Esofagite Eosinofila
diagnosi e novità terapeutiche

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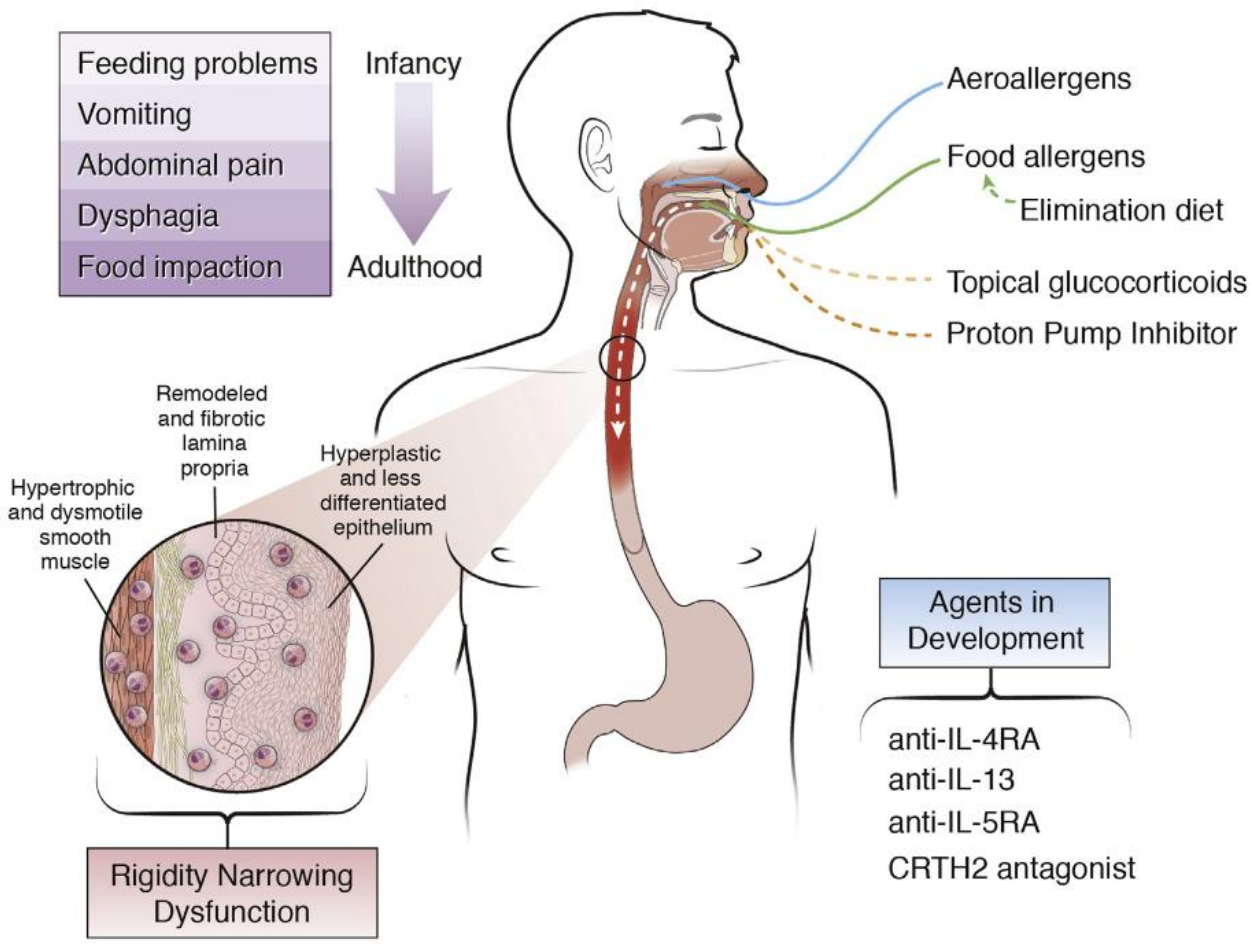
EUREOS
European Society of Eosinophilic Oesophagitis

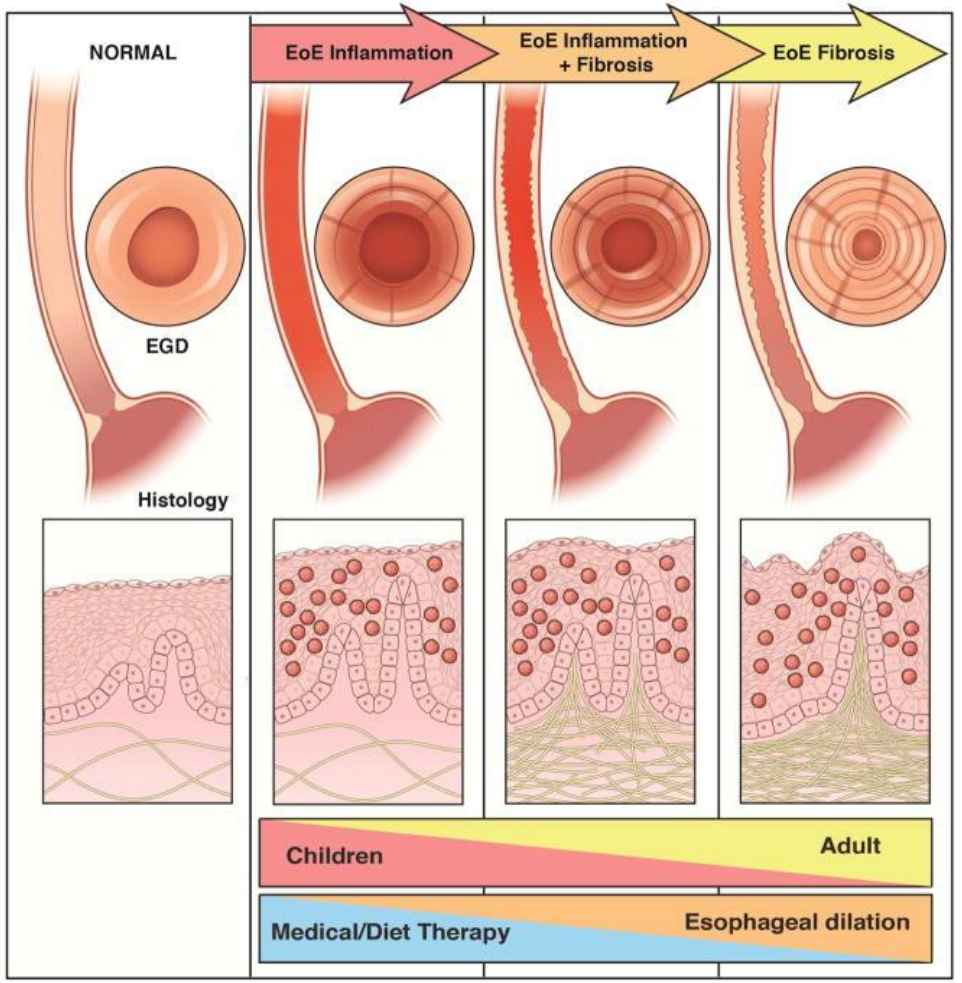
REGIONE DEL VENETO
Azienda Ospedale Università Padova

Disclosure

Sanofi, Dr FALK pharma, Ag Pharma, Aboca, Alfasigma, Stethos, Global Port LLC – Infomedica, Malesci

Definition





Eosinophilic esophagitis is a chronic, progressive, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.

O'Shea et al. Gastroenterology 2018
Dellon & Hirano, Gastroenterology 2018

Clinical Gastroenterology and Hepatology 2023;21:3270–3284

ESOPHAGUS

Global Incidence and Prevalence of Eosinophilic Esophagitis, 1976–2022: A Systematic Review and Meta-analysis

Check for updates

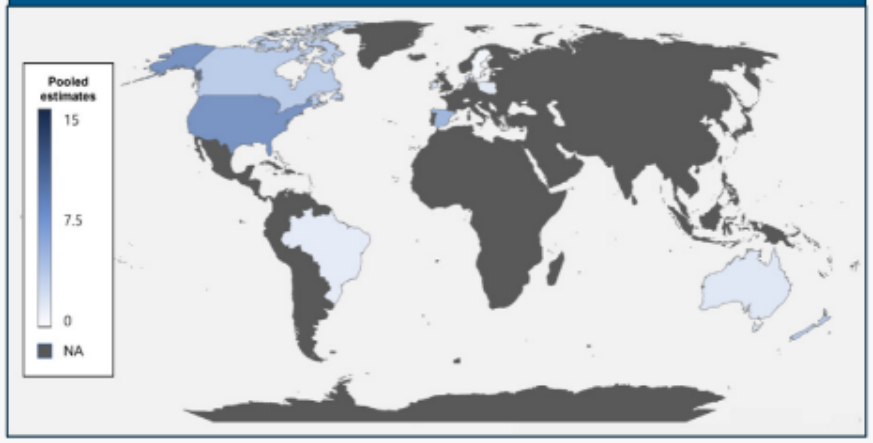
Global incidence and prevalence of eosinophilic esophagitis (EoE), 1976-2022

Systematic review
Meta-analysis

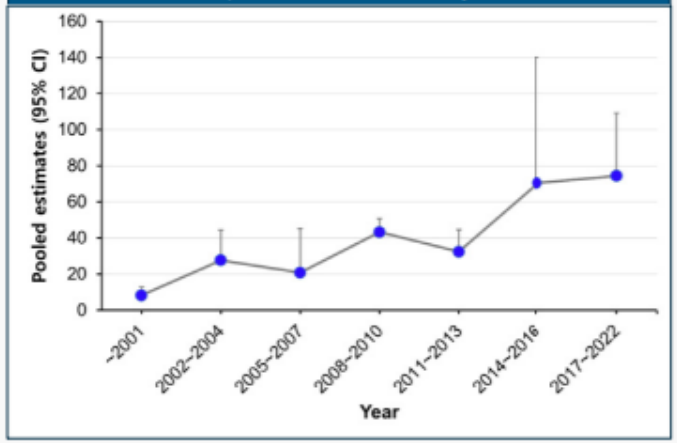
288 million participants

147,668 patients with EoE

Global map
15 countries across the five continents



Time trends of prevalence of EoE
cases per 100,000 inhabitant-years



- **Global incidence of EoE: 5.31 (95% CI, 3.98–6.63)** cases per 100,000 inhabitant-years
- **Global prevalence of EoE: 40.04 (95% CI, 31.10–48.98)** cases per 100,000 inhabitant-years

Clinical Gastroenterology and Hepatology

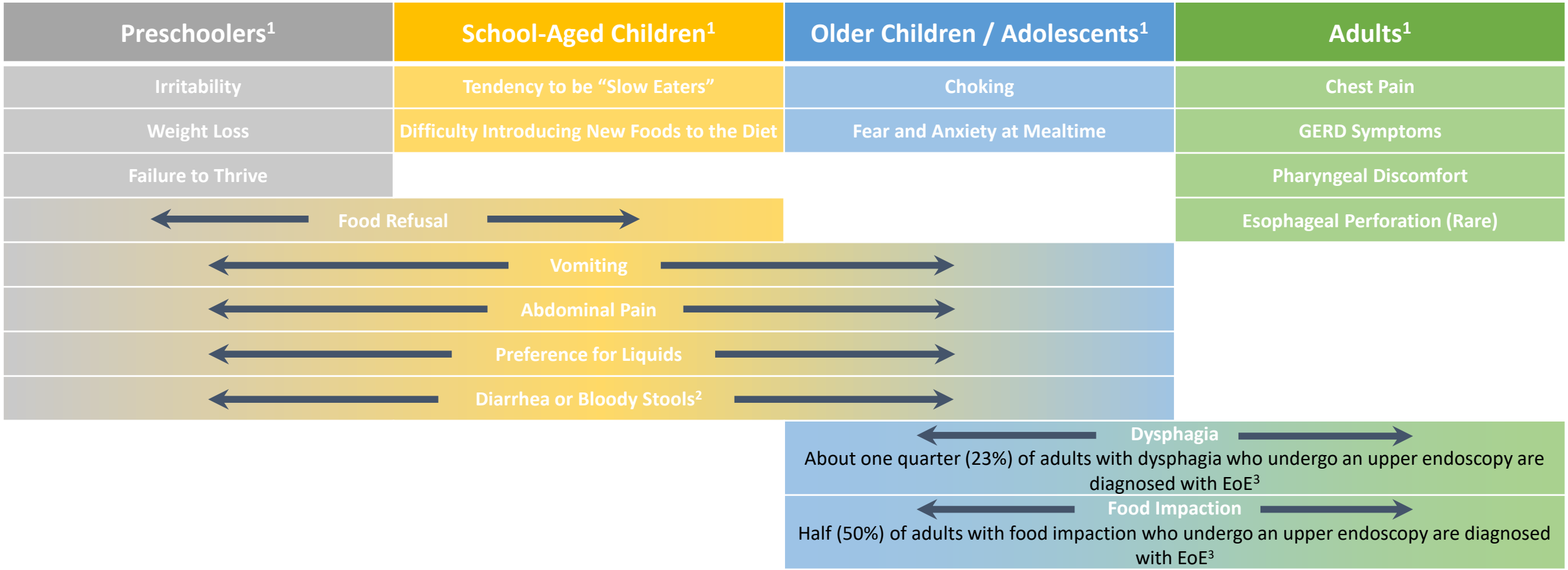
40 studies
288 million participants
147K EoE patients
15 countries
five continents

2nd cause of chronic esophagitis and 1st of dysphagia and food impaction

Men : Women = 3 : 1

Years at diagnosis <35yo

EoE Symptoms Vary Significantly Between Age Groups



1. Gomez Torrijos E, et al. *Front Med.* 2018;5:247. 2. Chehade M, et al. *J Allergy Clin Immunol Pract.* 2018; 6(5):1534–1544.e5. 3. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5(3):335–358.

Dysphagia/food impaction is often underreported due to patients unknowingly developing adaptive eating behaviours that mask EoE symptoms resulting in diagnostic delays[1,2]

I Imbibe fluids with meals[1]

M Modify food (cut into small pieces, puree)[1]

P Prolong mealtimes[1]

A Avoid textured food, such as meat and bread[1]

C Chew excessively[1]

T Turn away tablets/pills[1]

S Social avoidance[3]

What questions do you ask your patients in order to identify EoE symptoms and uncover adaptive behaviours, such as social avoidance?

Important both at diagnosis and when assessing treatment response

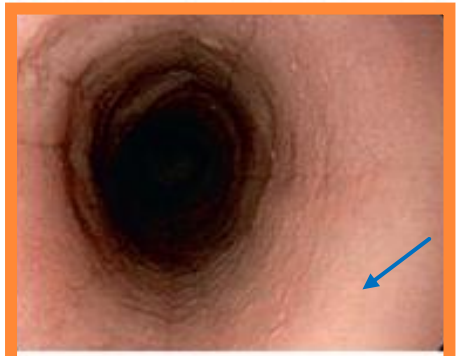
1. Hirano I, Furuta GT. *Gastroenterology*. 2020;158(4):840-851. 2. Muir AB, et al. *Clin Exp Gastroenterol.* 2019;12:391-399.
3. Rooij WE, et al. *J Neurogastroenterol Motil.* 2022;28(3):390-400.

