NEW YORK SOCIETY FOR GASTROENTEROLOGY & ENDOSCOPY
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# The Latest and Greatest on Eosinophilic Esophagitis

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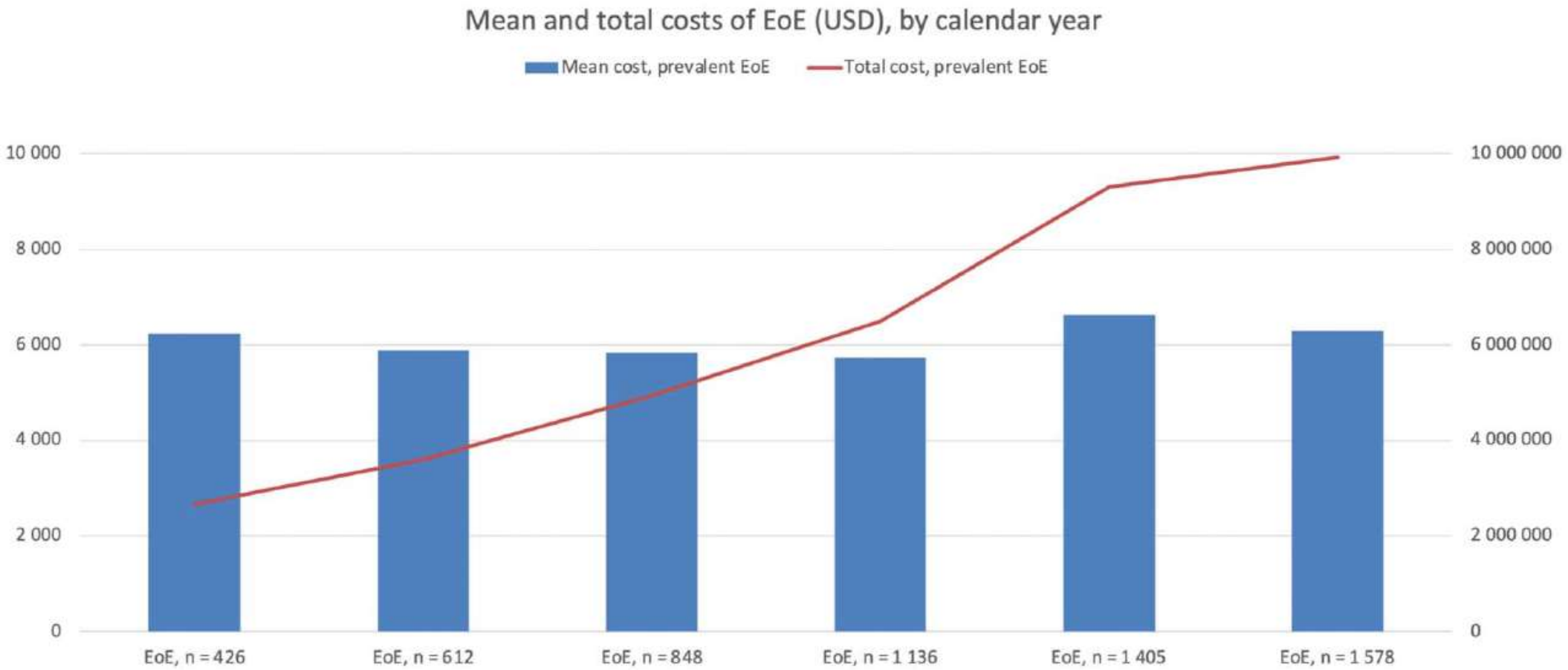
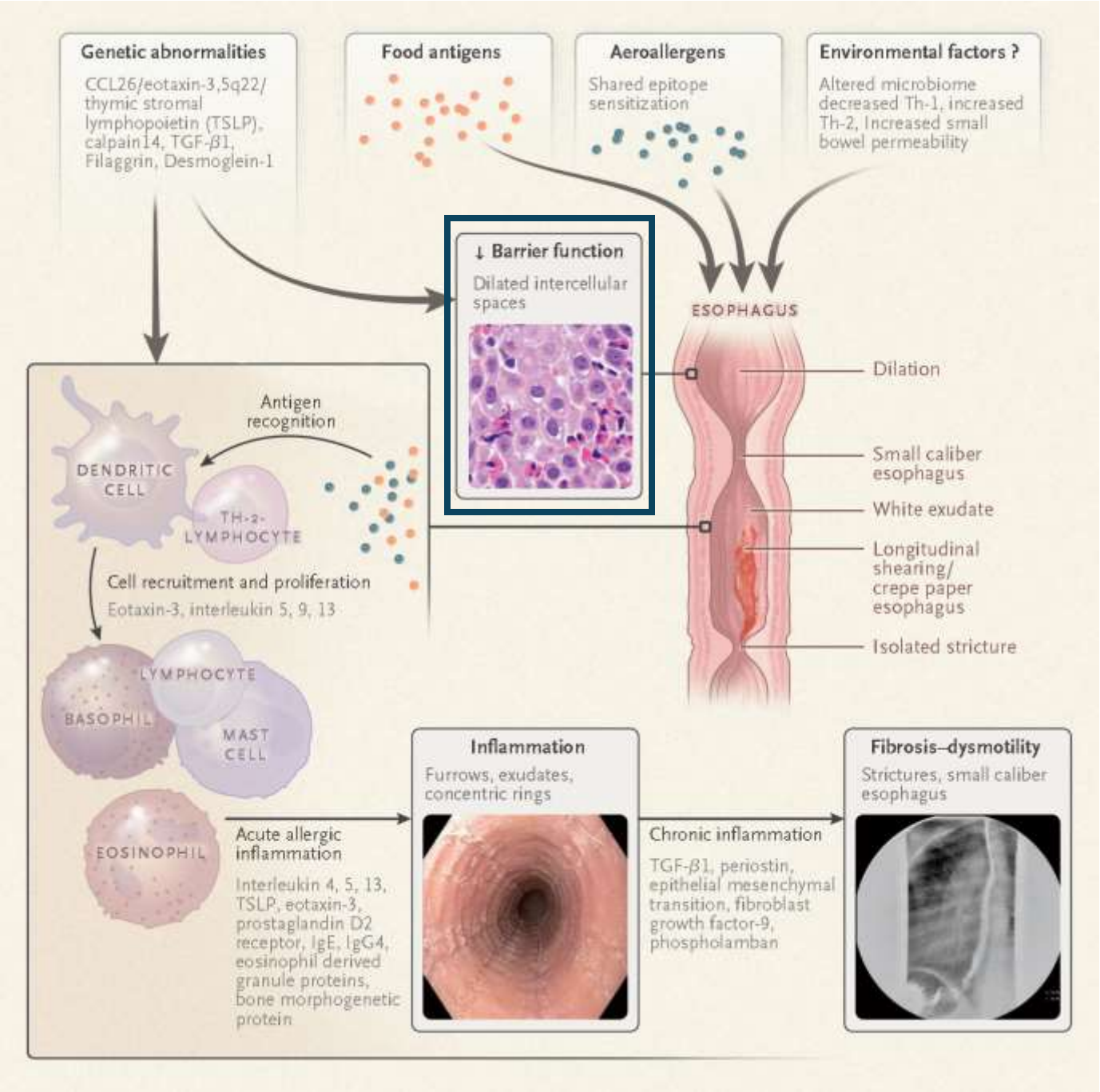
Consulting for Takeda, Sanofi-Regeneron, Astra Zeneca, Bristol Myers Squibb




| | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2011-2016 (average) |
|---|---|---|---|---|---|---|---|
| Mean cost | 6 236 | 5 894 | 5 829 | 5 725 | 6 630 | 6 290 | 6 101 |
| Total cost (per 1 million inhabitants) | 2 656 724 (280 161) | 3 606 938 (377 457) | 4 942 694 (512 469) | 6 504 105 (667 269) | 9 315 184 (945 606) | 9 925 429 (993 024) | |

**Figure 2.** Mean annual societal costs per patient (left axis, bar chart) and total annual societal cost (right axis, line chart) of all prevalent patients with EoE in Sweden by calendar year. Brackets indicate 95% confidence intervals. All costs were adjusted for inflation and converted from Swedish Krona (SEK), to USD according to the annual average exchange rate in 2023 (1 USD = 10.61 SEK). EoE, eosinophilic esophagitis; USD, US dollar.

