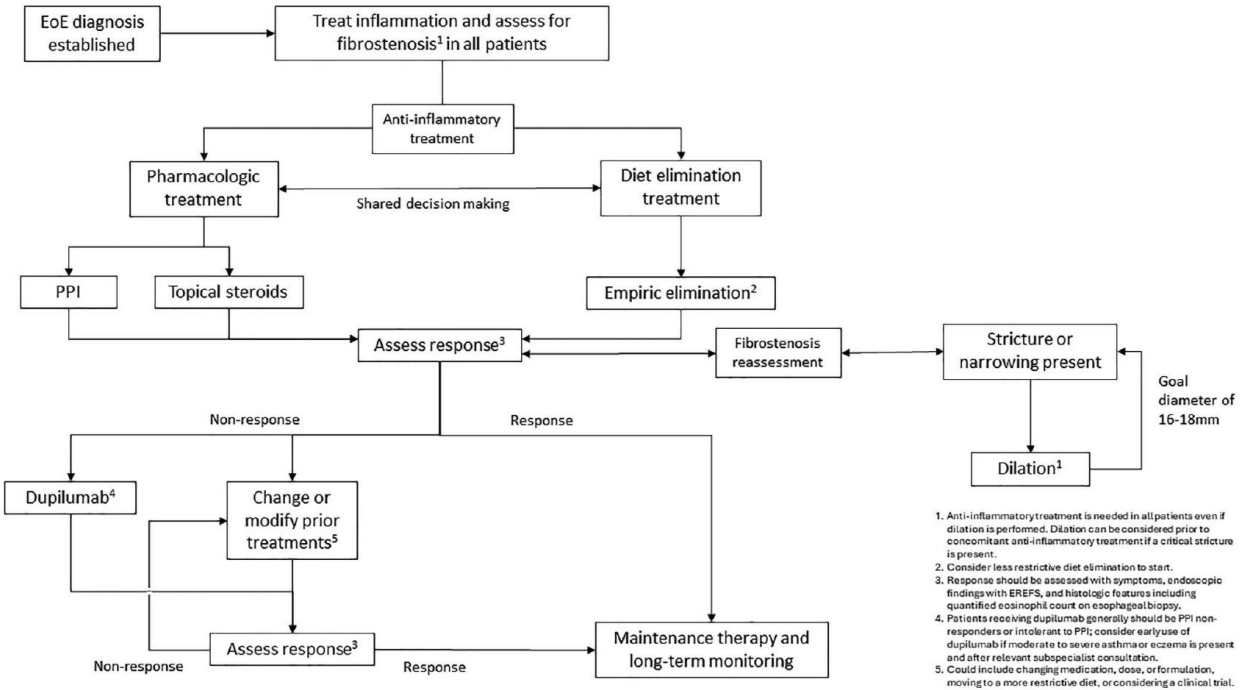


Epidemiology and Natural History of Eosinophilic Esophagitis
Dellon, Evan S. et al., Gastroenterology, Volume 154, Issue 2, 319 - 332.e3

Complications

- Strictures
- Food impactions
- Boerhaave
- Iatrogenic perforation
- Malnutrition
- Reduced QoL

Treatment-Algorithm



Treatment – PPI

- Potential therapeutic effect in some patients
- 2xdie > 1x/die, **dosing unclear**
- Maintenance of remission possible (70% after 1y)
- Recurrence of eosinophils 3-6 months after treatment stopp

Gutiérrez-Junquera C et al. J Pediatr Gastroenterol Nutr. 2018 Aug
Molina-Infante J et al. Am J Gastroenterol. 2015 Nov