Endoscopia: EoE-EREFS

Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS)[1]

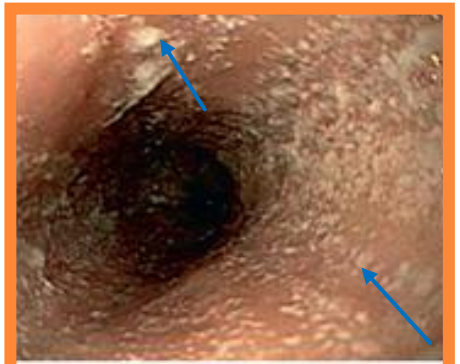
Un tool convalidato per determinare la presenza e la gravità di 5 reperti endoscopici durante le procedure endoscopiche[2]

Grado di severità[1,3]:
- Edema (0-1)
- Anelli (0-3)
- Essudati (0-2)
- Solchi (0-1)
- Stenosi (0-1)

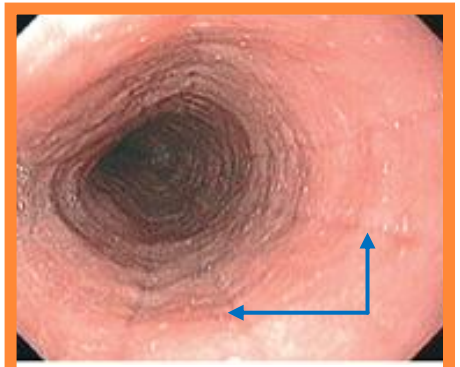


Edema
Diminuzione dei segni vascolari

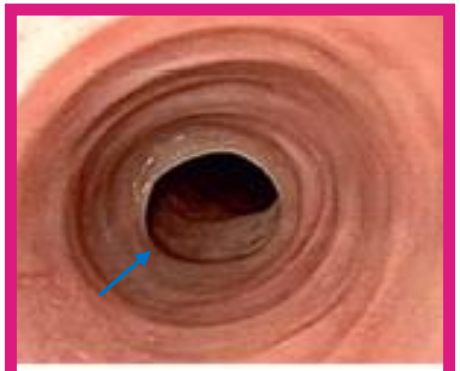
Rings
Creste circonferenziali ondulate



Exudates
Papule biancastre, placche



Furrows
Linee verticali,solchi longitudinali



Stricture
Restringimento esofageo

Caratteristiche dell'infiammazione attiva[4]

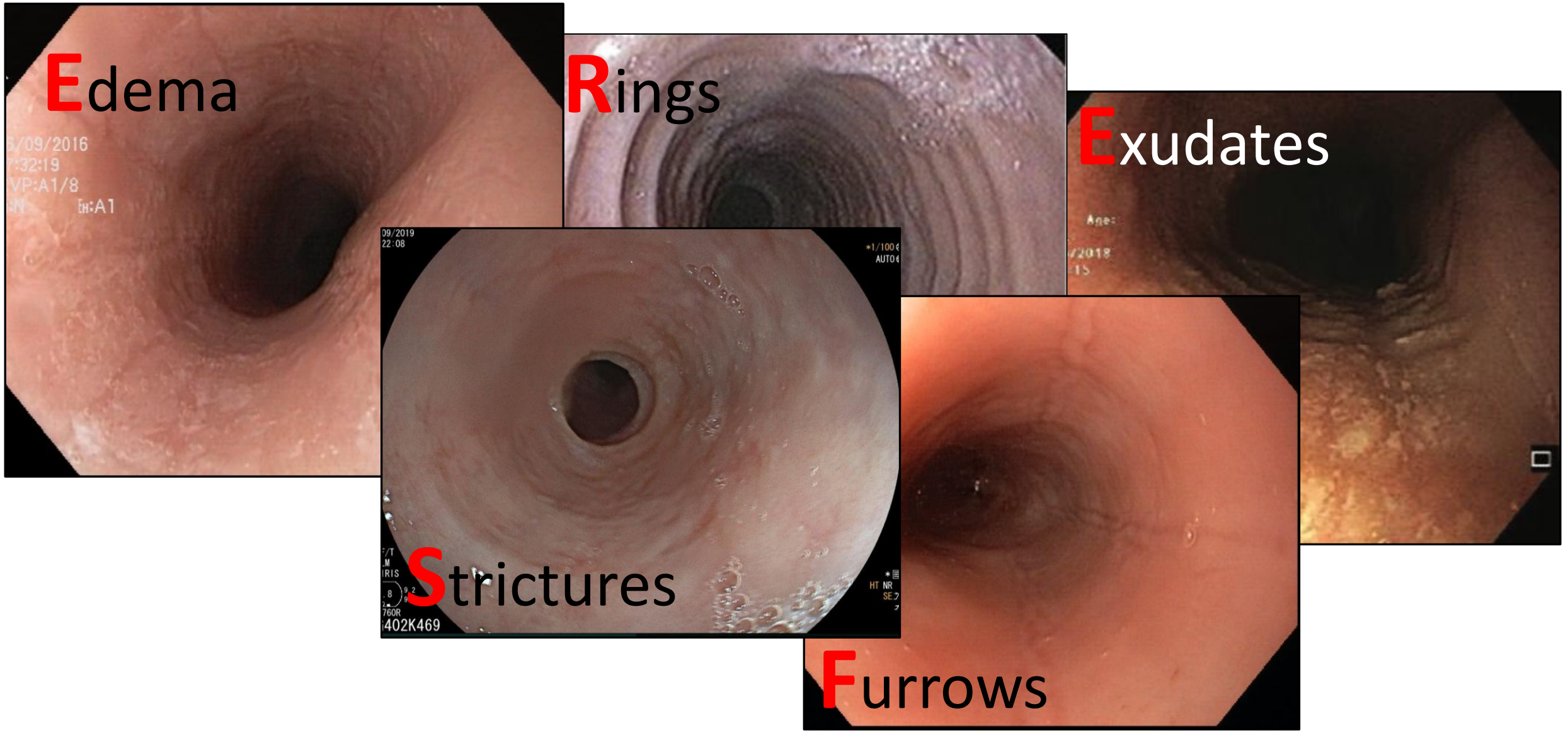
Caratteristiche dell'attività fibrotica[4]

I risultati endoscopici da soli non stabiliscono in modo affidabile una diagnosi di EoE e richiedono una valutazione dell'eosinofilia esofagea con le biopsie[2,5]

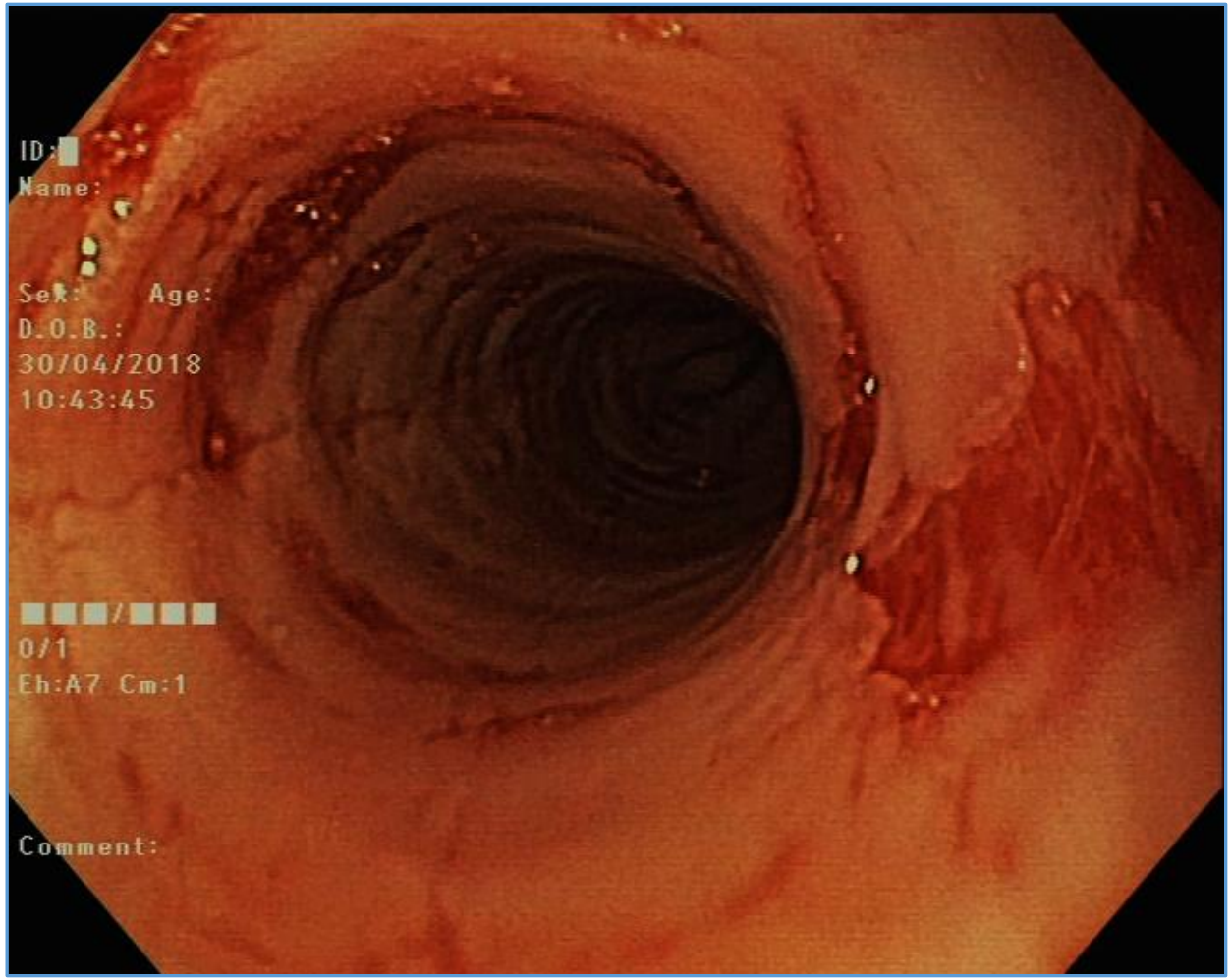
EoE, eosinophilic esophagitis.

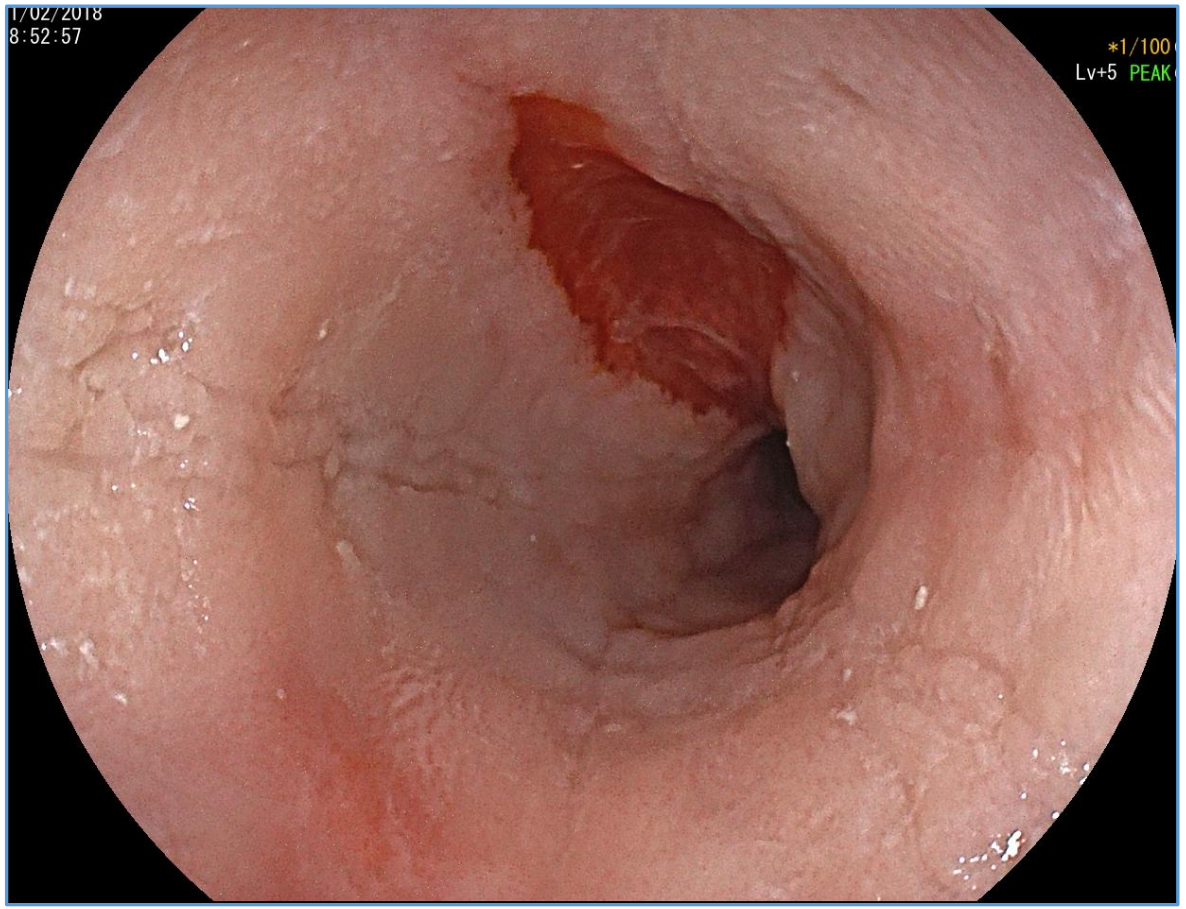
1. Hirano I, et al. *Gut*. 2013;62(4):489-495. 2. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5(3):335-358. 3. Hirano I. *Dig Dis*. 2014;32(1-2): 78-83. 4. Schoepfer AM, et al. *Gastroenterology*. 2013;145(6):1230-1236.
5. Dellon ES, et al. *Gastroenterology*. 2018;155(4):1022-1033.