Bozorg et al., Am J Gastroenterol 2024;119:2122–2125



| Main actor | Mechanism of tissue injury in EoE | Ref |
|---|---|---|
| Mucosal barrier | Impaired barrier structure<br>- Cadherin, filaggrin, claudin, occludin and desmoglein impairment | (12–16) |
| | Impaired barrier function<br>- Oncostatin M-, SPINK7- and calpain 14-mediated reduced TEER and increased FITC dextran flux | (22,23) |
| | Epithelial release of Th2-triggering alarmins (i.e. IL-33, IL-25 and TSLP) | (26–29) |
| | Allergens and microbes penetration in lamina propria and activation of Th2 inflammation | (24) |
| | IL-13 and IL-4<br>- Drivers of Th2 inflammatory process<br>- Promote migration and trafficking of eosinophils<br>- Involved in B cell class switching to IgE, leading to mast cell and basophil degranulation<br>- Mediates impairment of oesophageal epithelial cells and barrier dysfunction | (33–38) |

Santacroce et al. Gut (in press)

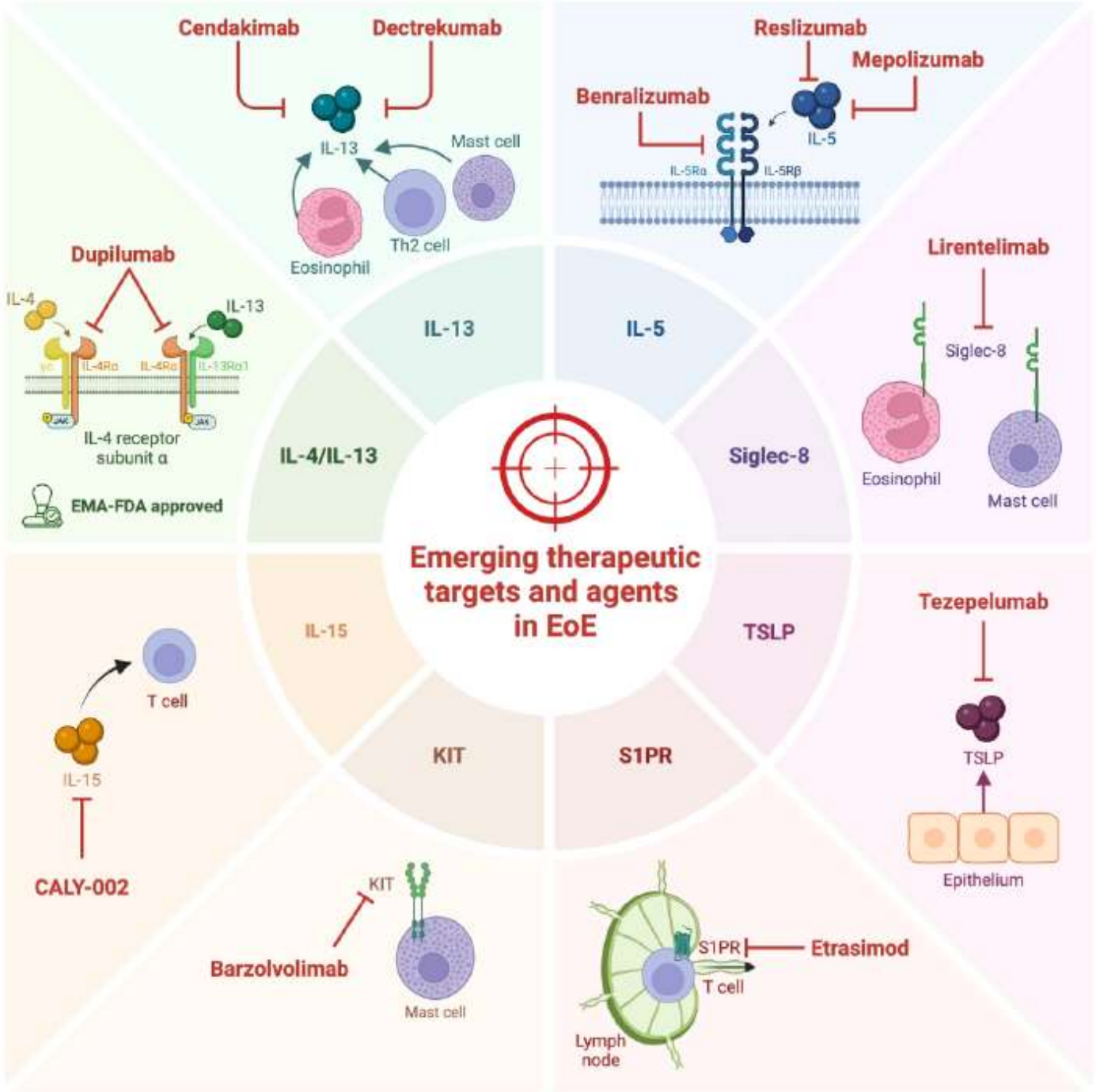
| | | |
|---|---|---|
| Cytokines | IL-5<br>- Eosinophil maturation, differentiation and survival | (39) |
| | IL-18<br>- Development of mature and pathogenic eosinophils | (40) |
| | Interferon $\alpha$ - Interferon $\gamma$<br>- Possible non-type 2 inflammatory networks in EoE | (43) |
| Chemokines | Periostin and eotaxin-3<br>- Eosinophil chemotaxis and activation | (41,42) |
| Immune cells | Eosinophils<br>- Defining feature of EoE; not clear correlation with disease severity and progression<br>- Infiltrating and degranulating in the epithelium during active EoE<br>- Type 2 inflammatory cytokines production (i.e. IL-4, IL-5, IL-13) | (44) |

| | |
|---|---|
| Mast cells<br>- Infiltrating and degranulating in the epithelium during active EoE<br>- Release of type 2 inflammatory mediators, prominently IL-13 | (46) |
| Th2 lymphocytes<br>- Promoting inflammation through type 2 inflammatory mediators (IL-4, IL-5, IL-13) and prostaglandins production<br>- Contributing to loss of barrier integrity through IL-13 | (18,51) |
| Group 2 innate lymphoid cells<br>- Bolstering type 2 inflammation through IL-4, IL-5, IL-9, and IL-13 production | (54) |
| Dendritic cells and basophils<br>- Induction and polarisation Th2 phenotype: cytokine production (IL-4, IL-12 and TSLP) and antigen presentation | (52) |
| B cells and immunoglobulins<br>- Increased B cells and IgE class switch recombination, despite EoE is characterised by non-IgE hypersensitivity<br>- Increased IgG4 which correlates with disease severity | (38,53) |

**Table 2. Summary of mechanisms of remodelling in EoE**

| Main actor | Mechanism of tissue remodelling in EoE | Ref |
|---|---|---|
| Epithelial cells | Epithelial proliferation:<br>- SFRP1-mediated basal zone hyperplasia<br>- CD74+CD104+ self-renewal epithelial cells depletion | (57,58) |
| | Impaired epithelial differentiation and cell-to-cell communication:<br>- Failure of NOTCH, LOX/BMP and TGF-β receptor signalling pathways<br>- Decrease in E-cadherin and ZO-1 and increase in N-cadherin | (59–62) |
| | Epithelial-to-mesenchymal transition, driven by IL-13 and β-catenin/Twist 1 transcription factors, leads to ECM accumulation | (62) |
| Lamina propria cells | Fibroblasts<br>- Activation and production of ECM under the stimulation of TGF-β<br>- Epithelial-fibroblast-endothelial-immune cell cross-talk leads to fibrogenesis | (64) |
| | Endothelial cells:<br>- IL-13-mediated endothelial TSPAN12 down-regulation contributes to fibrosis | (67) |

| | | |
|---|---|---|
| | Smooth muscle cells:<br>- Proliferation and contraction mediated by TGF-β1-induced phospholamban | (68) |
| | Macrophages:<br>- Modulation of fibrosis through GM-CSF and CCL18 | (69) |
| Molecules | TGF-β:<br>- Promote ECM deposition by myofibroblast<br>- Stimulate epithelial-to-mesenchymal transition<br>- Regulate smooth muscle cell proliferation and contractility | (70) |
| | Thrombospondin-1<br>- Profibrotic molecule, central in EoE ECM protein-protein interactome<br>- Induce fibroblast collagen I and α-SMA production | (71) |
| | TNFSF14/LIGHT<br>- Upregulated in EoE<br>- Promotes fibroblast remodelling | (72) |

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# Biologics Currently Being Investigated for Use in Patients With EoE

**Tezepelumab**

- TSLP inhibitor
- Orphan drug designation by FDA for treatment of EoE
- Phase III trial planned

**Benralizumab**

- IL-5 inhibitor
- Phase III trial in progress

**Lirentelimab**

- Siglec-8 inhibitor
- Phase II/III trial in progress

**Cendakimab**

- IL-13 inhibitor
- Also known as RPC4046 and CC-93538
- Phase III trial in progress

**Etrasimod**

- S1P receptor modulator
- Phase II trial in progress



Lucendo. BioDrugs. 2020;34:477. NCT04322708. NCT04543409. NCT04682639. NCT04753697. www.accessdata.fda.gov/scripts/opdlisting/oopd/.