Treatment – topicals steroids

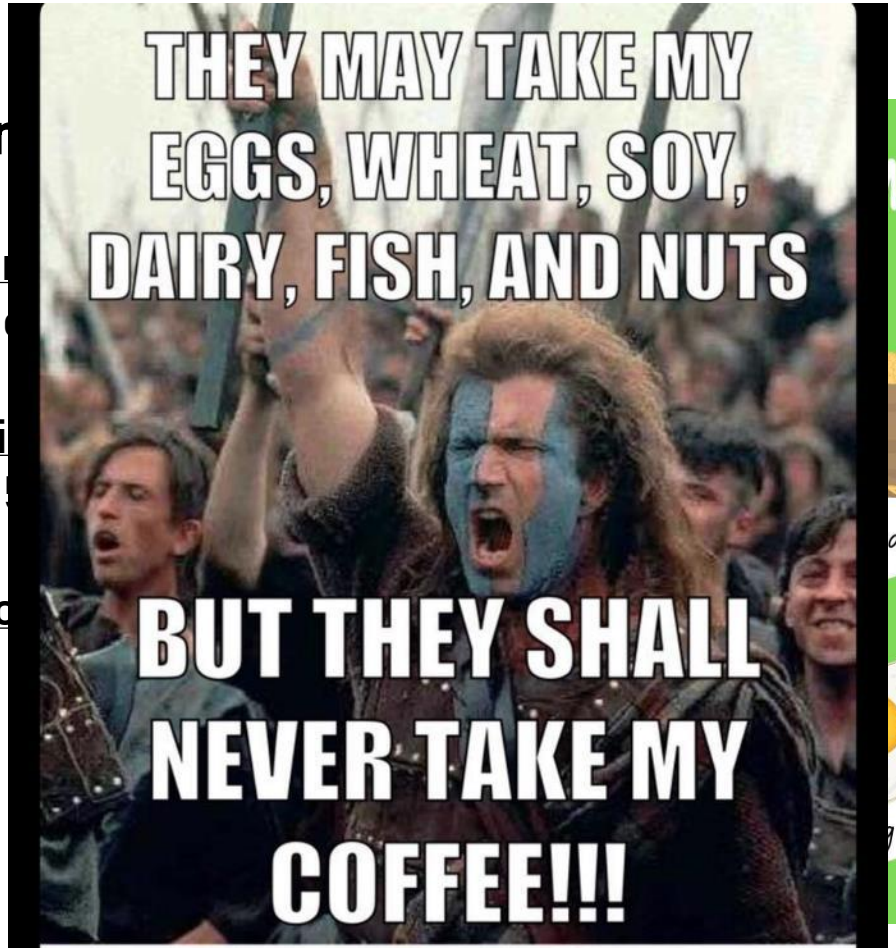
- Induction 2x1mg/die for 12 weeks
- Maintenance 2x0.5mg/die
- Publication of over 13 randomized, double-blind, placebocontrolled clinical trials in children and adults with EoE
- Response rate 60-70%

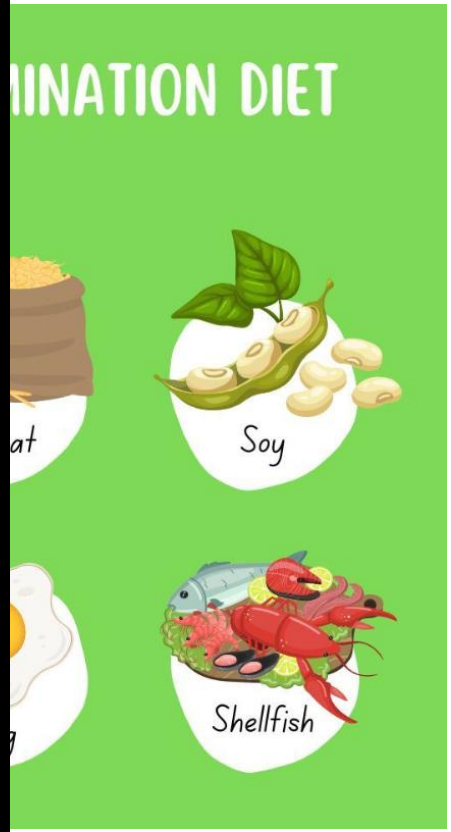
Treatment – Elir

Six food eliminatio
- Remission rate

Four food eliminati
- Remission rate

Two food eliminatio
- Remission 40%





Treatment – combination?