Endoscopy – EREFS score

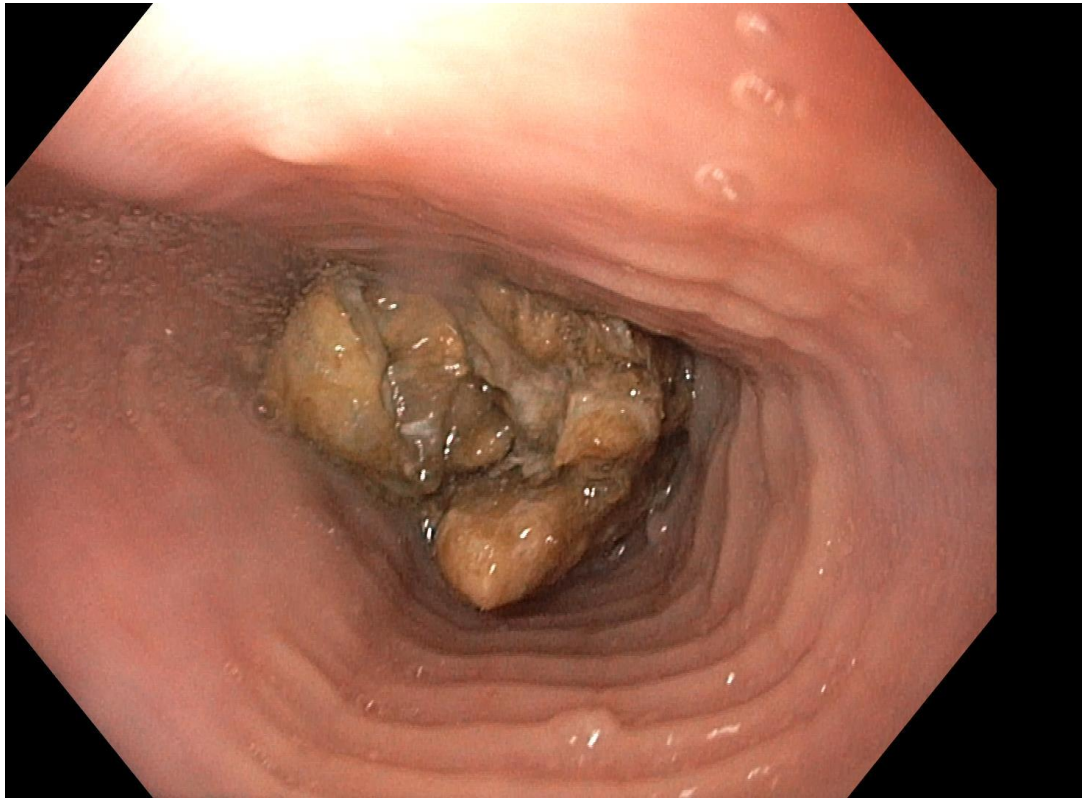


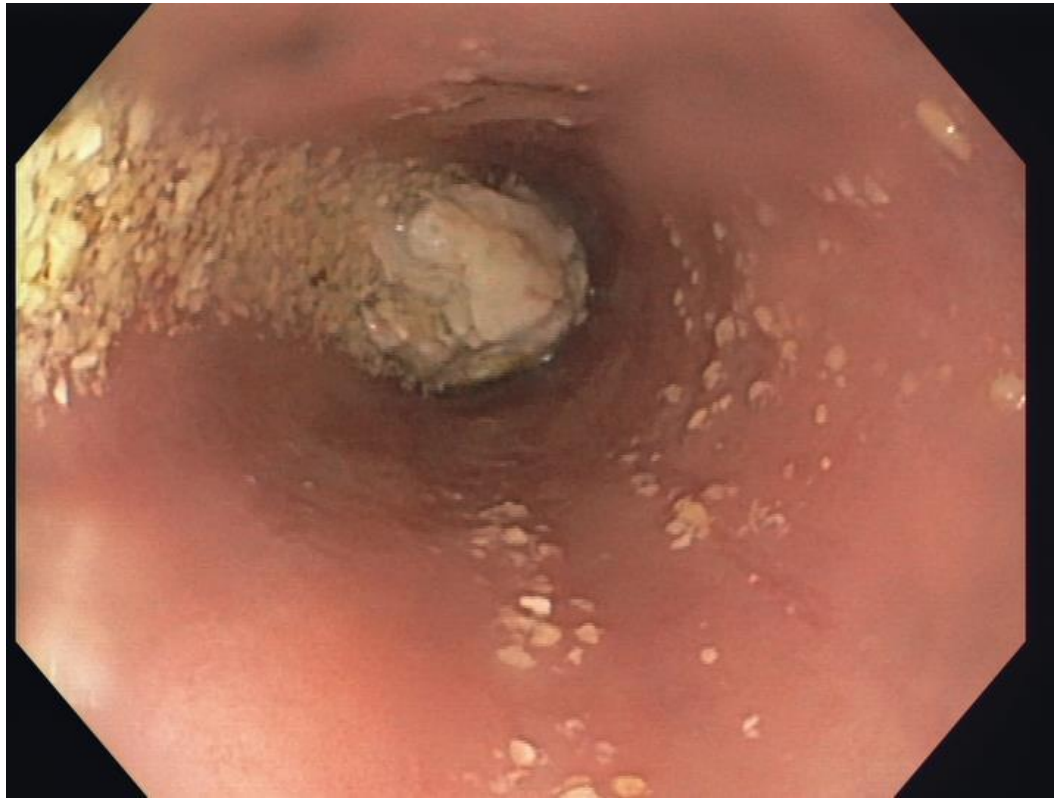
Crêpe-paper mucosa





Bolus impaction



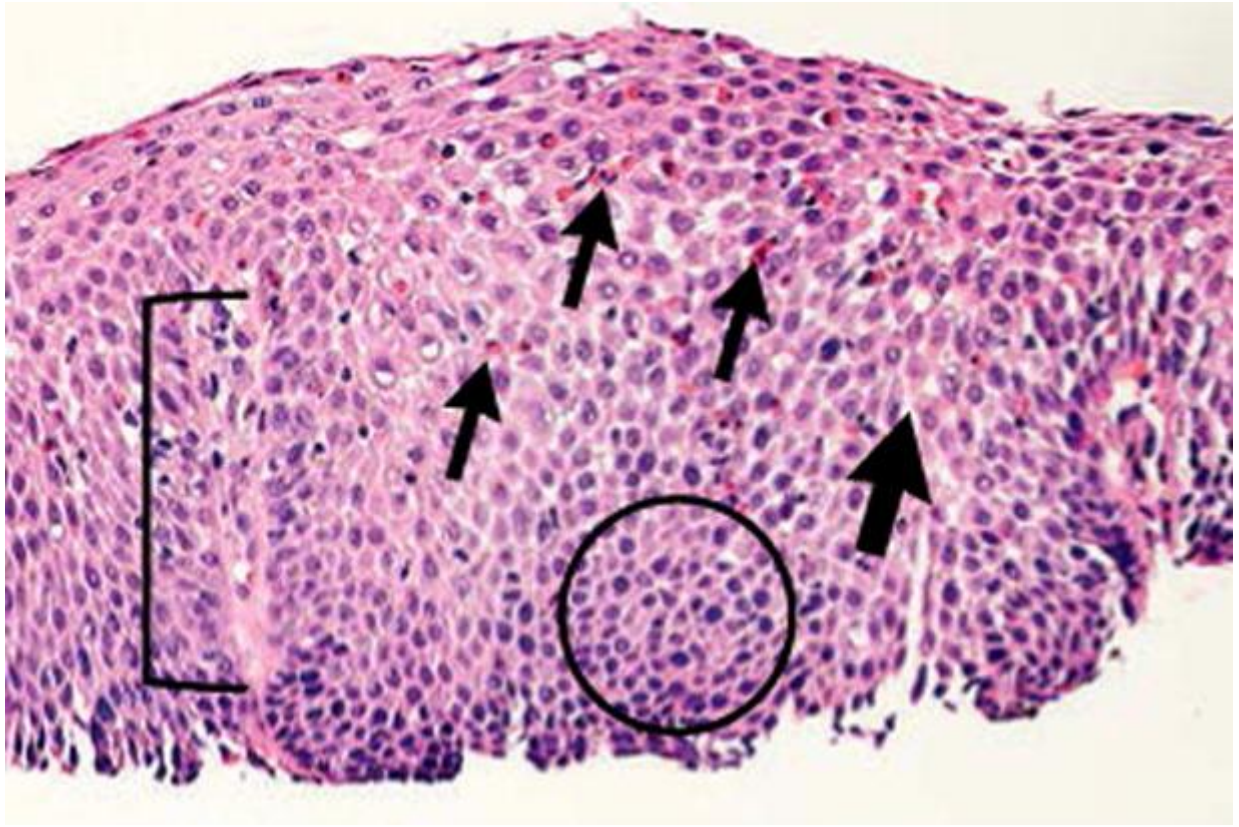


Histology

- Eosinophil infiltrated (≥ 15 eos/hpf)
- Eosinophili microabscess
- Superficial layering of eosinophils
- Dilated intercellular spaces (spongiosis)
- Extracellular eosinophil granules
- Basal zone hyperplasia
- Rete peg elongation
- Lamina propria fibrosis

What is the appropriate biopsy protocol for diagnosing and monitoring EoE?. **Statement 13:** At least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities.

LE: Moderate; **SR:** Strong in favor. **Agreement:** 100%, votes: strongly agree (100%).



Lucendo AJ, et al. UEG EoE guidelines 2017

Furuta GT, Katzka DA. N Engl J Med. 2015

EoE Diagnosis Requires a Comprehensive Assessment

EoE diagnostic criteria and algorithm[1]

Clinical presentation suggestive of EoE

Severity of symptoms varies considerably between patients and with age and duration of disease[1-4]

Endoscopic findings and coexisting type 2 inflammatory diseases are common[1]

Symptoms alone are not accurately correlated with histological disease activity[5-8]

↓ **Upper endoscopy with biopsy**

Esophageal eosinophilia

needed, from at least 2 different locations in the esophagus, typically in the distal and proximal halves of the esophagus[9]

Required for esophageal eosinophilia determination[1,10]

↓ **Evaluate for non-EoE disorders that cause or potentially contribute to EoE**

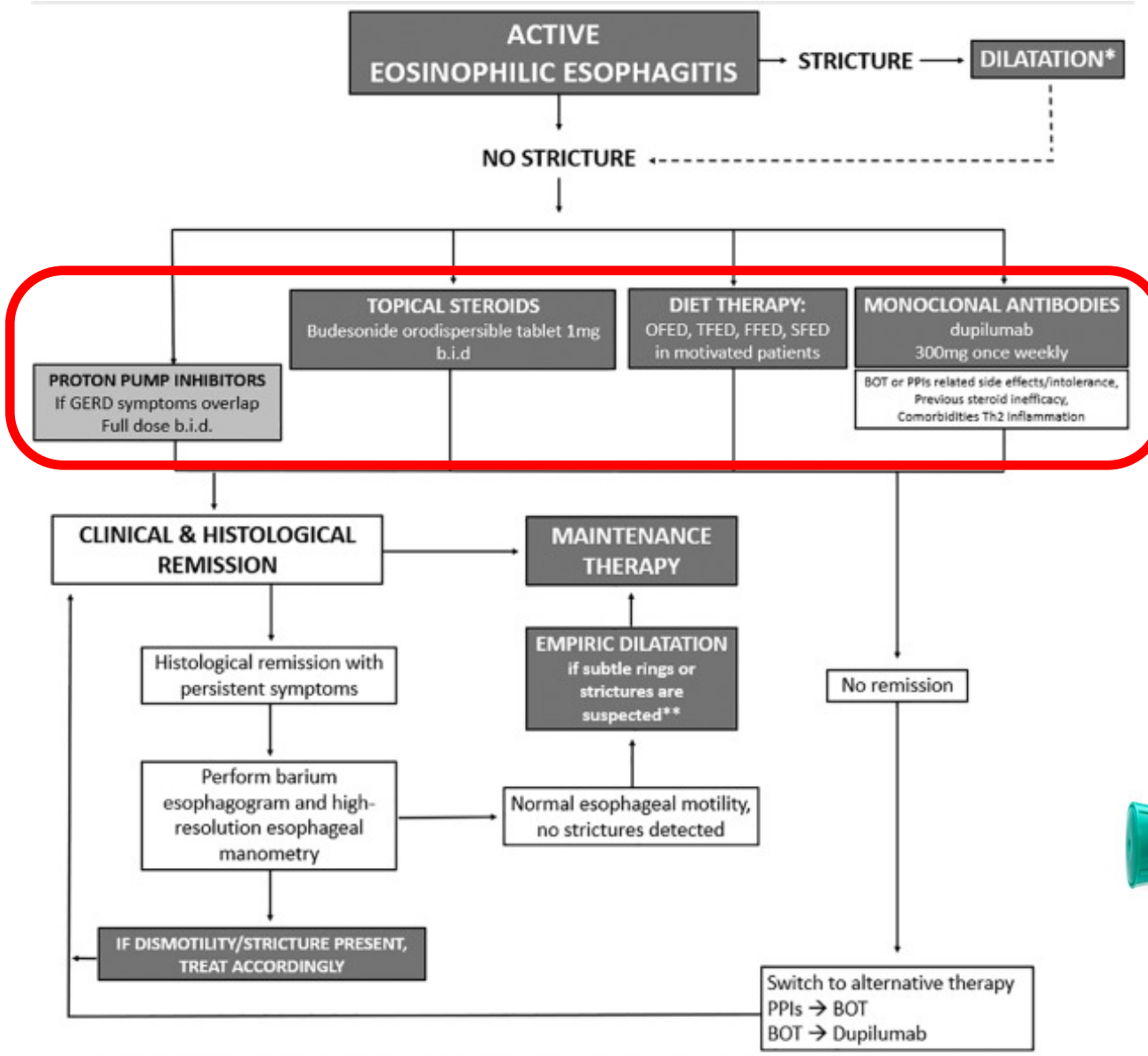
Eosinophilic esophagitis diagnosis

Diagnosis requires assessment of non-EoE disorders (eg, GERD, achalasia, Crohn's disease) that may contribute to esophageal eosinophilia[1,11]

EoE symptoms overlap with other GI disorders, which must be ruled out before a diagnosis is made[1,11]