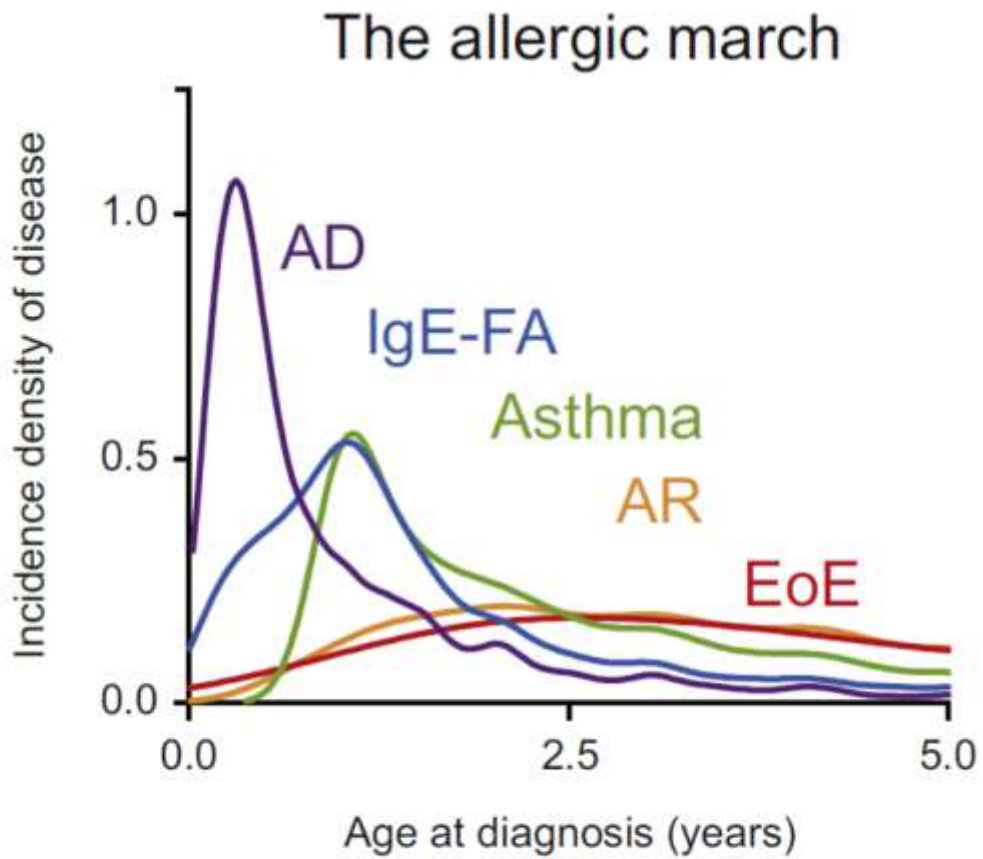
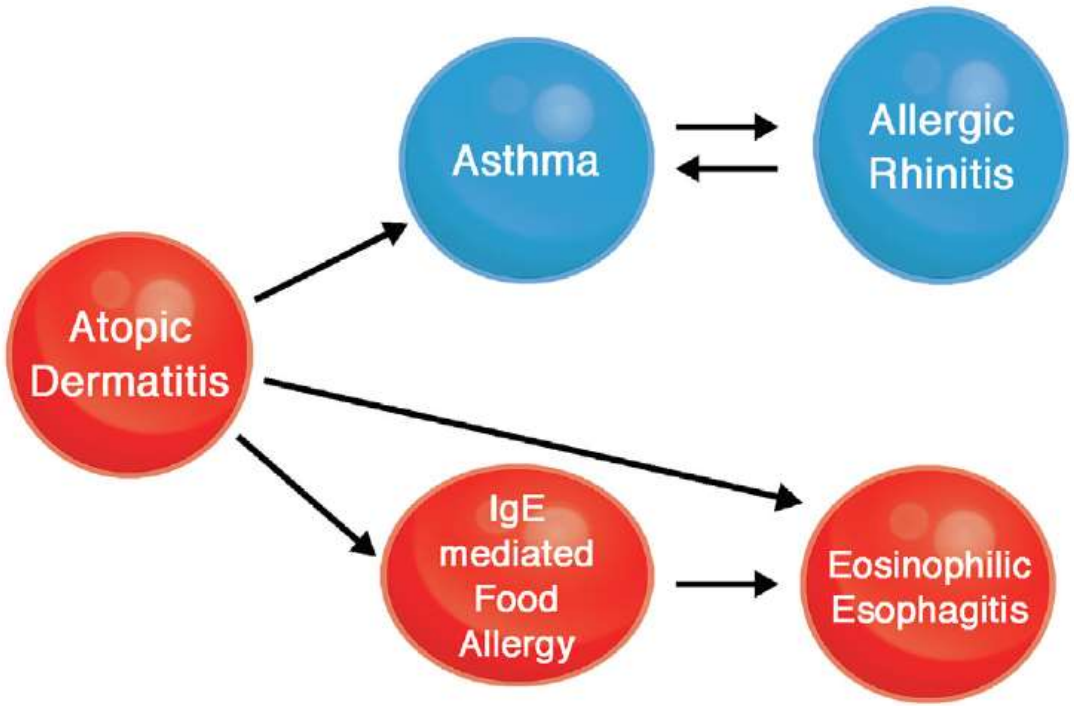



**FIGURE 1.** The allergic march. Density incidence of atopic dermatitis (AD), IgE-mediated food allergy (IgE-FA), asthma, allergic rhinitis (AR), and eosinophilic esophagitis (EoE) by age.




Spergel JM, et al. JACI 2023 (in press)