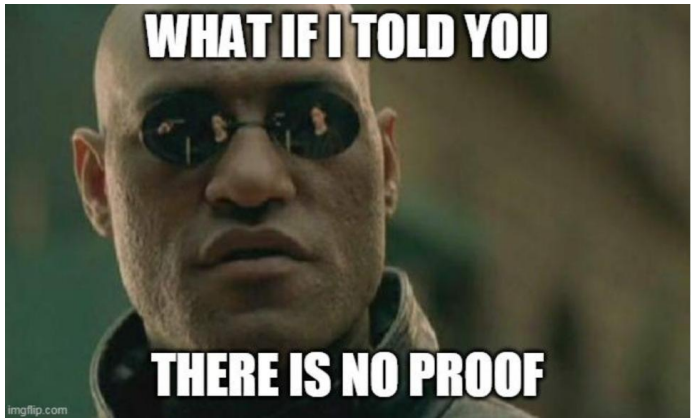
4-FED + PPI vs. PPI mono: Eos <10/hpf in 88% vs. 45% after 12w. Reduction in peak Eos/hpf from 45 to 4

Heine et al. J Allergy Clin Immunol. 2019
Leung J et al. Gastro Hep Advances 2022

Topical steroids + 2-FED: Reduction of median eos/hpf from 51 to 2. Improvement of symptoms

Reed CC et al. Dig Dis Sci. 2018

Treatment – no evidence



- Azathioprine
- Montelukast
- Anti-histamines
- Anti-TNF (IFX)

Biologicals - Dupilumab

- Monoclonal antibody against IL-4 receptor-α that blocks the effect of both IL-4 and IL-13
- Previously approved as add-on therapy for asthma and atopic dermatitis

Biologicals – Dupilumab

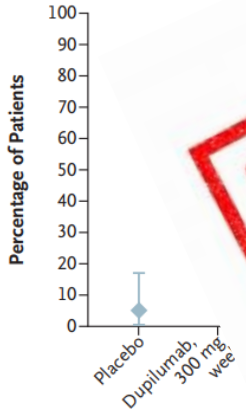
JOURNAL of MEDICINE

ARTICLE

nd Adolescents
sophagitis

M. Chehade, A.J. Bredenoord,
P. Kosloski, M.A. Kamal,
Mannent, E. Laws, B. Akinlade,
Ruddy, N. Patel, D.R. Weinreich,
Maloney, A. Giannelou, and A. Shabbir

A Histologic Remission at Wk 24 in Parts A and B



	Part A, Wk 24	
No. of Patients	39	42
No. of Patients with Response (%)	2 (5)	25 (60)

FDA APPROVED

3 RCT

12yo or above

- PPI non-responders
- **Patients with strictures excluded!**

Biolog

ESOPHAGUS

Real-World Ef
Refractory, ar
Esophagitis

Christopher J. Lee

- Retros
- Patien
- 85% w

Table 2. Endoscopic and Histologic Features and Treatment Response With Histologically Worse Prior EGD, the EGD Immediately Before Starting Dupilumab, and the First Clinical EGD While on Dupilumab (n = 46)