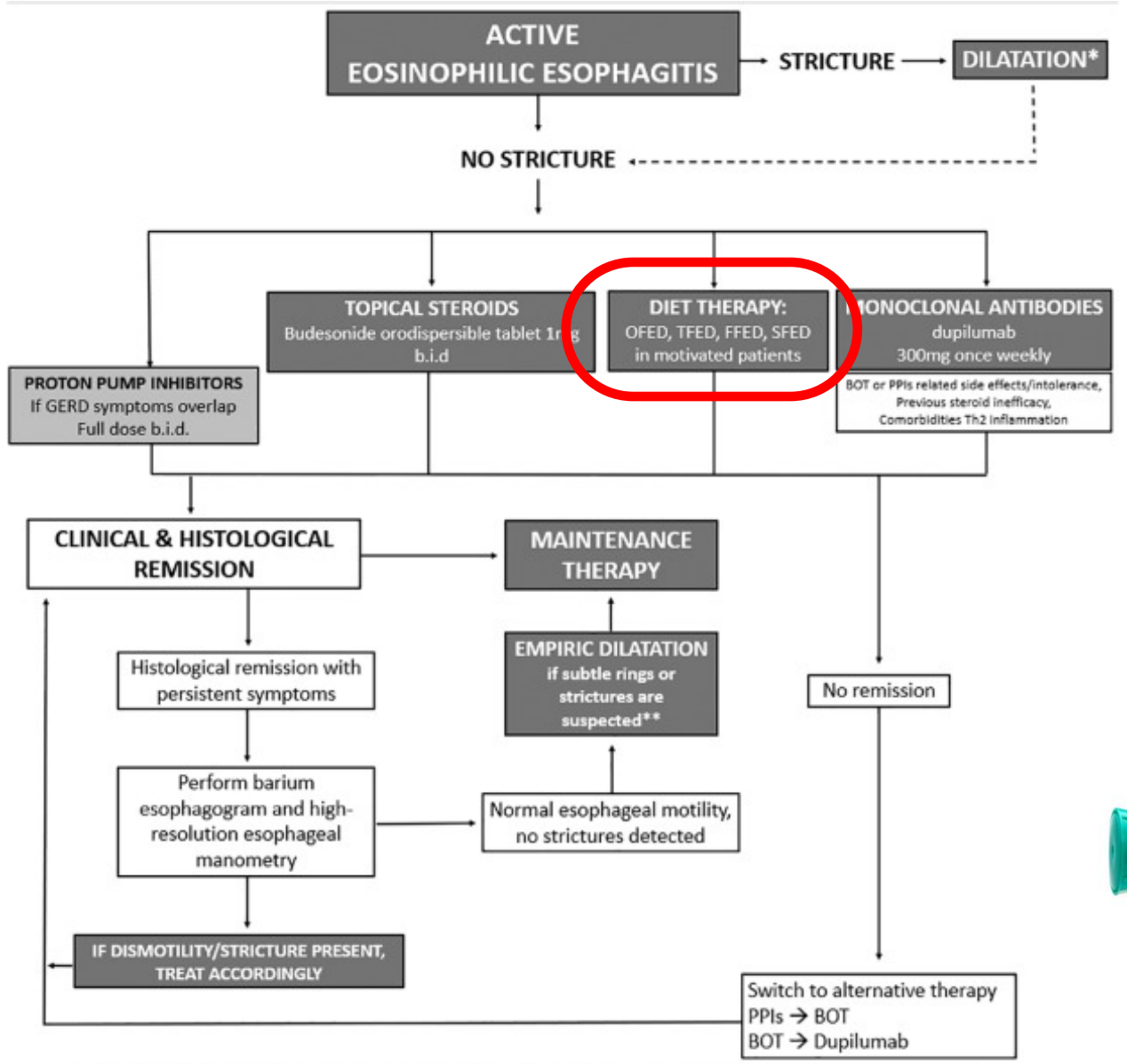
eos/hpf, eosinophils per high power field; GERD, gastroesophageal reflux disease; GI, gastrointestinal.

1. Dellon ES, et al. *Gastroenterology*. 2018;155(4):1022-1033. 2. Dellon ES, et al. *Clin Gastroenterol Hepatol*. 2009;7(12):1305-1313. 3. Enns R, et al. *Can J Gastroenterol.* 2010;24(9):547-551. 4. Spergel JM, et al. *J Pediatr Gastroenterol Nutr*. 2009;48(1):30-36. 5. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5(3):335-358. 6. Pentiuk S, et al. *J Pediatr Gastroenterol Nutr*. 2009;48(2):152-160. 7. Straumann A, et al. *Gastroenterology*. 2010;139(5):1526-1537. 8. Alexander JA, et al. *Clin Gastroenterol Hepatol*. 2012;10(7):742-749. 9. U.S. Department of Health and Human Services. FDA. CDER. 2019. 10. Nielsen JA, et al. *Am J Gastroenterol*. 2014;109(4):515-520. 11. Dellon ES, et al. *Am J Gastroenterol*. 2013;108(5):679-692. 12. Lucendo AJ, et al. *Clin Gastroenterol Hepatol*. 2016;14(1):13-22. 13. Davis BP. *Clin Rev Allergy Immunol*. 2018;55(1):19-42.



*If clinically viable, the achievement of histological remission before proceeding to esophageal dilatation is advisable
**Assessment of poor esophageal distensibility by means of esophageal panometry before dilatation is advisable

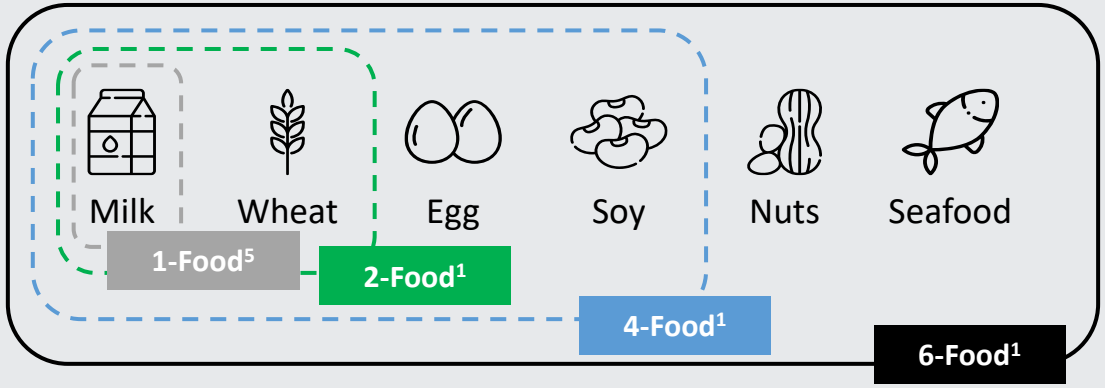
De Bortoli, Visaggi et al DLD 2024



De Bortoli, Visaggi et al DLD 2024

Empiric Elimination Diet Requires Strict Adherence

6, 4, 2, and 1-food elimination diets aim to eliminate the most common food allergens[1–3]



6-FED induces histological remission in 74% of patients[1]

4-FED induces histological remission in 50% of patients[1]

2-FED induces histological remission in 40% of patients[1]

1-FED induces histological remission in 34% of patients[3]

Limitations[4–6]

Repeat endoscopies are required after the reintroduction of each food	Increased risk of developing de-novo IgE-mediated food allergy upon food reintroduction
Dietary restrictions can limit long-term adherence to the diet	Large time commitment

FED, food elimination diet.

1. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5(3):335–358. 2. Wang R, et al. *Dig Dis Sci*. 2018;63(7):1756–1762. 3. Kliewer K, et al. *Gastroenterology*. 2021;160(6):S-109–S-110. Abstract Presented at DDW. 4. Molina-Infante J, et al. *J Allergy Clin Immunol.* 2018;141(4):1365–1372. 5. Gonsalves N. *Gastroenterol Hepatol*. 2015;11(4):267–276. 6. Hirano I, et al. *Gastroenterology*. 2020; 158:1776–1786.

Allergy-Based Elimination Diet May Not Accurately Predict Food Triggers

Elimination of foods testing positive in a skin-prick or patch test for the food allergen[1]

Skin-prick test*

Patch test*

Development of optimal allergy testing methods for the identification of food triggers in EoE is an area of active investigation[3,4]

Induce histologic remission in 30% of adult patients[2]

Induce histologic remission in <50% of pediatric patients[2]

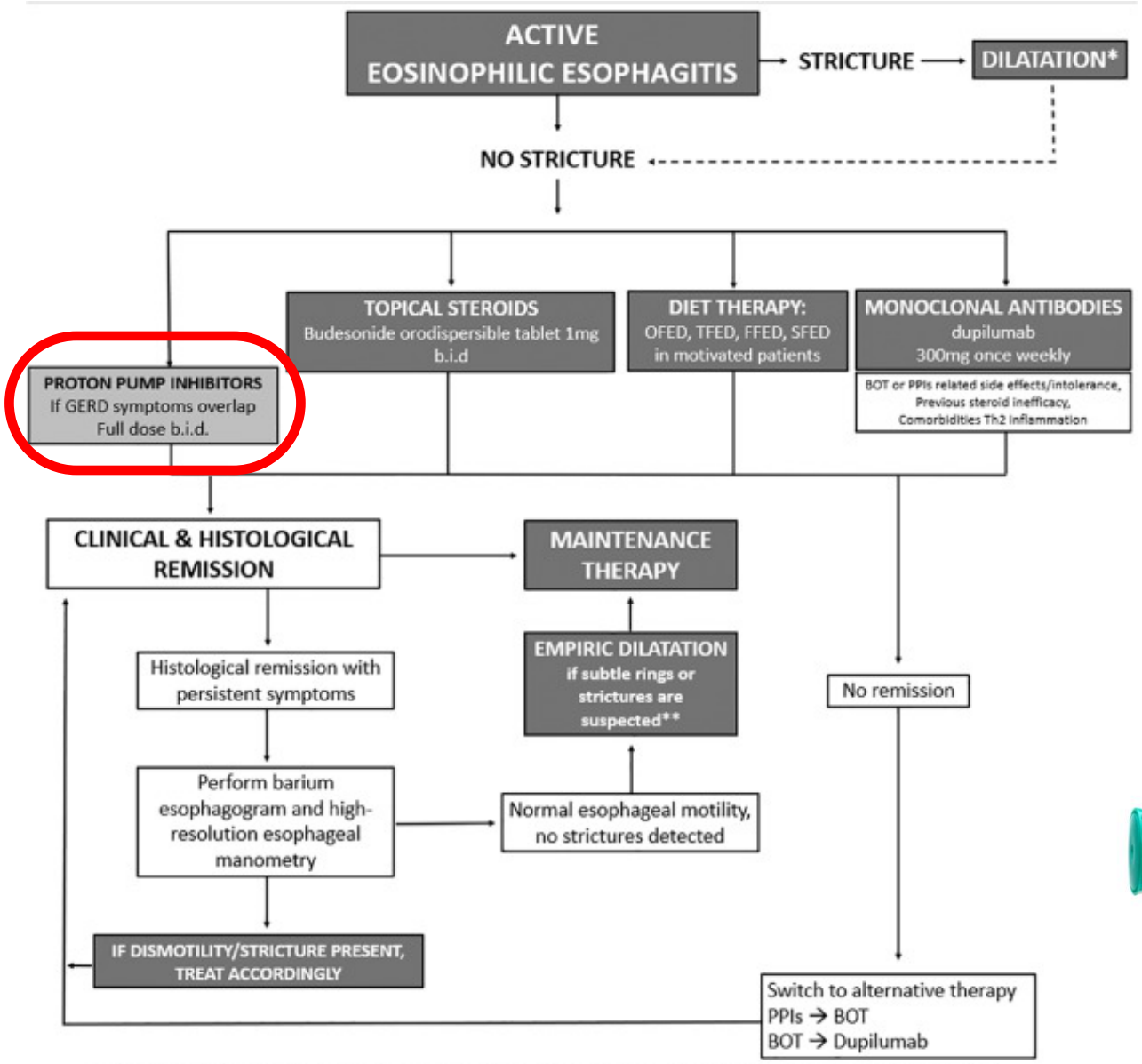
Limitations

Allergy tests are IgE based and they may not accurately predict actual food triggers as EoE is primarily non-IgE mediated[2-5]

*allergy-based skin prick and patch testing may not always identify foods which exacerbate EoE.

IgE, immunoglobulin E.

1. Gómez-Aldana A, et al. *World J Gastroenterol*. 2019;25(32):4598–4613. 2. Lucendo AJ, et al. *United European Gastroenterol J*. 2017;5(3):335–358. 3. Gonsalves N. *Gastroenterol Hepatol*. 2015;11(4):267–276. 4. Spergel J, et al. *J Allergy Clin Immunol* 2002;109:363–368. 5. Barbosa AC, et al. *J Allergy Clin Immunol Pract*. 2018;6(2):451–456.e1.



De Bortoli, Visaggi et al DLD 2024

SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis

Alfredo J. Lucendo,* Ángel Arias,‡ and Javier Molina-Infante§

- 33 studies (619 patients);
- Histological remission on PPI therapy (<15 eos/hpf) is 50.5% (95% CI 42.2-58.7%) symptom improvement 60.8% (95% CI 42.2-58.7%)

Lucendo AJ et al. Clin Gastroenterol Hepatol. 2016

ORIGINAL ARTICLE

ueg journal WILEY

Effectiveness of PPI treatment and guideline adherence in 236 patients with eosinophilic oesophagitis—Results from the population-based DanEoE cohort shows a low complication rate

-236 adult EoE from the North Denmark Region.
-68% completely symptom-free. 49% in histological remission

Frandsen *et al. UEGJ 2021*

APT Alimentary Pharmacology & Therapeutics WILEY

Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry

- 630 patients (76 children)
- Histological remission on PPI therapy (<15 eos/hpf) 48.8%, symptom improvement 71.0%

Laserna-Mendieta et al. APT 2020

Twice-Daily Proton Pump Inhibitor Induces Higher Remission Rate in Eosinophilic Esophagitis Than Once-Daily Regimen Regardless of Total Daily Dose

Muftah, Mayssan MD, MPH[1,2,*]; Goldin, Alison H. MD, MPH[1,2,*]; Barshop, Kenneth MD[2,3]; Hsu Blatman, Karen MD[2,4]; Hamilton, Matthew J. MD[1,2]; Lo, Wai-Kit MD, MPH[1,2]; Hornick, Jason L. MD, PhD[2,5]; Chan, Walter W. MD, MPH, FACG[1,2]

Author Information

The American Journal of Gastroenterology 119(5):p 991-995, May 2024. | **DOI:** 10.14309/ajg.0000000000002712

-305 patients

-Treatments: omeprazole 20 or 40 mg daily vs 20 or 40 mg twice-daily, for ≥8 weeks.

-42.3% achieved histologic response to PPI, with higher rates for twice-daily (moderate 52.8%/high 54.3%) than once-daily (standard 11.8%/moderate 10%) dosing ($P < 0.0001$).

Mayssan et al AJG 2024

- A trend towards increased efficacy was observed when PPI was administered among patients with a pathological pH monitoring (65.4% vs 49.3%)
- Duration of at least 8weeks even if extending up to 12 wks provides higher remission rates (OR 2.7; 95% CI, 1.5-5.3)
- Patients with an inflammatory rather than stricturing phenotype are more likely to achieve remission with PPI (OR, 3.7; 95% CI, 1.5-5.3)

Lucendo AJ et al. Clin Gastroenterol Hepatol. 2016
Laserna-Mendieta et al. Clin Gastroenterol Hepatol. 2020

ACTIVE EOSINOPHILIC ESOPHAGITIS → STRICTURE → DILATATION*

NO STRICTURE

TOPICAL STEROIDS
Budesonide orodispersible tablet 1mg b.i.d

DIET THERAPY:
OFED, TFED, FFED, SFED in motivated patients

MONOCLONAL ANTIBODIES
dupilumab
300mg once weekly
BOT or PPIs related side effects/intolerance, Previous steroid inefficacy, Comorbidities Th2 inflammation

PROTON PUMP INHIBITORS
If GERD symptoms overlap
Full dose b.i.d.