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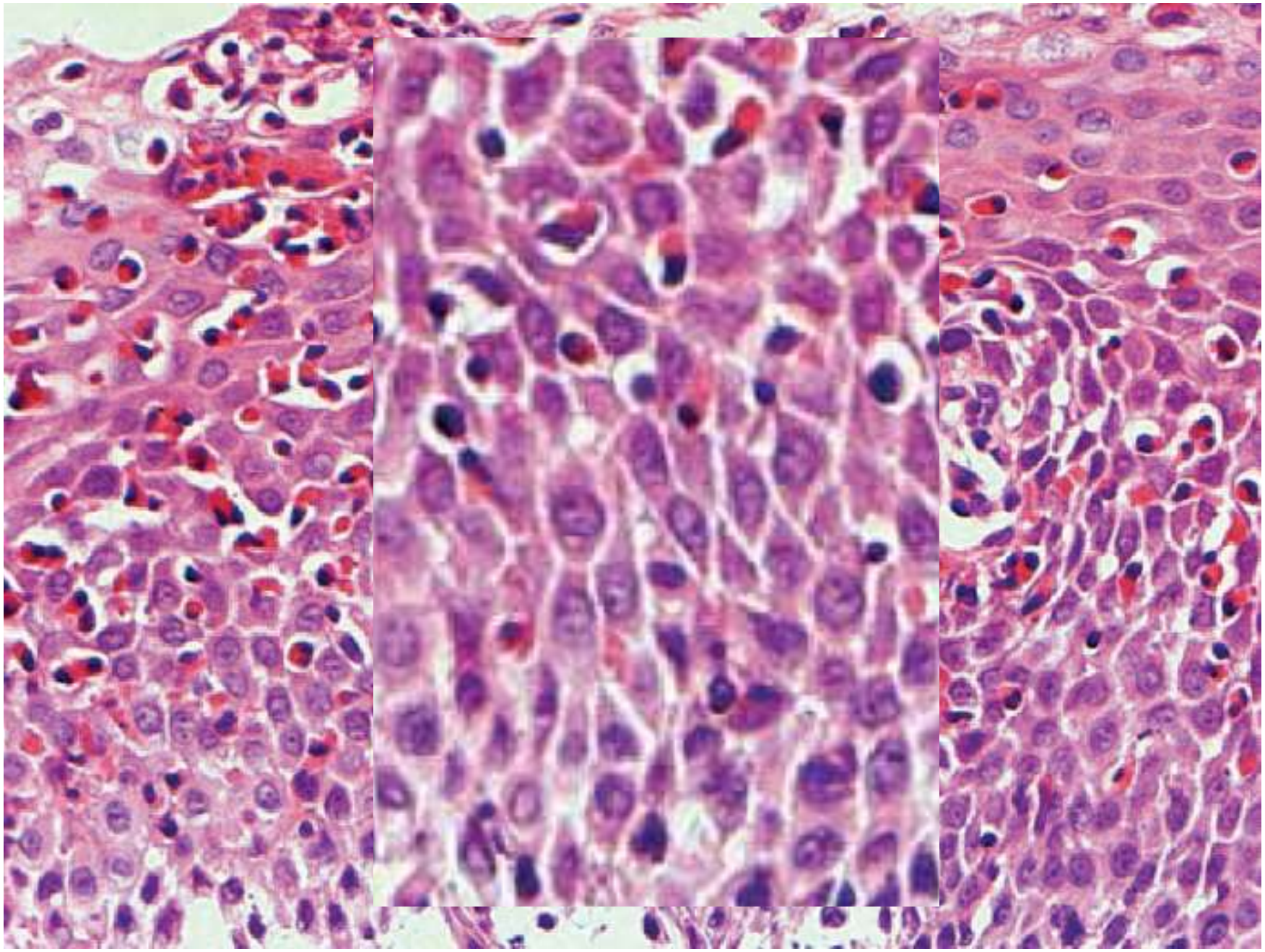
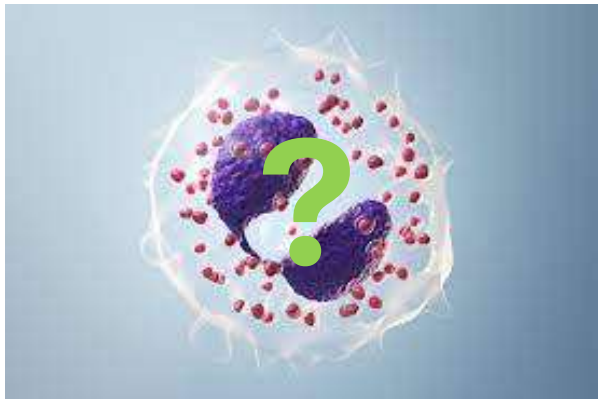
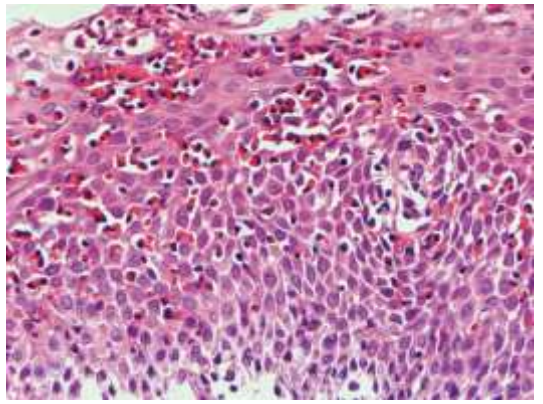


Chang Pathology (January 2008) **40(1)**, pp. 3–8




EREFS



EoEHSS

EEsAI

DSQ

# Index of Severity in EoE (I-SEE)

| Clinical features of severity | Points assigned |
|---|---|
| **Symptoms and complications** | |
| ***Symptoms*** | |
| None | 0 |
| Weekly | 1 |
| Daily | 2 |
| Multiple times per day or disrupting social functioning | 4 |
| ***Complications*** | |
| None | 0 |
| Food impaction with emergency department visit or endoscopy (patient ≥18 years) | 2 |
| Food impaction with emergency department visit or endoscopy (patient <18 years) | 4 |
| Hospitalization due to EoE | 4 |
| Esophageal perforation | 15 |
| Malnutrition with body mass index <5th percentile or decreased growth trajectory | 15 |
| Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory treatments | 15 |
| **Inflammatory features** | |
| ***Endoscopy (edema, furrows, and/or exudates)*** | |
| None | 0 |
| Localized | 1 |
| Diffuse | 2 |
| ***Histology*** | |
| <15 eos/hpf | 0 |
| 15-60 eos/hpf | 1 |
| >60 eos/hpf | 2 |
| **Fibrostenotic features** | |
| ***Endoscopy (rings, strictures)*** | |
| None | 0 |
| Present, but endoscope passes easily | 1 |
| Present, but requires dilation or a snug fit when passing a standard endoscope | 2 |
| Cannot pass standard upper endoscope, repeated dilations in an adult ≥18 years, or any dilation in a child <18 years | 15 |
| ***Histology*** | |
| None | 0 |
| Basal zone hyperplasia or lamina propria fibrosis (or dyskeratotic epithelial cells/ surface epithelial alterations if no lamina propria) | 2 |
| **Category** | **Total score** |
| Inactive | <1 |
| Mild | 1-6 |
| Moderate | 7-14 |
| Severe | ≥15 |