	Worst	Predupilumab	Postdupilumab	P^a	P^b
Endoscopic findings, n (%)					
Exudates	37 (80)	39 (85)	9 (20)	<.001	<.001
Rings	35 (76)	31 (67)	21 (46)	.008	<.001
Edema	37 (80)	36 (78)	21 (46)	<.001	<.001
Furrows	44 (96)	39 (85)	14 (30)	<.001	<.001
Stricture	34 (74)	37 (80)	33 (72)	.13	.71
Diameter, *mm*, means ± SD	11.1 ± 4.2	13.9 ± 3.2	16.0 ± 3.0	<.001	<.001
Narrowing	33 (71)	36 (78)	32 (70)	.13	.65
Dilation	32 (70)	33 (72)	30 (65)	.32	.48
Balloon	14 (44)	11 (33)	8 (27)	–	–
Wire-guided bougie	18 (56)	22 (67)	22 (63)	–	–
Postdiameter, *mm*, means ± SD	13.6 ± 3.5	15.9 ± 2.3	17.0 ± 2.0	.001	<.001
EREFS components, n (%)					
Exudates	1.09 ± 0.69	1.20 ± 0.69	0.16 ± 0.41	<.001	<.001
Rings	1.30 ± 1.01	0.87 ± 0.74	0.42 ± 0.56	<.001	<.001
Edema	0.87 ± 0.40	0.80 ± 0.40	0.39 ± 0.47	<.001	<.001
Furrows	1.01 ± 0.40	0.95 ± 0.56	0.24 ± 040	<.001	<.001
Stricture	0.74 ± 0.44	0.80 ± 0.40	0.72 ± 0.46	.04	.71
Total EREFS, means ± SD	5.01 ± 1.88	4.62 ± 1.84	1.89 ± 1.31	<.001	<.001
Peak eosinophil count, *eos/hpf*, means ± SD	104.0 ± 67.6	70.0 ± 68.6	9.0 ± 12.0	<.001	<.001
Responses, n (%)					
<15 eos/hpf	0 (0)	5 (11)	37 (80)	<.001	<.001
≤6 eos/hpf	0 (0)	4 (9)	26 (57)	<.001	<.001
0 eos/hpf	0 (0)	4 (9)	13 (28)	.05	<.001
Symptom	5 (11)	8 (17)	42 (91)	<.001	<.001
Endoscopic	2 (1)	1 (2)	42 (91)	<.001	<.001

Biologicals – Dupilumab

10. We suggest dupilumab as a treatment for EoE in individuals 12 years of age or older who are nonresponsive to PPI therapy (quality of evidence: moderate; strength of recommendation: conditional).

Biologicals - Others

Cen

12. We cannot make a recommendation for or against cendakimab, benralizumab, lirentelimab, mepolizumab, or reslizumab as a treatment for EoE.

Reslizumab

Treatment – Dilatation

- Focal constriction of esophagus («stricture»)
- Diffuse longitudinal narrowing («narrow caliber esophagus»)

In patients with fibrostenotic EoE, dilation therapy should occur in conjunction with effective medical or diet elimination anti-inflammatory therapy because dilation alone does not impact EoE disease activity

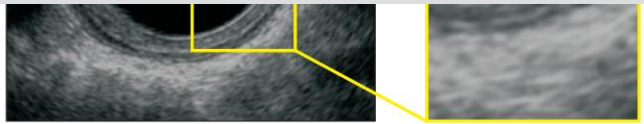
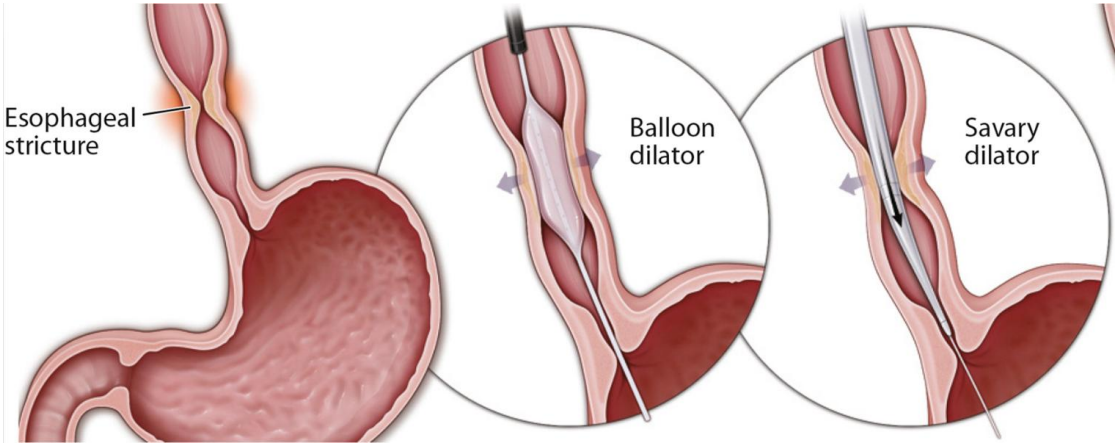