CLINICAL & HISTOLOGICAL REMISSION

MAINTENANCE THERAPY

Histological remission with persistent symptoms

EMPIRIC DILATATION
if subtle rings or strictures are suspected**

Perform barium esophagogram and high-resolution esophageal manometry

Normal esophageal motility, no strictures detected

No remission

IF DISMOTILITY/STRICTURE PRESENT, TREAT ACCORDINGLY

Switch to alternative therapy
PPIs → BOT
BOT → Dupilumab

*If clinically viable, the achievement of histological remission before proceeding to esophageal dilatation is advisable
**Assessment of poor esophageal distensibility by means of esophageal panometry before dilatation is advisable

De Bortoli, Visaggi et al DLD 2024

Swallowed topical steroids

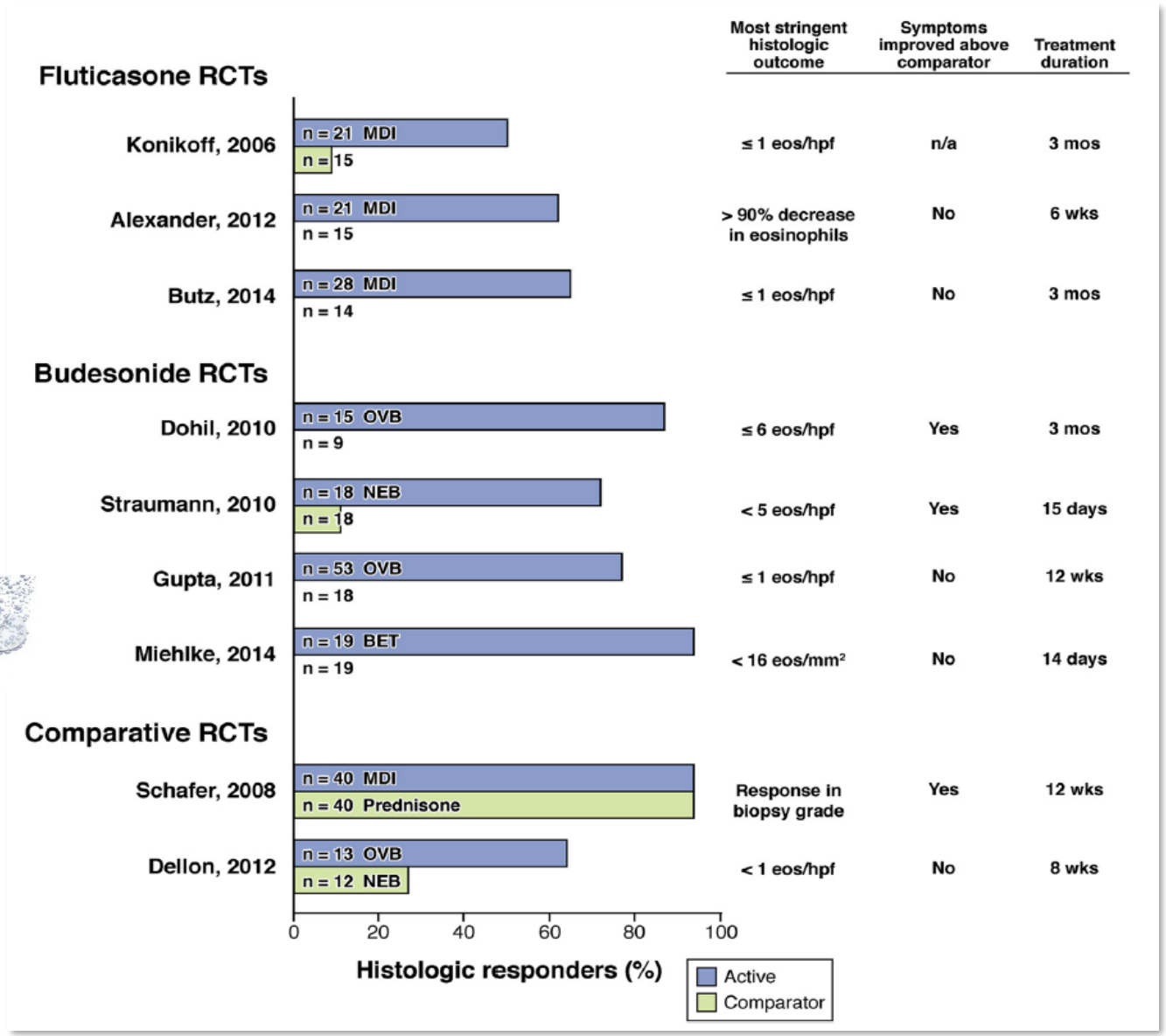
Topical swallowed corticosteroids
Initial doses (see references for preparation and administration information)
Fluticasone (puffed and swallowed through a metered-dose inhaler)
Adults: 440-880 μg twice daily
Children: 88-440 μg twice to 4 times daily (to a maximal adult dose)
Budesonide (as a viscous suspension)
Children (<10 y): 1 mg daily
Older children and adults: 2 mg daily
Systemic corticosteroids
For severe cases (eg, small-caliber esophagus, weight loss, and hospitalization)
Prednisone: 1-2 mg/kg

-FTC nebulized suspension (asthma drugs)
-BDS nebulized suspension (asthma drugs)
-BDS oral viscous suspension
-BDS orodispersible tablet

- Same effectiveness of oral prednisone with reduced bioavailability. No systemic effects (hyperphagia, weight gain, and/or cushingoid features)
- Esophageal candidiasis reported in 10% of patients. Adrenal insufficiency reported from uncontrolled observational studies, in a minority of patients.
- Systemic corticosteroids are not generally recommended in EoE.

Lucendo AJ, et al United European Gastroenterol J. 2017
Liacouras CA et al., J Allergy Clin Immunol 2011; 129:3–20
Philpott H, et al. Aliment Pharmacol Ther. 2018;47:1071–1078

Systemic and Topical Steroids in EoE



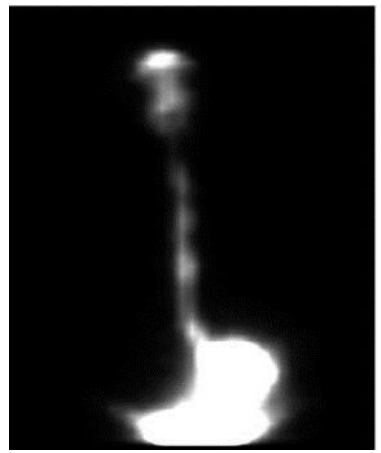
Dellon ES, et al. et al. Gastroenterology 2014;147:1238–1254

STCs compared: nebulized vs viscous

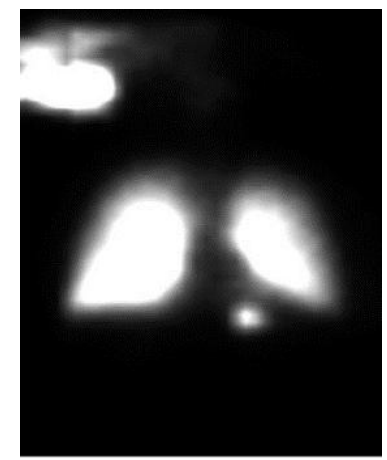
Viscous Topical is More Effective than Nebulized Steroid Therapy for Patients with Eosinophilic Esophagitis

Evan S. Dellon, MD MPH[1,2], Arif Sheikh, MD[3], Olga Speck, MD PhD[4], Kimberly Woodward, MD[4], Ann B. Whitlow, CNMT[3], Jessica M. Hores, BA[1], Marija Ivanovic, PhD[3], Allen Chau, CNMT[3], John T. Woosley, MD PhD[4], Ryan D. Madanick, MD[1,2], Roy C. Orlando, MD[1,2], and **Nicholas J. Shaheen, MD MPH[1,2]**

OVB



NEB



- 25 EoE pts, BDS 1 mg b.i.d. **NEB** vs **OVB**, for 8 weeks
- Lower post treatment eosinophils count in OVB (p=0.02)
- Scintigraphic-mesured mucosal-drug contact time was higher in OVB (p<0.005) and was inversely correlated with eosinophils count (R= −0.67; p=0.001)

E.S. Dellon, Gastroenterology. 2012 August ; 143(2): 321–324.e1

STCs compared: viscous vs orodispersible tablet

A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis

Stephan Miehlke,[1] Petr Hruz,[2] Michael Vieth,[3] Christian Bussmann,[4]

- 76 active pts, 2 weeks treatment: BET_1 (2mg/day), BET_2 (4mg/day), BVS (4mg/day), placebo
- **BET** and **BVS** both highly effective
- Safe treatments (local candida in 10% pts)
- 80% of patients prefer BET

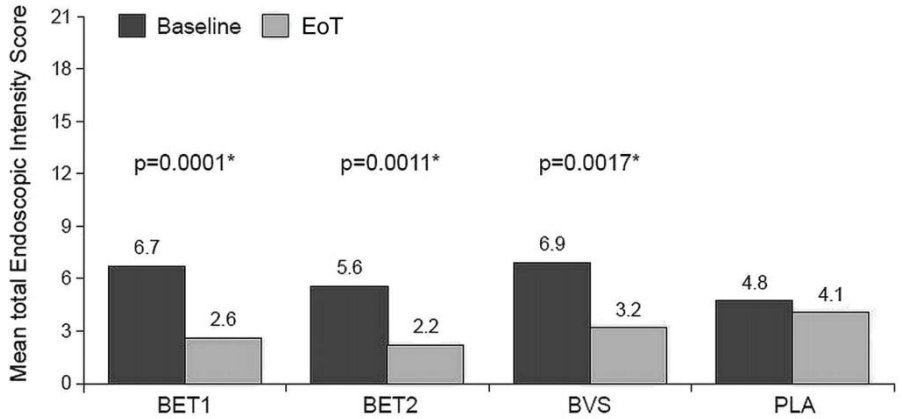


Figure 4 Total endoscopic intensity score (* vs change in placebo). BET1, effervescent tablets for orodispersible use 2×1 mg/day; BET2, effervescent tablets for orodispersible use 2×2 mg/day; BVS, budesonide viscous suspension 2×5 mL (0.4 mg/mL)/day; EoT, end of treatment; PLA, placebo.

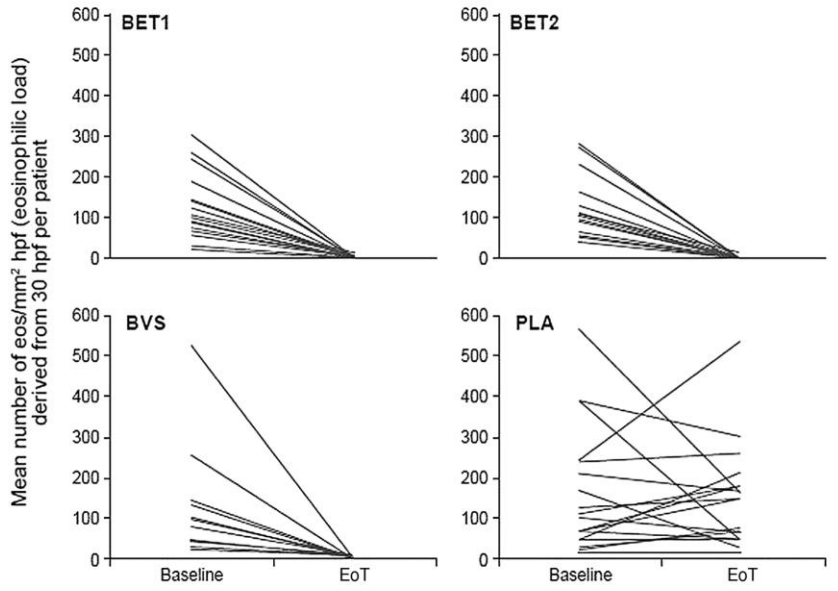
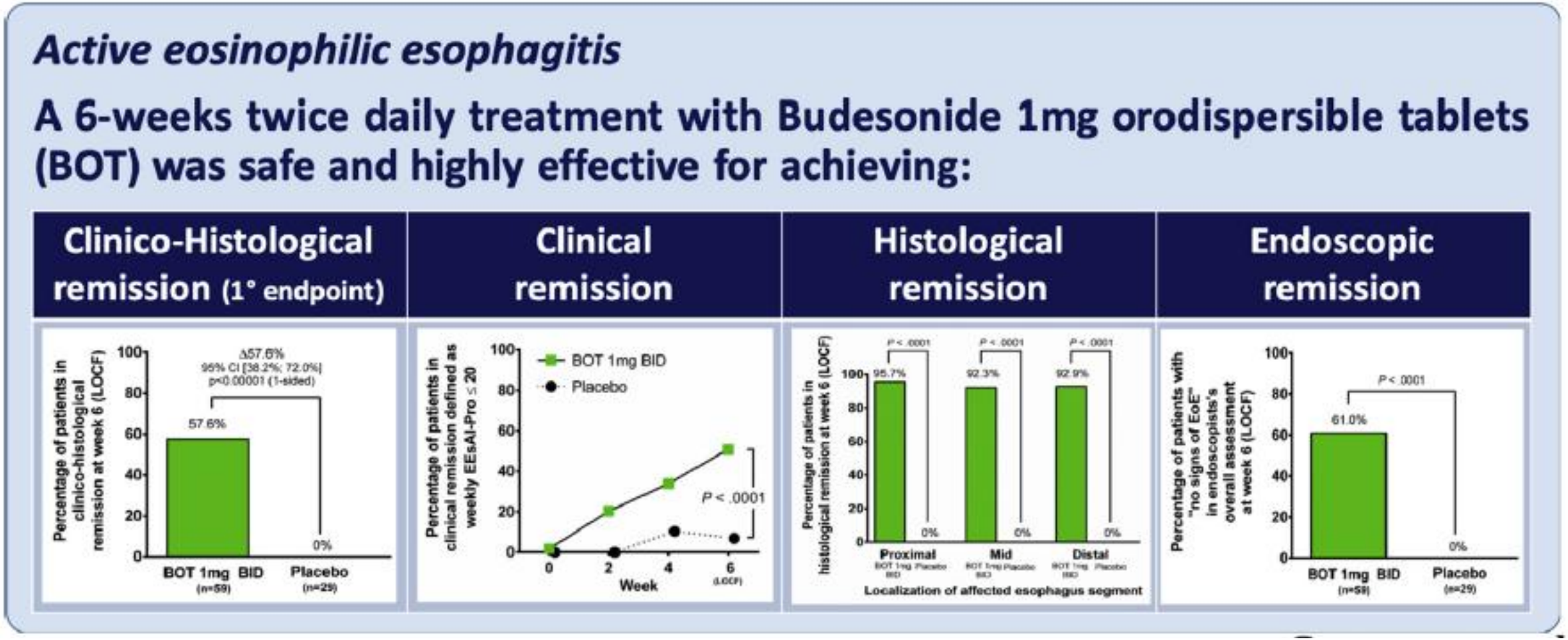


Figure 2 Effect of treatment on eosinophilic load. BET1, effervescent tablets for orodispersible use 2×1 mg/day; BET2, effervescent tablets for orodispersible use 2×2 mg; BVS, budesonide viscous suspension 2×5 mL (0.4 mg/mL)/day; EoT, end of treatment; PLA, placebo.