Dellon ES. Gastroenterology & Hepatology Volume 19, Issue 8 August 2023

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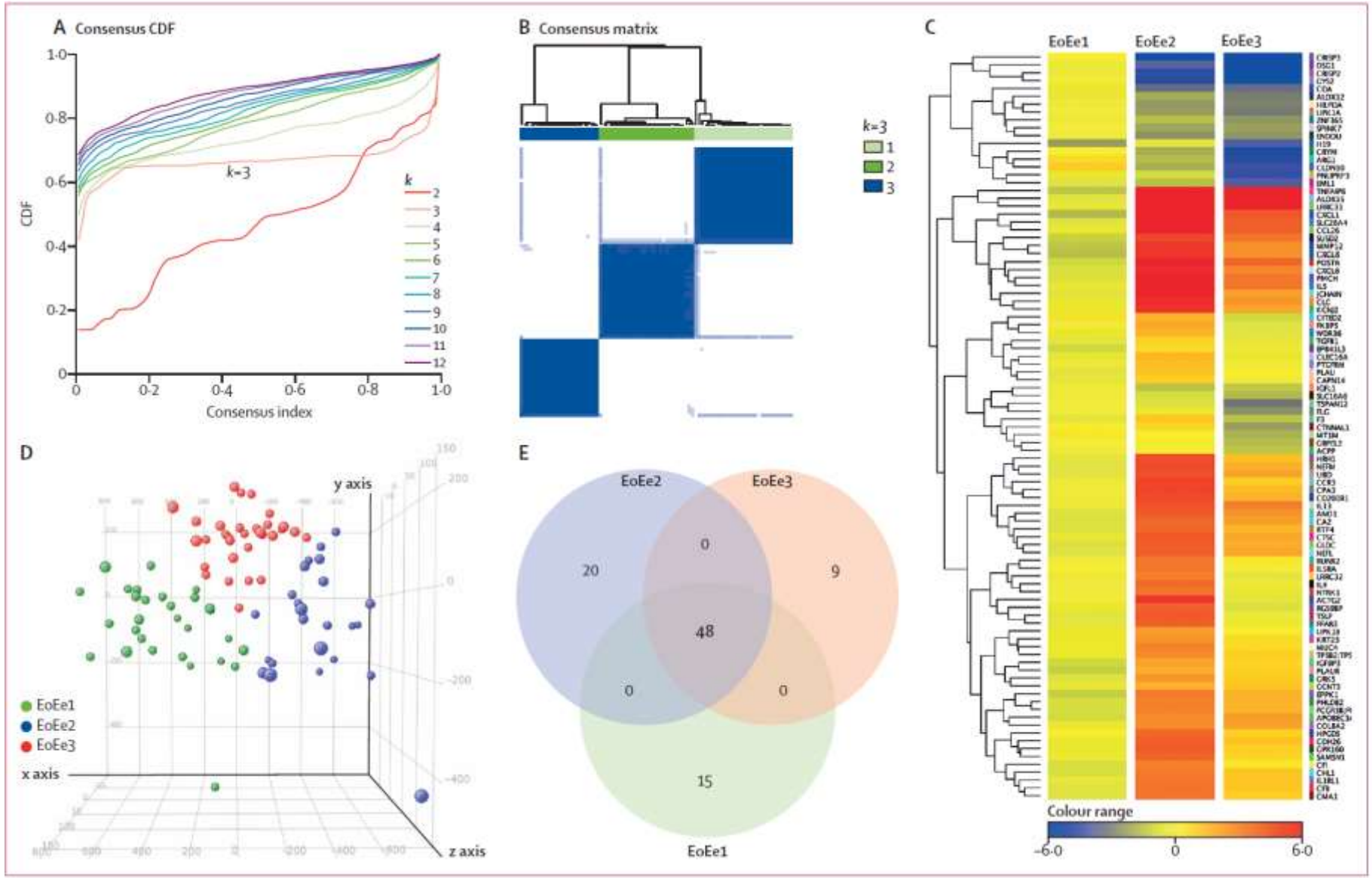
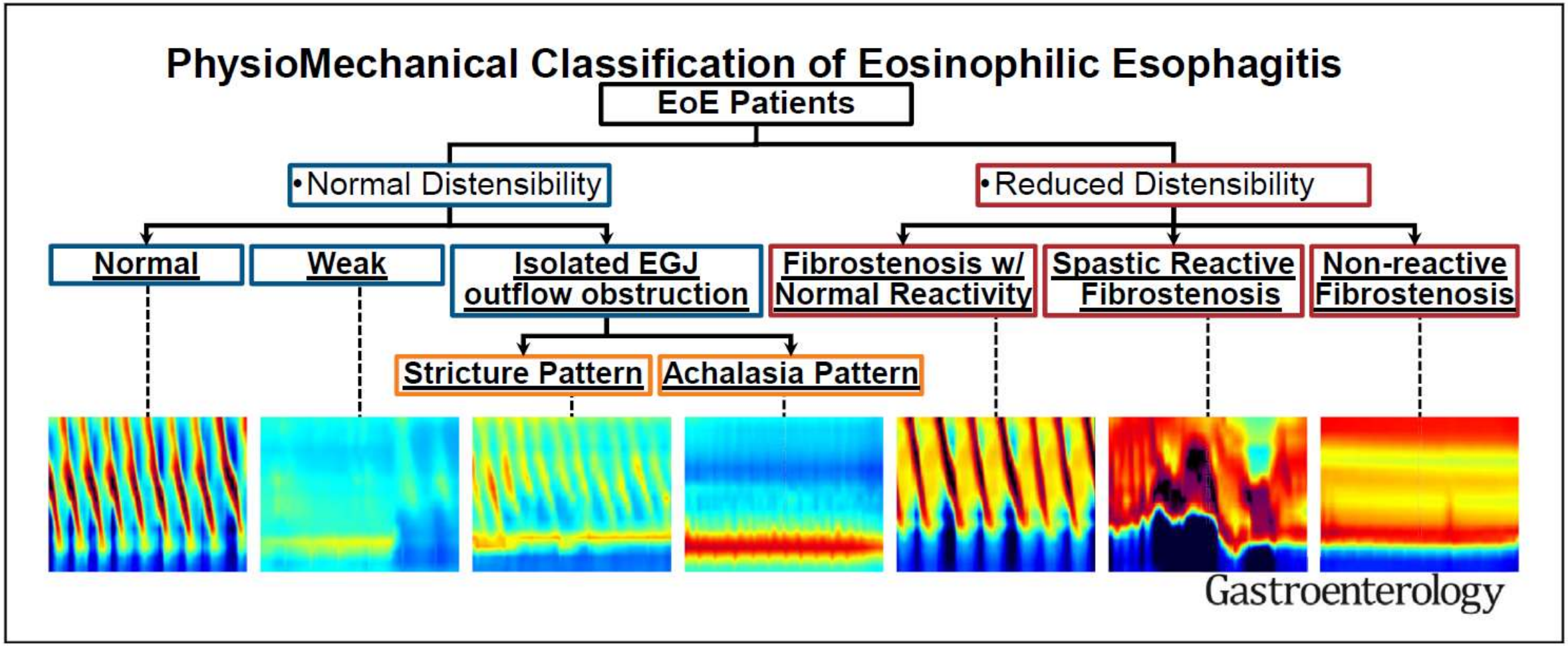
# Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: a cross-sectional study



# Phenotypes of Eosinophilic Esophagitis




Carlson DA, et al. Gastroenterology 2023;165:552–563

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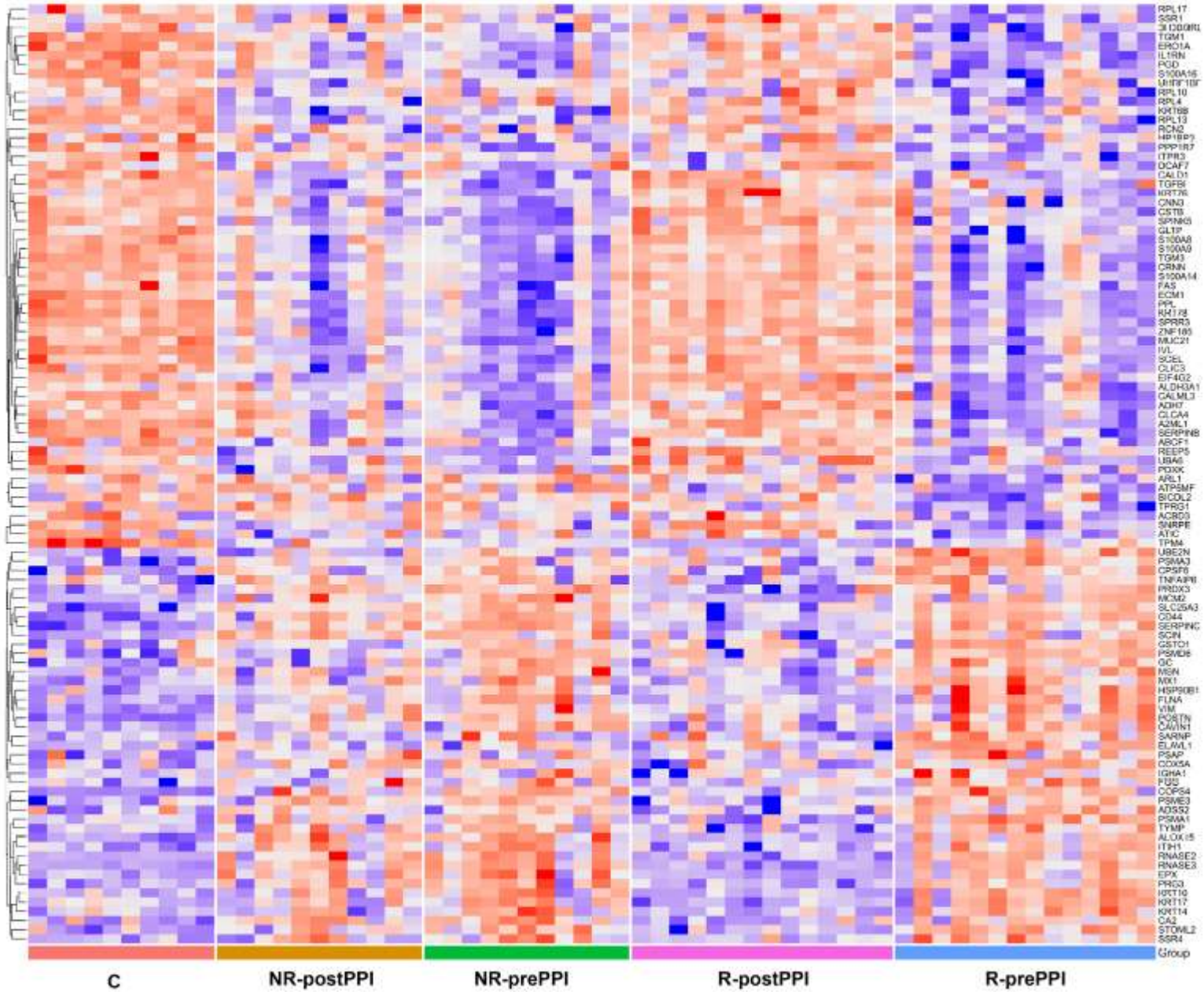
# Proton pump inhibitor effect on esophageal protein signature of eosinoph ation of treatment re