Fig. 1. Typical measurements obtained by endoscopic ultrasonography. The total esophageal wall thickness (black double-headed arrow) and the thickness from the surface to the muscular layer (white double-headed arrow) were measured at 20 MHz and 12 MHz using the GF-UM2000.

Suzuki Y, Ochiai Y, Hosoi A, et al. Mucosal and submucosal thickening of esophageal wall is a promising factor in the development of symptoms in eosinophilic esophagitis. Gut Liver 2024;18(1):50–9.

Treatment – Dilatation

- Safe procedure: Perforation in <0.5% of dilatations
- Endpoint of endoscopic dilatation: Mucosal disruption
- Goal of luminal diameter: 16mm



Treatment – Dilatation

- **You can only treat strictures if you see them**

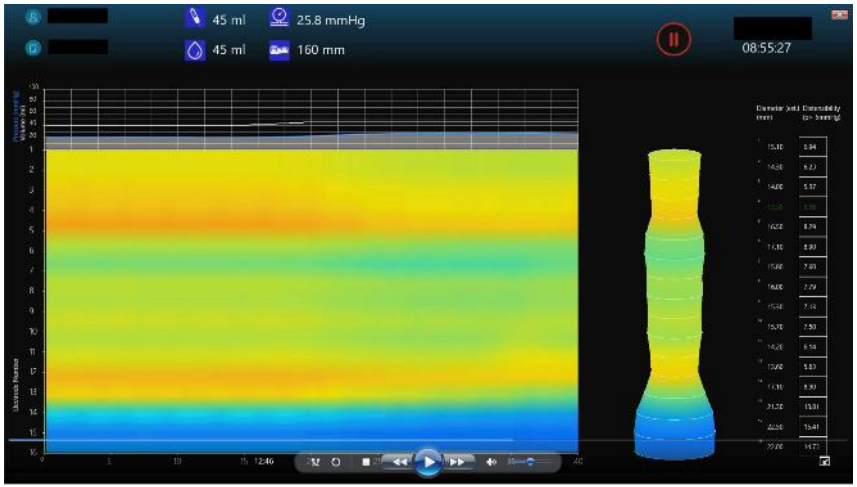
- Strictures in EoE can be <u>difficult to recognize</u>
  - Esophagrogram vs. endoscopy:
    - Sensivity only 25% for cut-off diameter <15mm!

  - 71% symptomatic response rate to dilation in patients without percieved esophageal narrowing at endoscopy!

Gentile N, Katzka D, Ravi K, et al. Aliment Pharmacol Ther 2014

Treatment – Endo-/EsoFlip

- Data suggests increased sensitivity for esophageal stricture detection in EoE
- **Underuse of Endo/EsoFlip in our practice?**