Miehlke S, Gut. 2016;65(3):390–399.

Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for EoE in a Randomized Placebo-Controlled Trial



The primary end point was complete remission, based on clinical and histologic factors, including dysphagia and odynophagia severity 2 on a scale of 0–10 on each of the 7 days before the end of the double-blind phase and a peak eosinophil count <5 eosinophils/high power field

N=88 EoE patients

Lucendo A, et al. et al. Gastroenterology 2019 Jul;157(1):74-86.e15

Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for EoE in a Randomized Placebo-Controlled Trial

Variable	BOT→BOT,[a] n (%) (n = 23)	Placebo→BOT,[b] n (%) (n = 28)
Any TEAE	13 (56.5)	16 (57.1)
Severe TEAE		
Esophageal food impaction		
TEAE related to study drug	6 (26.1)	13 (46.4)
Serious adverse events	0 (0)	0 (0)
TEAE leading to withdrawal from the study	0 (0)	1 (3.6)
Lip edema and oral paraesthesia, both of mild intensity and recovered	0 (0)	1 (3.6)
TEAE related to study drug and leading to withdrawal from the study	0 (0)	1 (3.6)
TEAEs by occurring in ≥2 patients in any treatment group:		
Gastrointestinal disorders	3 (13.0)	2 (7.1)
Gastroesophageal reflux disease	2 (8.7)	1 (3.6)
Infections and infestations	4 (17.4)	12 (42.9)
Suspected local fungal infection,[c] thereof:	4 (17.4)	10 (35.7)
Histologically confirmed[d]	2 (8.7)	7 (25.0)
Histologically confirmed[d] with suspected endoscopic signs	1 (4.3)	6 (21.4)
Histologically confirmed[d] with suspected endoscopic signs and clinical symptoms	0 (0)	0 (0)
Nervous system disorders	4 (17.4)	1 (3.6)
Headache	4 (17.4)	1 (3.6)

bid, twice daily; TEAE, treatment-emergent adverse events.
[a]BOT→BOT: Patients who received BOT 1 mg bid and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1mg bid
[b]Placebo→BOT: Patients who received placebo and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.
[c]Local fungal infection (included suspected cases of candida infection, esophageal candidiasis, oral candidiasis, and oropharyngeal candidiasis) was suspected and assessed as an adverse event if any of the following criteria was fulfilled: suspected clinical symptoms, suspected endoscopic findings, suspected histologic assessment in H&E-stained biopsies (even without any endoscopic signs or clinical symptoms).
[d]Histologically confirmed by Grocott staining.

- After 12 weeks, 85% of patients had achieved remission.
- Six-week and 12-week BOT administration were safe and well tolerated; 5% of patients who received BOT developed symptomatic, mild candida, which was easily treated with an oral antifungal agent

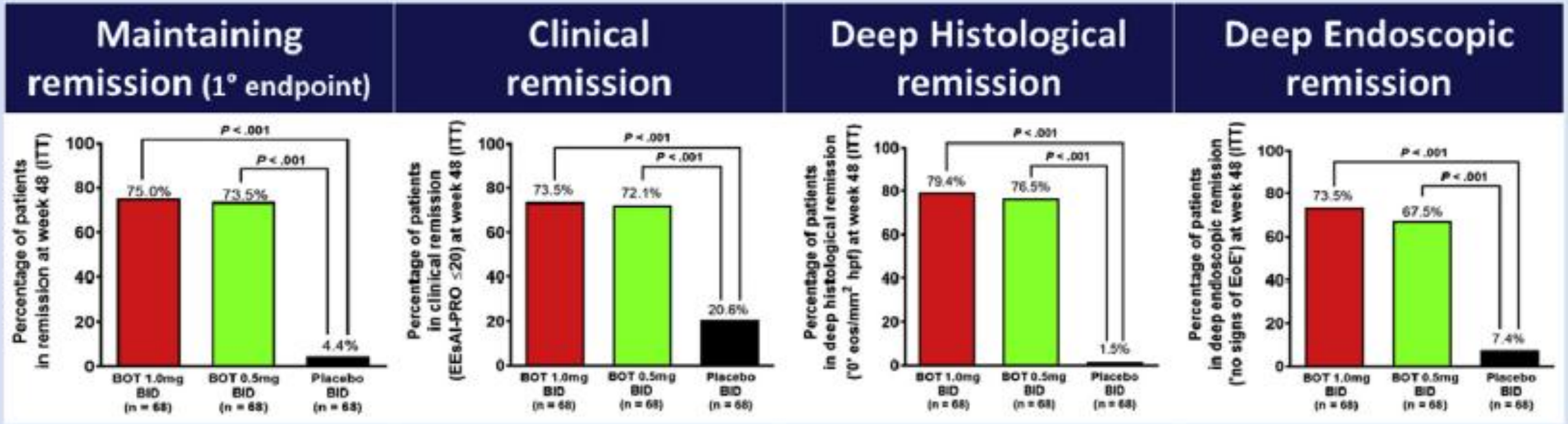
N=88 EoE patients

Lucendo A, et al. et al. Gastroenterology 2019 Jul;157(1):74-86.e15

Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With EoE

Quiescent eosinophilic esophagitis

A 48-weeks twice daily treatment with Budesonide 0.5mg or 1mg orodispersible tablets (BOT) was safe and highly effective for achieving:

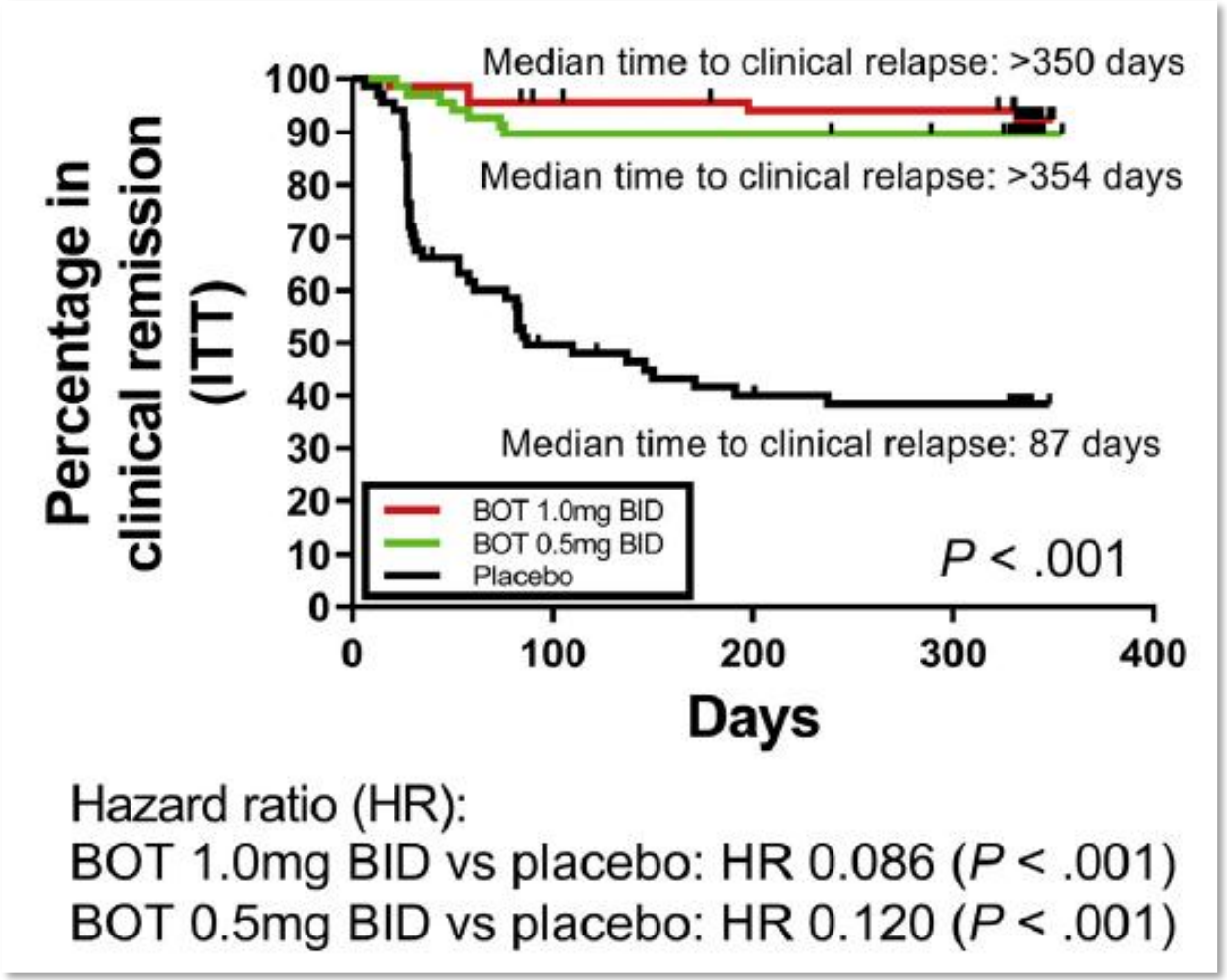


Maintenance of remission was defined as absence of clinical and histologic relapse and no premature withdrawal for any reason

N=204 EoE patients

Lucendo A, et al. et al. Gastroenterology 2020 Nov;159(5):1672-1685.e5

Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With EoE

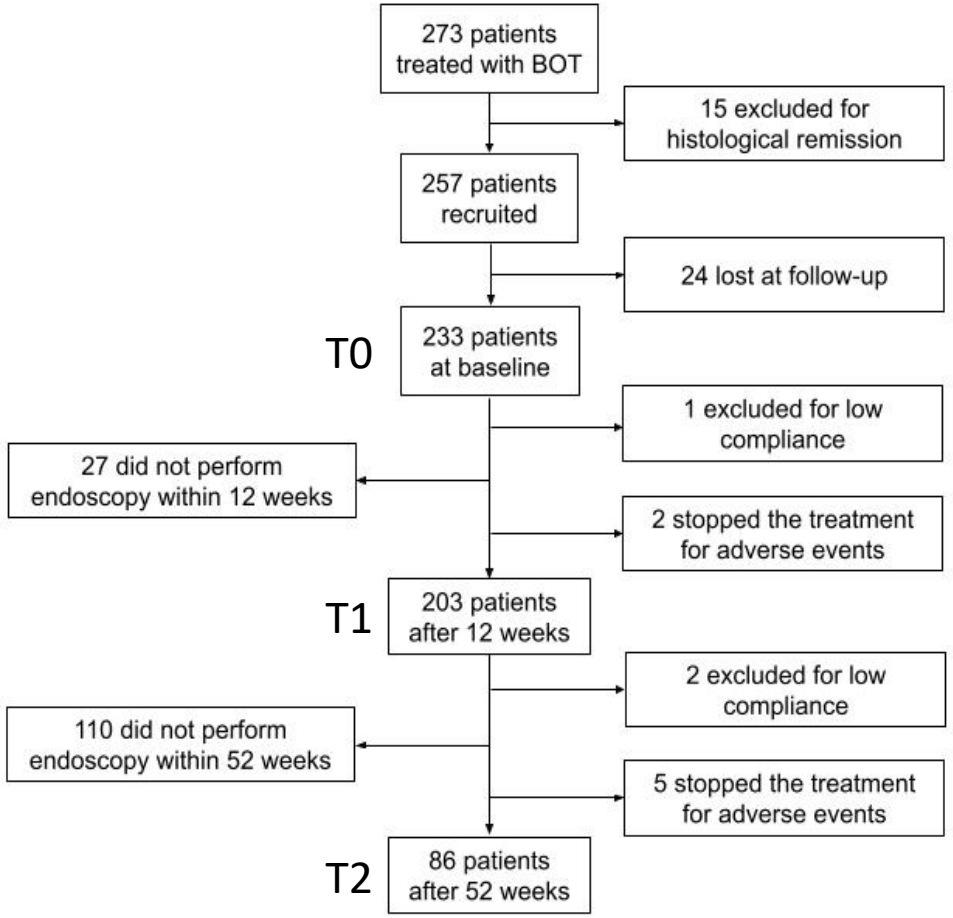


- The frequency of adverse events was similar in the BOT and placebo groups.
- Morning serum levels of cortisol were in the normal range at baseline and did not significantly change during treatment.
- Four patients receiving BOT developed asymptomatic, low serum levels of cortisol.
- Clinically manifested candidiasis was suspected in 16.2% of patients in the BOT 0.5 mg group and in 11.8% of patients in the BOT 1.0 mg group; all infections resolved with treatment

N=204 EoE patients

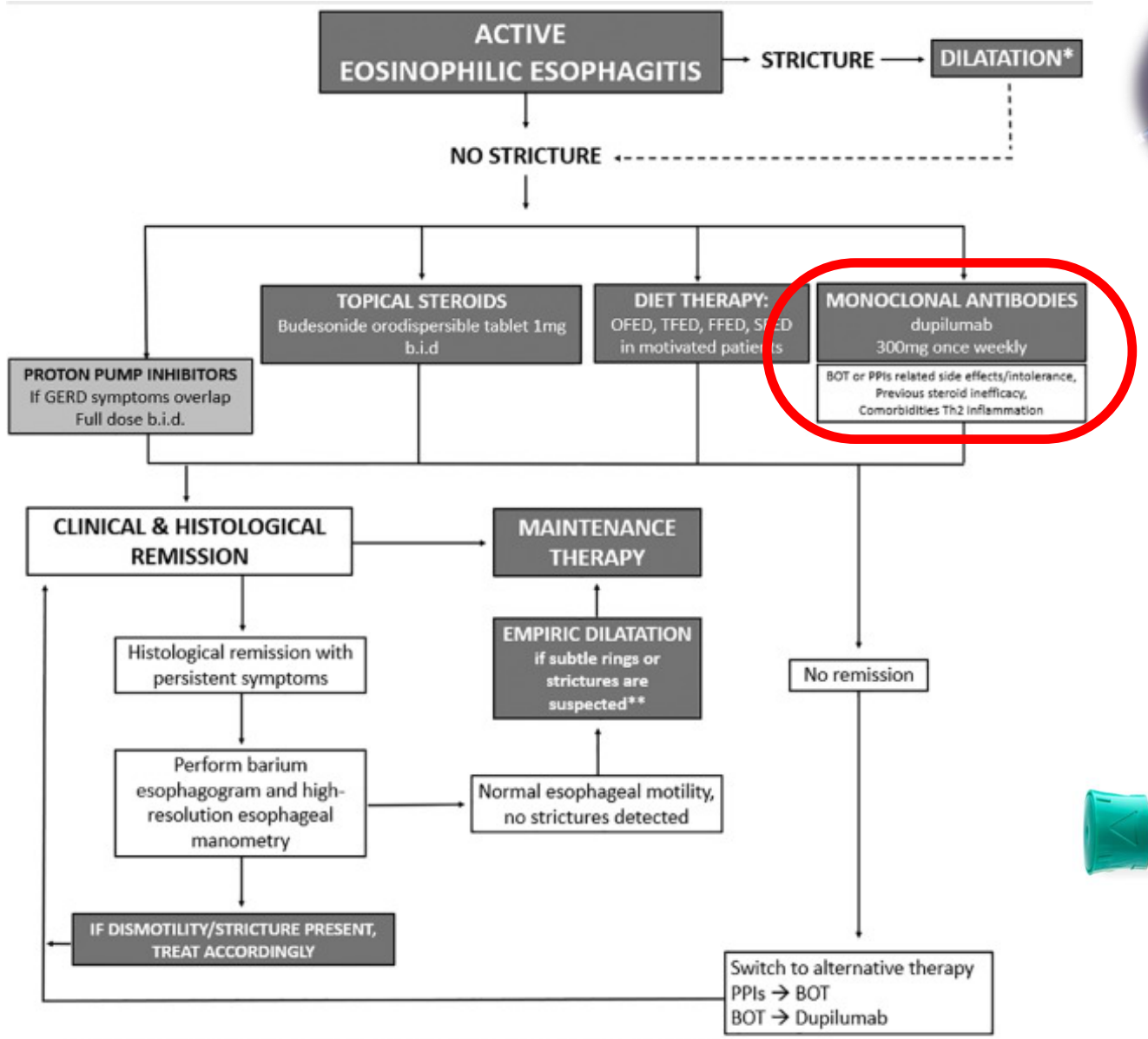
Lucendo A, et al. et al. Gastroenterology 2020 Nov;159(5):1672-1685.e5