Molina-Jiménez et al. Allergy. 2024;00:1–16

# Diet Therapy

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# One-food versus six-food elimination diet therapy for the treatment of eosinophilic oesophagitis: a multicentre, randomised, open-label trial

*Kliewer KL, et al.* ***Lancet Gastroenterol Hepatol*** **2023; 8: 408–21**

| | 1FED (n=67) | 6FED (n=62) | Percentage point difference* | p value |
|---|---|---|---|---|
| <15 eos/hpf† | 23 (34%; 23 to 46) | 25 (40%; 28 to 53) | 6% (–11 to 23) | 0·58 |
| ≤10 eos/hpf | 20 (30%; 19 to 41) | 23 (37%; 25 to 49) | 7% (–9 to 24) | 0·46 |
| ≤6 eos/hpf | 12 (18%; 9 to 27) | 20 (32%; 21 to 44) | 14% (–0 to 29) | 0·069 |
| ≤1 eos/hpf | 4 (6%; 0 to 12) | 12 (19%; 10 to 29) | 13% (2 to 25) | 0·031 |

Data are n (%; 95% CI) or % (95% CI). p values were calculated with Fisher's exact test. 1FED=one-food elimination diet. 6FED=six-food elimination diet. eos/hpf=eosinophils per high-power field. *6FED versus 1FED. †Primary endpoint.

*Table 2:* Proportion of patients in histological remission (intention-to-treat population)

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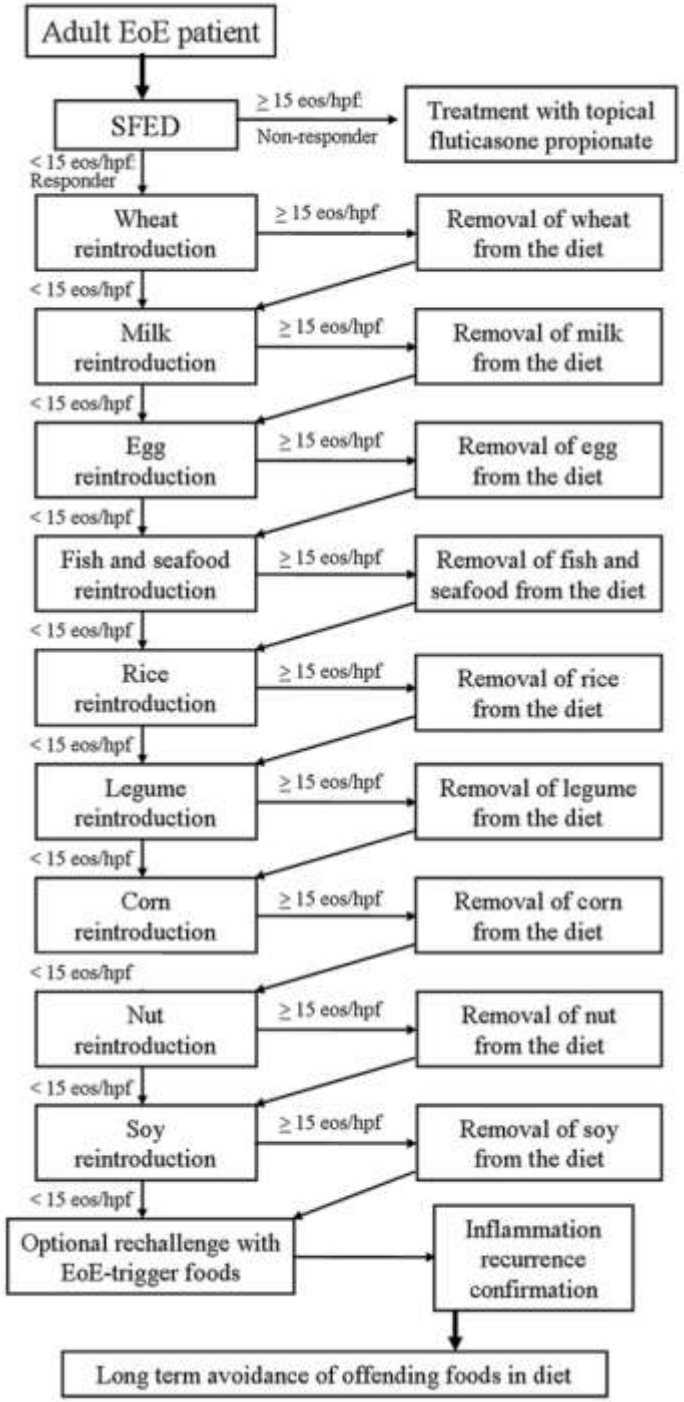


Lucendo AJ, JACI. 2013;131:797

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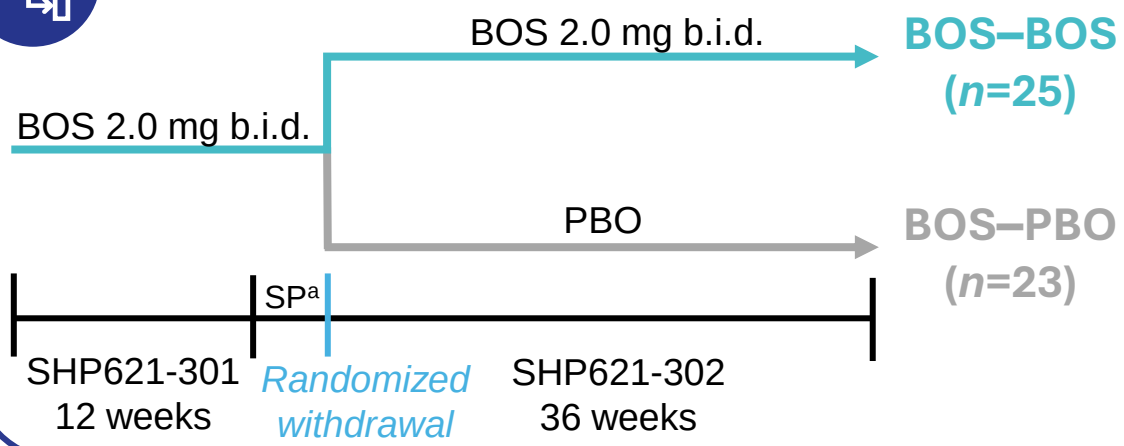
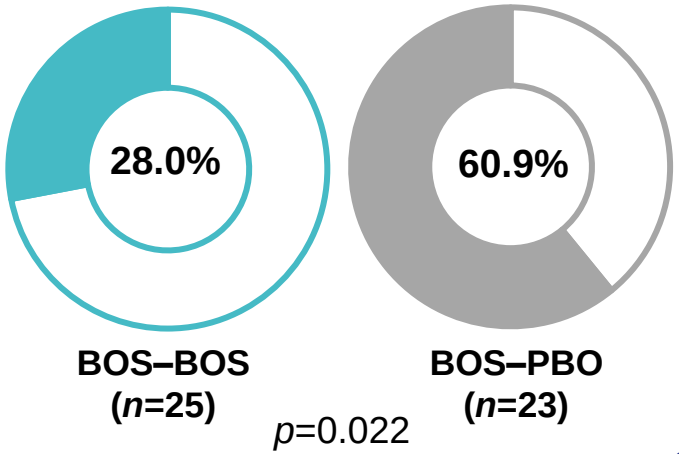
# Effect of randomized treatment withdrawal of budesonide oral suspension on clinically relevant efficacy outcomes in patients with eosinophilic esophagitis: a *post hoc* analysis