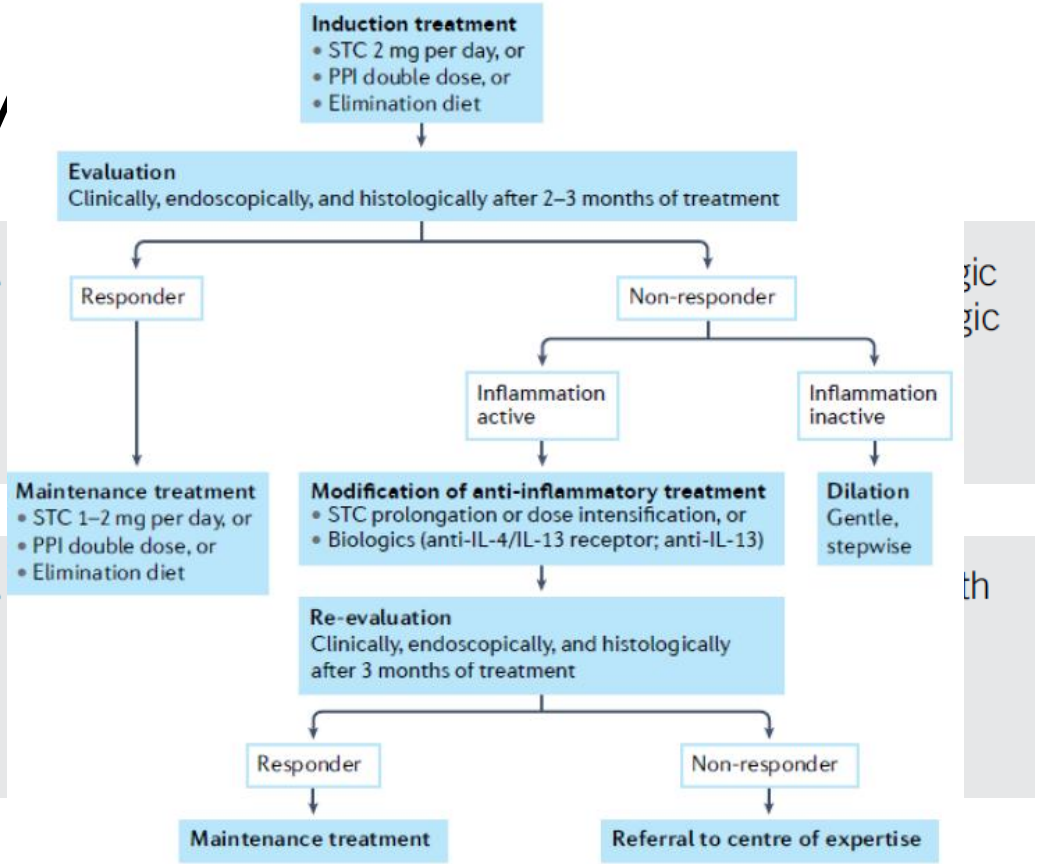
Chen JW, Pandolfino JE, Lin Z, et al. Endoscopy 2016

Treatment – Maintenance Therapy

16. We suggest continuation of effective dietary or pharmacologic therapy for EoE to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities (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).

Treatment – M


Induction treatment
• STC 2 mg per day, or
• PPI double dose, or
• Elimination diet
Evaluation
Clinically, endoscopically, and histologically after 2–3 months of treatment
Responder
Non-responder
Inflammation active
Inflammation inactive
Maintenance treatment
• STC 1–2 mg per day, or
• PPI double dose, or
• Elimination diet
Modification of anti-inflammatory treatment
• STC prolongation or dose intensification, or
• Biologics (anti-IL-4/IL-13 receptor; anti-IL-13)
Dilation
Gentle, stepwise
Re-evaluation
Clinically, endoscopically, and histologically after 3 months of treatment
Responder
Non-responder
Maintenance treatment
Referral to centre of expertise

Future Directions

Future Directions – Areas for future research

- Noninvasive Biomarkers
  - Treatment response
    - Predicting treatment response

- Identification of phenotypes and endotypes associated with progression to fibrostenosis

- EDUCATION

Future Directions – Treatment options

- Tezepelumab → Thymic stoma lymphopoietin
- Barzovolizumab → Mast cells
- JAK-Inhibitors
- Alpha-1 trypsin inhibitors

Thank you for you attention!