Effectiveness and Safety of Orodispersible Budesonide Tablet for Induction and Maintenance of Remission in Eosinophilic Esophagitis: A Multicentre Real-world Prospective Study



- Deep histological remission achieved by 84% of patients at T1
- Sustained deep remission at T2 in 78% (86pts).
- 15% experienced a loss of histological response at treatment tapering.
- Primary non-responders were 8%, and secondary non-responders were 3%.
- No serious adverse effects
- Mild side effects in 12% of pts (mostly oral symptoms)

Maniero, Ghisa et al. submitted



De Bortoli, Visaggi et al DLD 2024

EoE is Primarily a Type 2 Inflammatory Disease

Types of Immunity[1,2]:

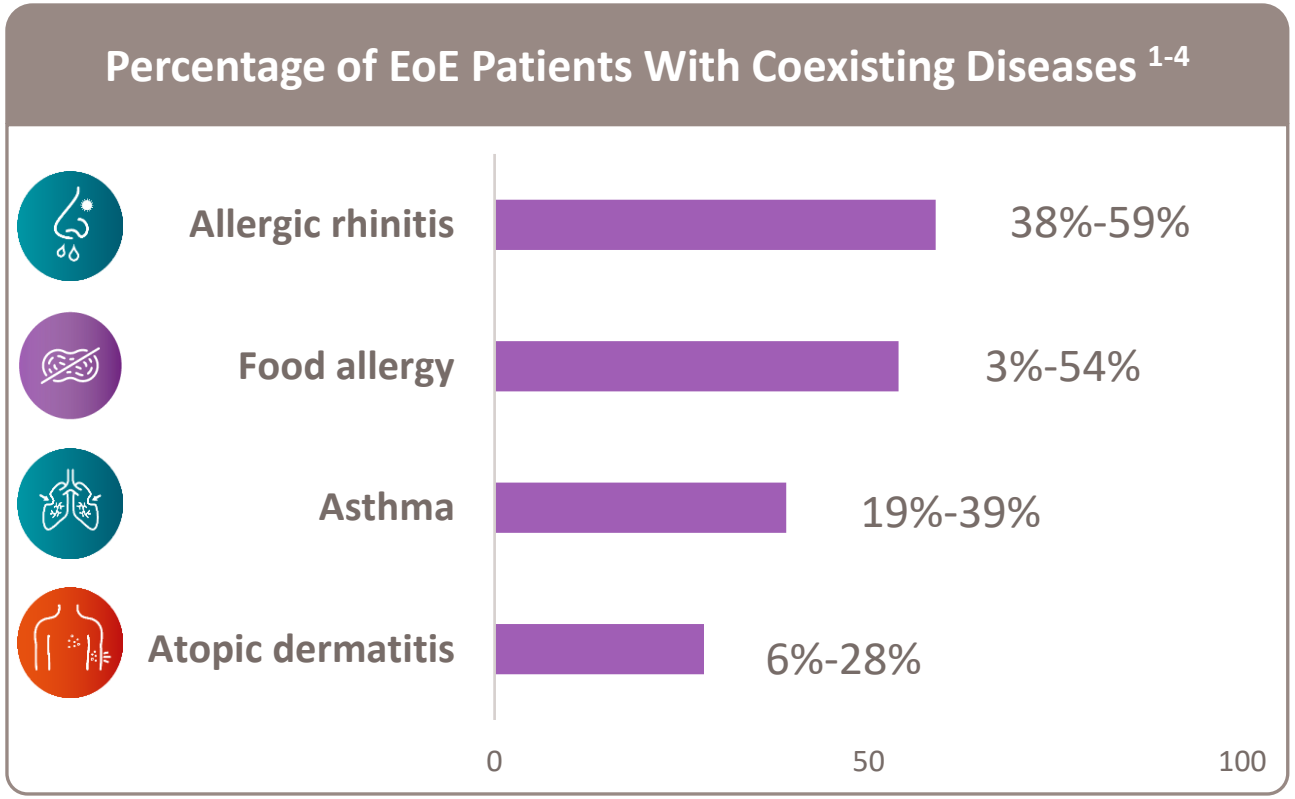
	TYPE 1	TYPE 2	TYPE 3
Primary immune cells[1-6]	Innate: Neutrophil, ILC1, NK; Adaptive: Th1	Innate: ILC2, Mast cell, Basophil, Eosinophil; Adaptive: Th2 cell, Tfh2	Innate: Neutrophil, ILC3; Adaptive: Th17, Th22
Key cytokines[2,3,6-9]	IL-2, IFNγ, TNFβ, IL-12, IL-18, IL-17	IL-4, IL-5, IL-13, IL-31, IL-25, TSLP, IL-33	IL-17 A/F, IL-6, IL-22, IL-23
Functions[2,3,8]	• Protection against intracellular bacteria and protozoa, viruses	• Protection against helminths and venoms	• Protection against extracellular bacteria and fungi
Associated inflammatory diseases[2,4,6]	• Lupus • Rheumatoid arthritis • Multiple sclerosis • Insulin-dependent diabetes mellitus • Inflammatory bowel diseases	• **Eosinophilic esophagitis** • Atopic dermatitis (eczema) • Asthma • Chronic rhinosinusitis with nasal polyps	• Psoriasis • Rheumatoid arthritis • Multiple sclerosis • Insulin-dependent diabetes mellitus • Inflammatory bowel diseases

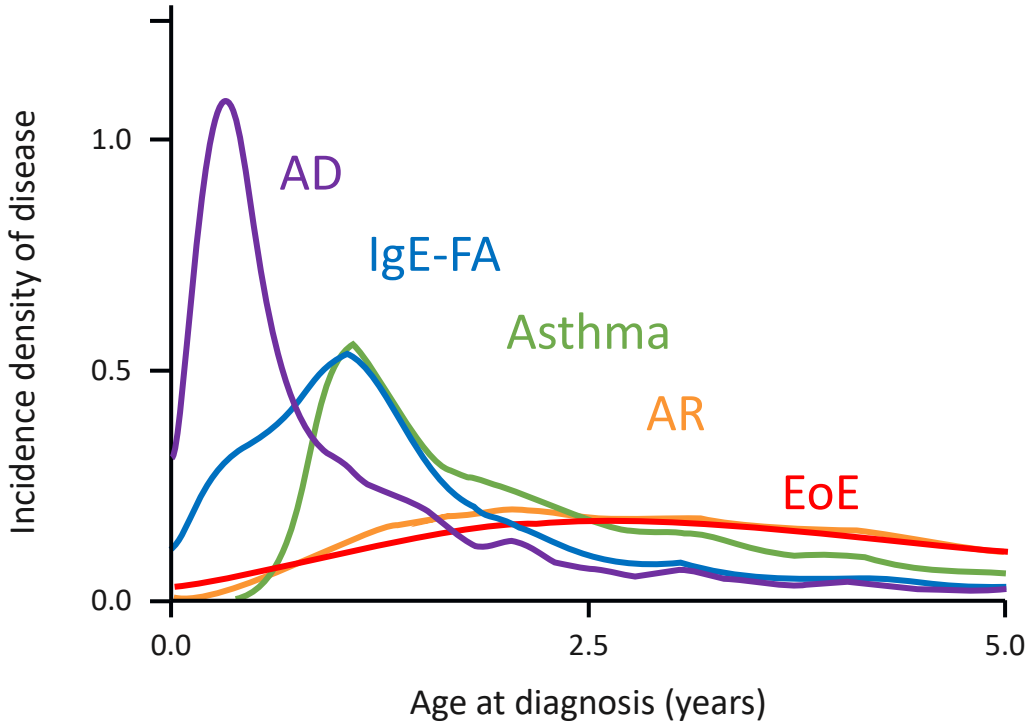
Simplified depiction based on key published information, not meant to be exhaustive in nature. IL-25 is also known as IL-17E.

IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; NK, natural killer cell; Tfh, T follicular helper cell; Th, T helper cell; TNFβ, tumor necrosis factor beta; TSLP, thymic stromal lymphopoietin.

1. Hopp RJ. *Pediatr Allergy Immunol Pulmonol*. 2020;33(1):12-18. 2. Annunziato F, et al. *J Allergy Clin Immunol.* 2015;135(3):626-635. 3. Kaiko GE, et al. *Immunology*. 2008;123(3):326-338. 4. Gandhi NA, et al. *Expert Rev Clin Immunol*. 2017;13(5):425-437. 5. Gong F, et al. *Front Immunol*. 2019;10:2918. 6. Eyerich K, Eyerich S. *J Eur Acad Dermatol Venereol*. 2018;32(5):692-703. 7. Nakashini K, et al. *Annu Rev Immunol*. 2001;19:423-474. 8. Raphael I, et al. *Cytokine*. 2015;74(1):5-17. 9. Racca F, et al. *Front Physiol*. 2022;12:815842.

Type 2 Inflammatory Diseases Commonly Coexist in Adult Patients With EoE



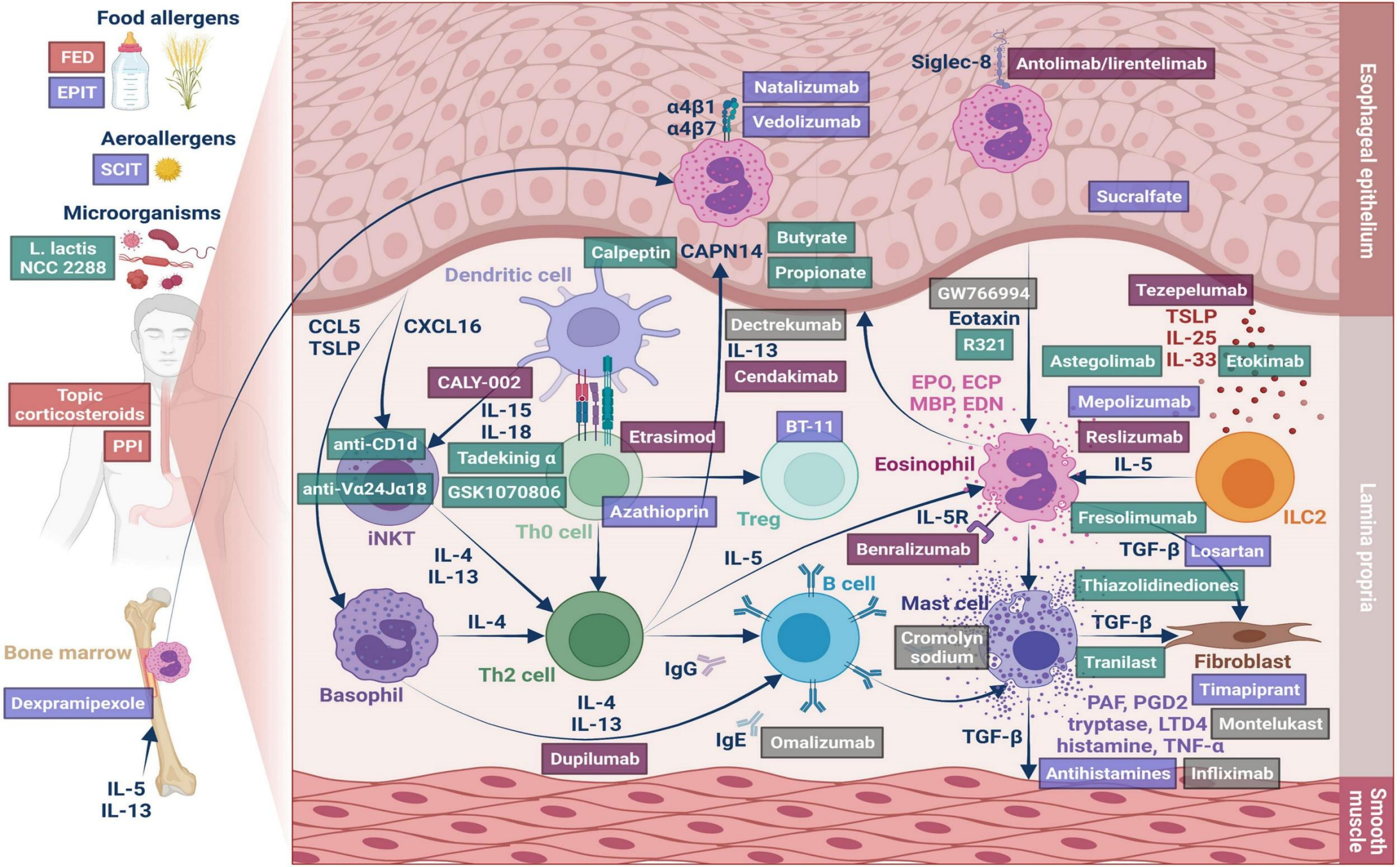


AD, atopic dermatitis; AR, allergic rhinitis; IgE-FA, immunoglobulin E-mediated food allergy.

EoE, eosinophilic esophagitis.