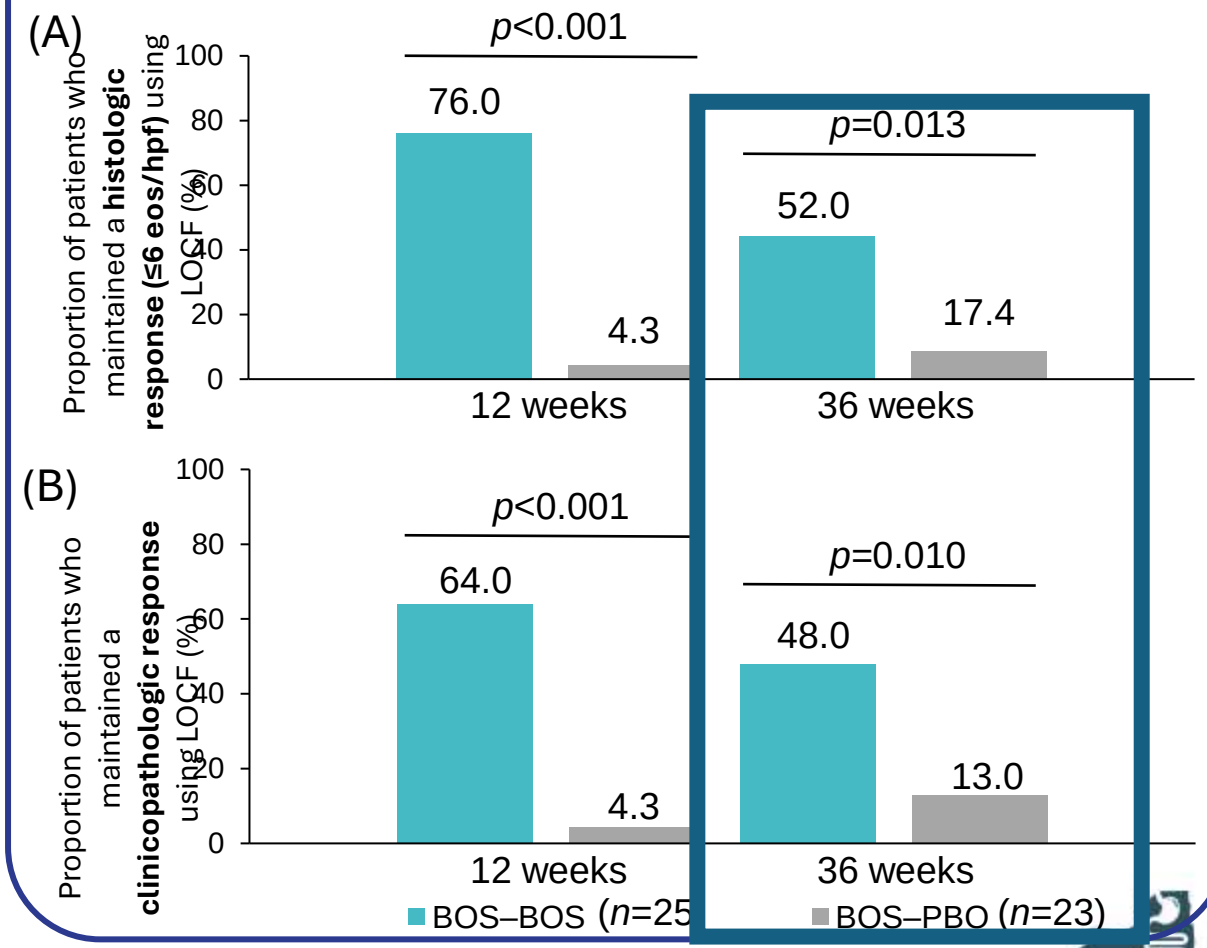
**Phase 3, double-blind, randomized withdrawal study**




A significantly greater proportion of BOS–PBO than BOS–BOS patients **relapsed** (≥15 eos/hpf [≥1 esophageal region] and ≥4 days of dysphagia [DSQ]) over 36 weeks of therapy using a *post hoc* alternative definition of relapse




Significantly more BOS–BOS than BOS–PBO patients maintained a (A) **histologic response** and a (B) **clinicopathologic response** at weeks 12 and 36 of therapy



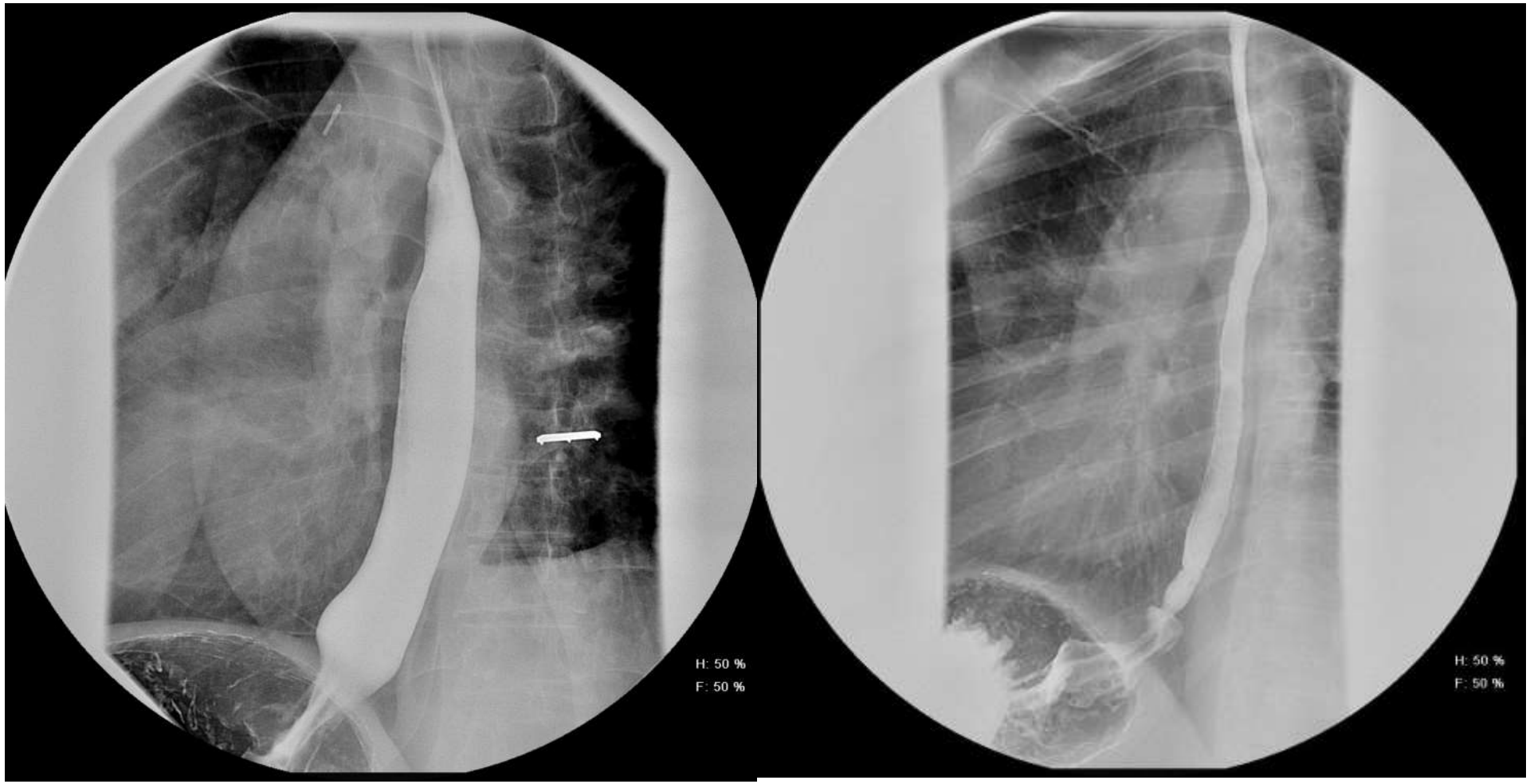

[a]4-week SP, during which patients continued treatment with BOS 2.0 mg b.i.d.

b.i.d., twice daily; BOS, budesonide oral suspension; DSQ, Dysphagia Symptom Questionnaire; eos/hpf, eosinophils per high-power field; LOCF, last observation carried forward; PBO, placebo; SP, screening period

Dellon ES, et al. *Therap Adv Gastroenterol* 2024

Normal

Eosinophilic Esophagitis

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# Reducing Eosinophil Counts in Eosinophilic Esophagitis in Children Is Associated With Reduction in Later Stricture Development

Alexandra Strauss Starling, MD[1], Yue Ren, MS[2], Hongzhe Li, PhD[2], Jonathan M. Spergel, MD[3], Amanda B. Muir, MD[4], Kristle L. Lynch, MD[1], Chris A. Liacouras, MD[4] and Gary W. Falk, MD, MS, MACG[1]

Am J Gastroenterol 2024;119:2002–2009

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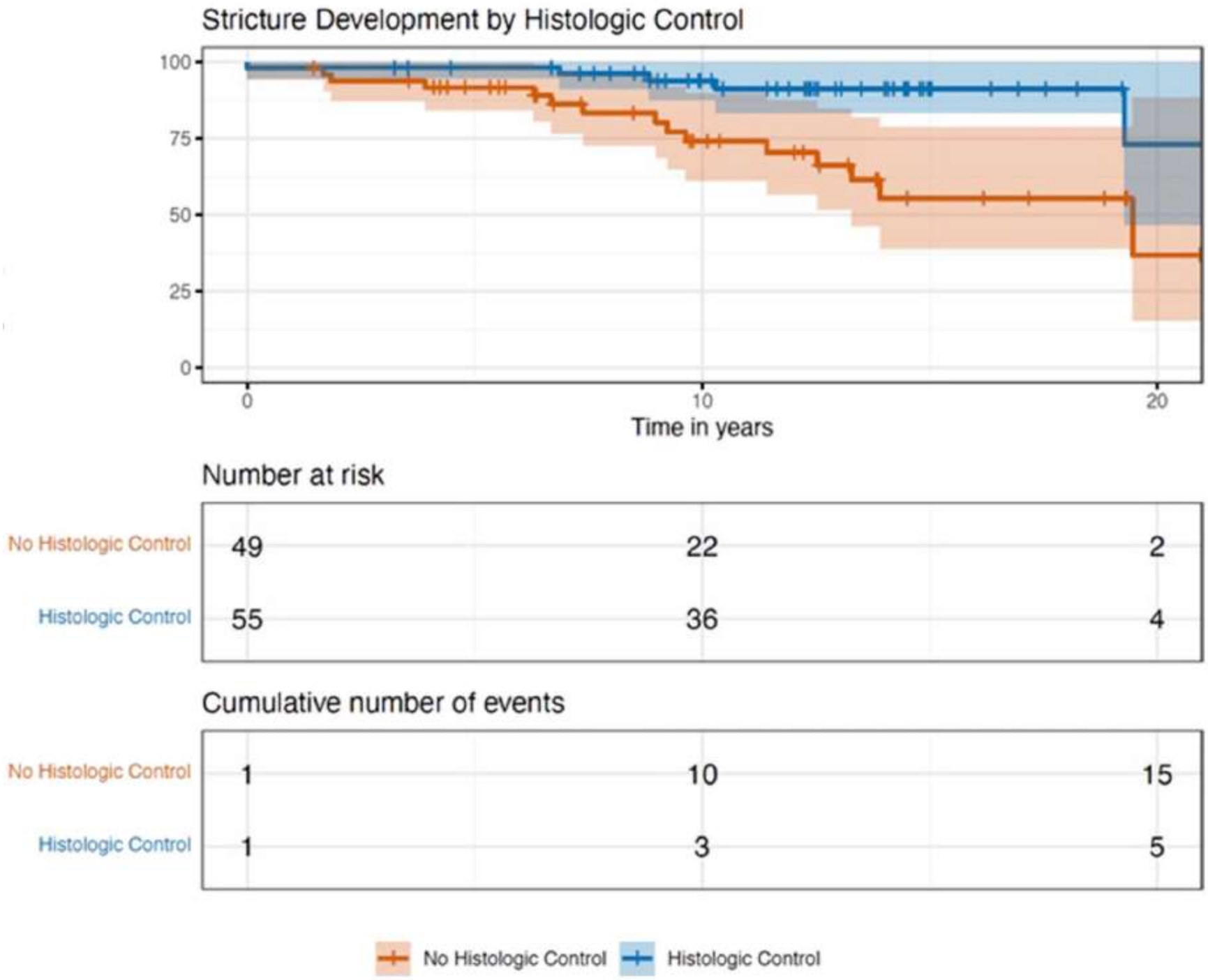
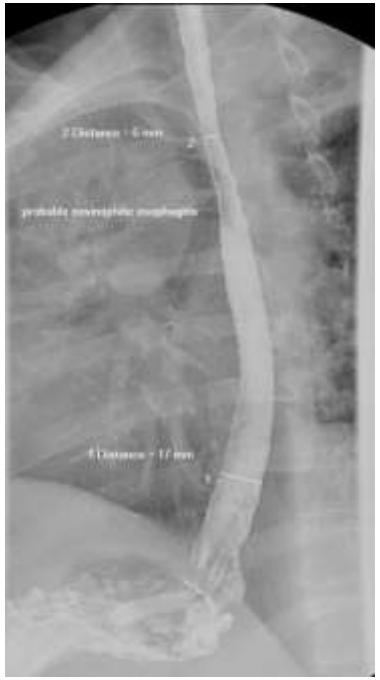
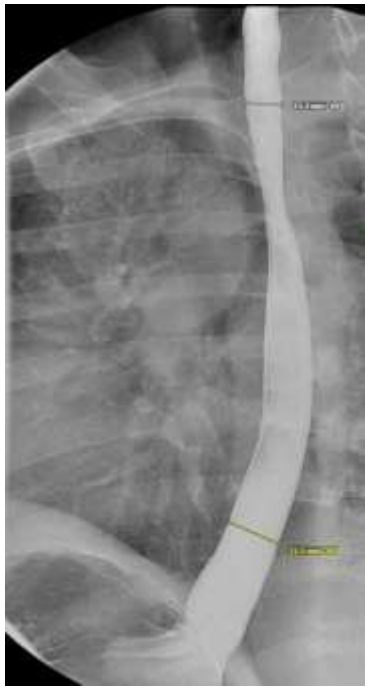



Starling et al. Am J Gastroenterol 2024;119:2002–2009

# Course of Esophageal Strictures in Eosinophilic Esophagitis Using Structured Esophagram Protocol



31 months
On Treatment

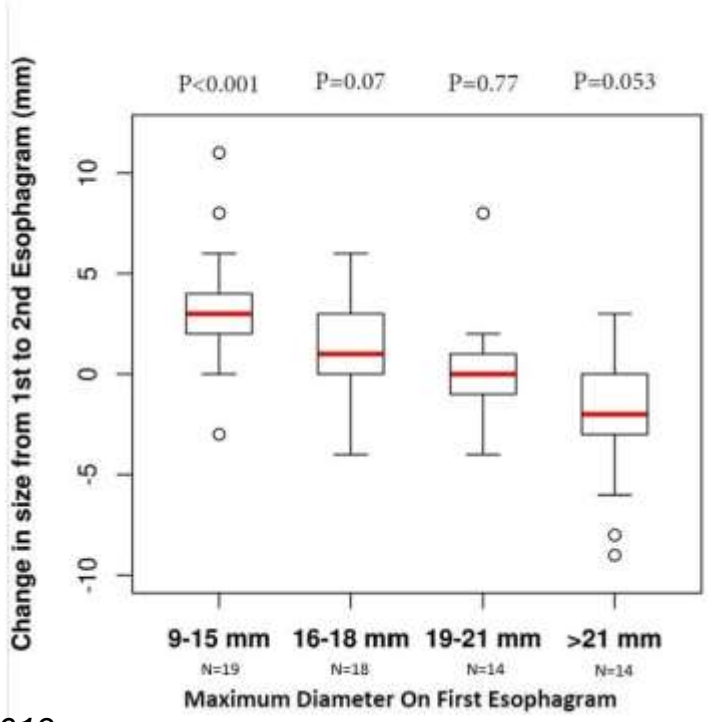


Median Maximum Diameter Change Per Year, mm (IQR)

- Active Disease: 0.0 (-0.4-0.6)
- Inactive Disease: 0.8 (0.0-5.3)

2.6 years

*P=.019*




Snyder et al., GastroHepAdv (in press)

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# Summary of EoE Present and Future

- EoE will continue to increase worldwide including Asia
- The etiology is unclear but likely multifactorial  including genetic, allergic, microbial and iatrogenic origins
- Diet therapy will become more attractive with a one food elimination diet
- Therapies will continue to emerge as we further dissect the pathways
- Lifelong maintenance treatment is suggested and will be tailored based on the identification of severity and prognostic phenotypes.