Dellon ES, et al. *Clin Gastroenterol Hepatol.* 2014;12(4):589-596.e1. 2. Prasad GA, et al. *Clin Gastroenterol Hepatol.* 2009;7(10):1055-1061. 3. Hruz P, et al. *J Allergy Clin Immunol.* 2011;128(6):1349-1350.e5. . Chehade M, et al. *J Allergy Clin Immunol Pract*. 2018;6(5):1534-1544.e5. Hill DA, et al. J Allergy Clin Immunol Pract. 2018;6(5):1528–1533

TYPE 2 INFLAMMATION: DRUGS



Racca F, et al. Front Physiol. 2022 Jan 12;12:815842

Learnings From Clinical Trials of Biologics in EoE

MoA	Name of therapy	Phase 1	Phase 2	Phase 3	Clinical trial outcomes
Anti–IL-5[1]	Mepolizumab[2-4]				Modestly reduced esophageal eosinophilia but failed to significantly improve symptoms
	Reslizumab[5-7]				
Anti–IL-13[1]	Dectrekumab (QAX576)[1,8]				
Anti-IgE[1]	Omalizumab[9-11]				No significant improvements in esophageal eosinophilia or dysphagia
Anti–IL-5Rα[1]	Benralizumab[12,13]				Significantly reduced esophageal eosinophilia but did not improve symptoms
Anti–Siglec-8[1]	Lirentelimab (AK002)[14,15]				Met histologic but not symptom-related co–primary endpoint

Clinical trial status updated as of October 3, 2023.
IgE, immunoglobulin E; IL, interleukin; MoA, mechanism of action; Siglec-8, sialic acid–binding immunoglobulin-like lectin 8.

1. Racca F, et al. *Front Physiol*. 2022;12:815842. 2. Dellon E, et al. Presented at Digestive Disease Week 2023; May 6-9, 2023; Chicago, IL. Oral presentations 463, 464. 3. Straumann A, et al. *Gut*. 2010;59(1):21-30. 4. GSK pipeline. Accessed August 23, 2023. https://www.gsk.com/en-gb/innovation/pipeline/. 5. Spergel JM, et al. *J Allergy Clin Immunol*. 2012;129(2):456-463. 6. Clinicaltrials.gov. Last updated September 2, 2016. Accessed October 3, 2023. clinicaltrials.gov/ct2/show/NCT00538434 7. Teva pipeline. Accessed August 23, 2023. https://www.tevapharm.com/globalassets/tevapharm-vision-files/teva-innovative-and-biosimilar-pipeline-august-2-2023.pdf. 8. Rothenberg ME, et al. *J Allergy Clin Immunol*. 2015;135(2):500-507. 9. Clinicaltrials.gov. Last updated May 20, 2016. October 3, 2023. clinicaltrials.gov/ct2/show/NCT00123630 10. Clayton F, et al. *Gastroenterology*. 2014;147(3):602-609. 11. Genentech pipeline. Accessed August 23, 2023. https://www.gene.com/medical-professionals/pipeline 12. Rothenberg M, et al. Presented at Digestive Disease Week 2023; May 6-9, 2023; Chicago, IL. Oral presentation 610. 13. AstraZeneca pipeline. Accessed August 23, 2023. https://www.astrazeneca.com/our-therapy-areas/pipeline.html#respiratory. 14. Dellon ES, et al. Presented at the 2022 American College of Gastroenterology Annual Meeting; October 21-26, 2022; Charlotte, NC. Poster O201. 15. Allakos Clinical. Accessed August 23, 2023. https://www.allakos.com/clinical/#overview.

Approved and Emerging Therapeutics for EoE

MoA	Name of therapy	Phase 1	Phase 2	Phase 3	Approved*	Clinical trial details
Swallowed topical corticosteroids[1-4]	Budesonide orodispersible tablet[1]				✓	***Approved in EU and other countries** **Ages 18+**
	Budesonide oral suspension[2]				✓	**Approved in US**
	Fluticasone propionate orally disintegrating tablet (APT-1011)[3]					Completed: May 2022 Ages 18+
	Mometasone furoate (ESO-101)[4]					Primary completion date: October 2023 Ages 18-70
Anti–IL-4Rα (anti-IL-4/13)[5]	Dupilumab[5-7]				✓	***Approved in EU, US, and other countries** **Ages 1+**
					✓	**Ages 1-11 approved**
Anti–IL-13[8]	Cendakimab (RPC-4046, CC-93538)[9]					Primary completion date: Dec 2023 Ages 12-75
Anti-TSLP[8]	Tezepelumab[10]					Primary completion date: May 2026 Ages 12-80
S1P receptor modulator[8]	Etrasimod[11]					Primary completion date: September 2022 Ages 18-65
mTB chaperonin 60.1 peptide[12]	IRL201104[13]					Completed: October 2022 Ages 18-75
Anti-KIT[14]	Barzolvolimab (CDX-0159)[15]					Primary completion date: March 2025 Ages 18+

Clinical trial status updated as of October 3, 2023. *Budesonide orodispersible tablet (Jorveza) is approved for treatment of EoE in adults older than 18 years by the EMA (0.5 mg bid or 1 mg bid, Dr. Falk Pharma GmbH).[1] Dupilumab 300 mg qw (Dupixent) is approved by the EMA for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or are not candidates for conventional medicinal therapy.[5]

EMA, European Medicines Agency; EoE, eosinophilic esophagitis; US FDA, United States Food and Drug Administration; IL, interleukin; MoA, mechanism of action; S1P, sphingosine-1-phospate; TSLP, thymic stromal lymphopoietin.

1. Jorveza (budesonide orodispersible tablet) [summary of product characteristics]. Freiburg, Germany: Dr. Falk Pharma GmbH; 2020. 2. Takeda Press Release. Accessed September 25, 2023. https://www.takeda.com/newsroom/newsreleases/2023/Takeda-Announces-FDA-Acceptance-of-NDA-Resubmission-of-TAK-721-budesonide-oral-suspension-for-the-Short-Term-Treatment-of-Eosinophilic-Esophagitis-EoE/3. ClinicalTrials.gov. Updated June 12, 2023. Accessed September 18, 2023. https://clinicaltrials.gov/ct2/show/NCT04281108 4. ClinicalTrials.gov. Updated September 21, 2023. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/record/NCT04849390 5. Dupixent (dupilumab) [summary of product characteristics]. Sanofi Winthrop Industrie in Gentilly, France; 2023. 6. ClinicalTrials.gov. Last updated June 5, 2023. Accessed September 18, 2023. https://clinicaltrials.gov/ct2/show/NCT04394351 7. Sanofi Press Release. Accessed September 29, 2023. https://www.sanofi.com/en/media-room/press-releases/2023/2023-09-26-05-30-00-2749151 8. Racca F, et al. *Front Physiol*. 2022;12:815842. 9. ClinicalTrials.gov. Last updated September 28, 2023. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/NCT04753697 10. ClinicalTrials.gov. Last updated September 28, 2023. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/NCT05583227 11. Clinicaltrials.gov. Last updated July 24, 2023. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/NCT04682639 12. Revolo BIotherapeutics Product Dev Landscape. Accessed September 18, 2023. https://revolobio.com/product-development-landscape-1104/ 13. Clinicaltrials.gov. Last updated December 8, 2022. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/NCT05084963 14. Celldex Therapeutics Pipeline. Accessed September 18, 2023. https://celldex.com/pipeline/overview/ 15. Clinicaltrials.gov. Last updated September 8, 2023. Accessed October 3, 2023. https://clinicaltrials.gov/ct2/show/NCT05774184

Dupilumab Is a Dual Inhibitor of IL-4 and IL-13 Signaling Pathways

1 IL-4 and IL-13 bind to receptors containing a shared subunit, IL-4Rα[1]

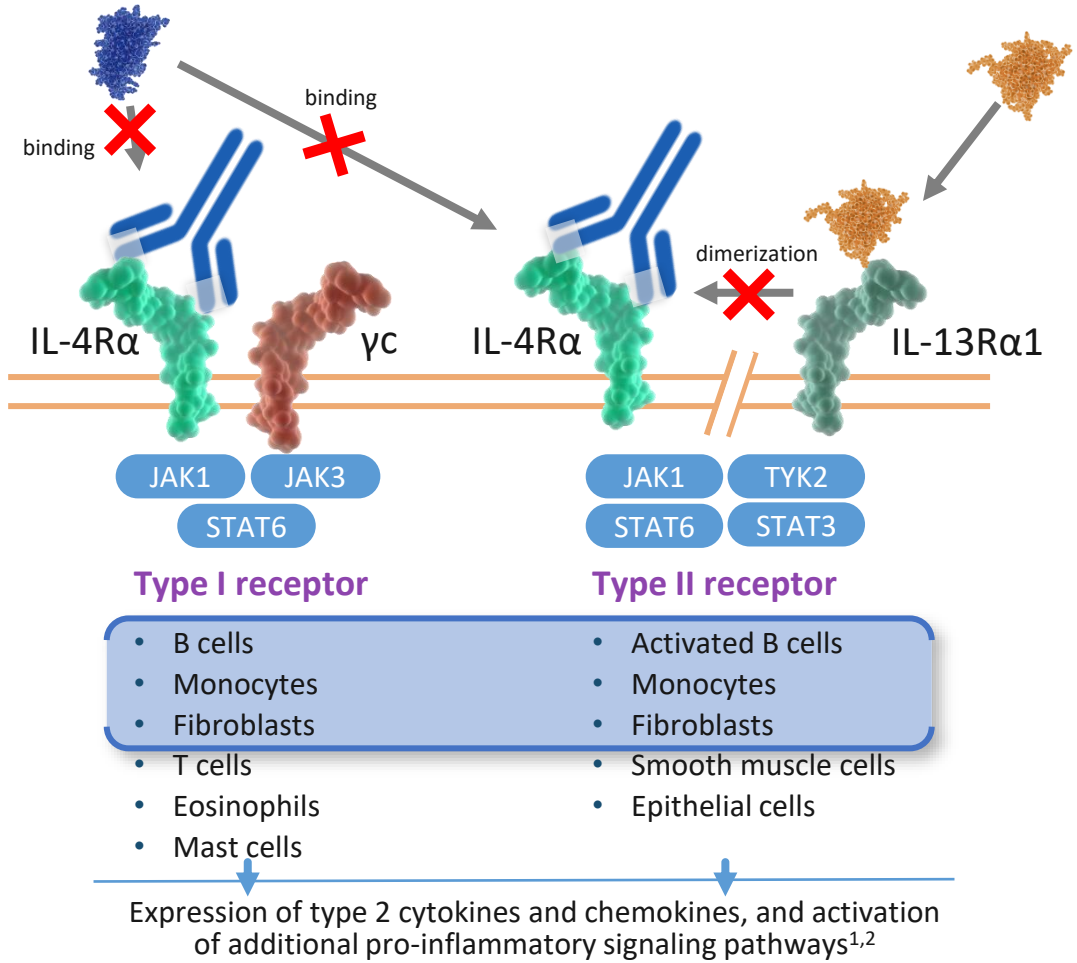
IL-4

IL-13

2 Dupilumab is a human monoclonal antibody that binds specifically to IL-4Rα, the shared receptor component for IL-4 and IL-13, thus inhibiting the dual signaling pathways of both IL-4 and IL-13[1]

Dupilumab

3 Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor[1]



IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2.

1. Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15(1):35–50. 2. Harb H, Chatila, TA. *Clin Exp Allergy.* 2020;50:5–14

Dupilumab Was Evaluated in Patients With EoE in the LIBERTY EoE TREET Study

LIBERTY EoE TREET:

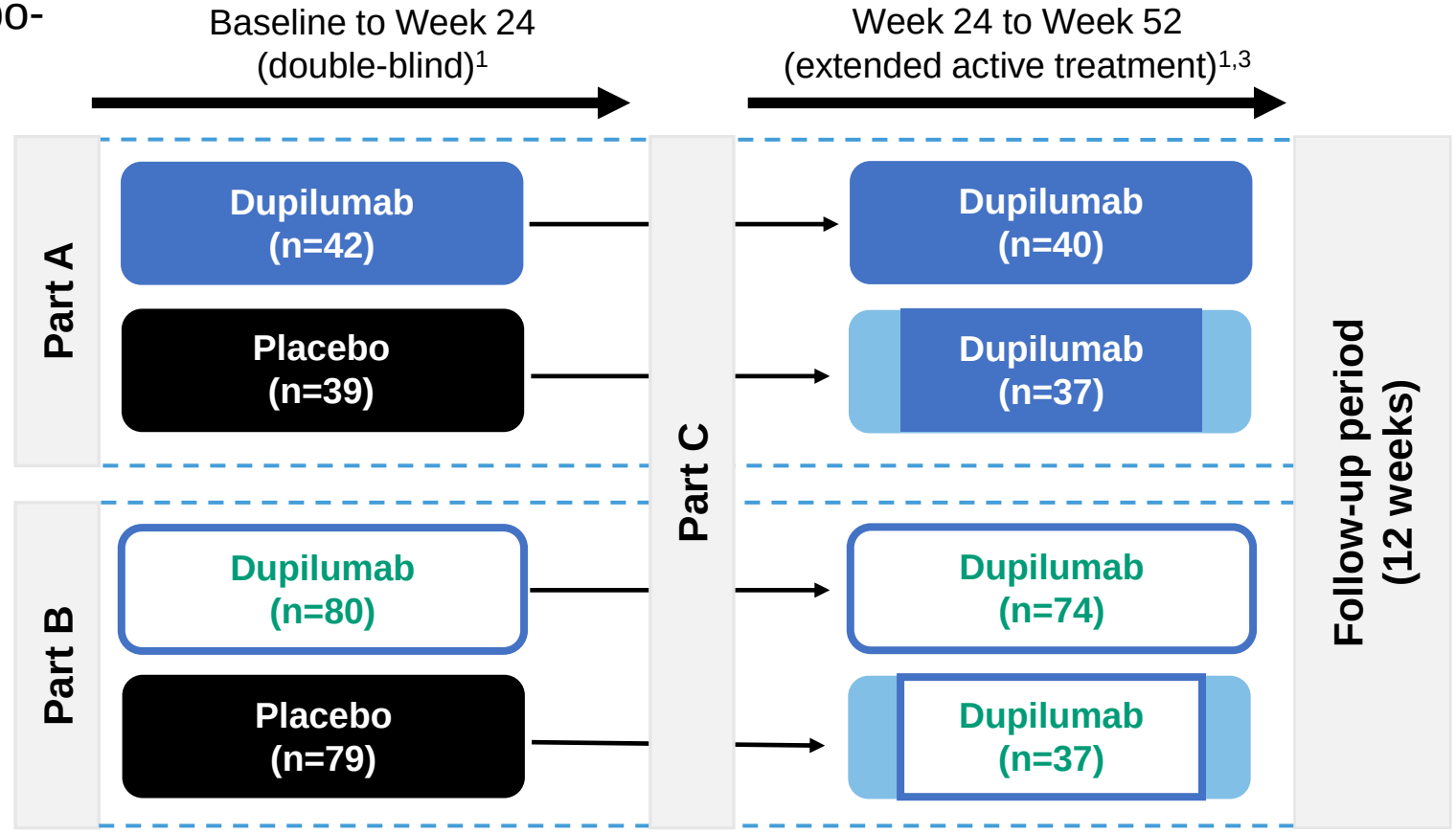
3-part,* randomised, double-blind, placebo-controlled study in EoE[1,2]

Population[1,2]

- Aged ≥12 years weighing ≥40 kg diagnosed with EoE in whom PPI therapy had failed
- Peak cell count ≥15 eos/hpf despite 8 weeks of high-dose PPI therapy
- Baseline DSQ score ≥10

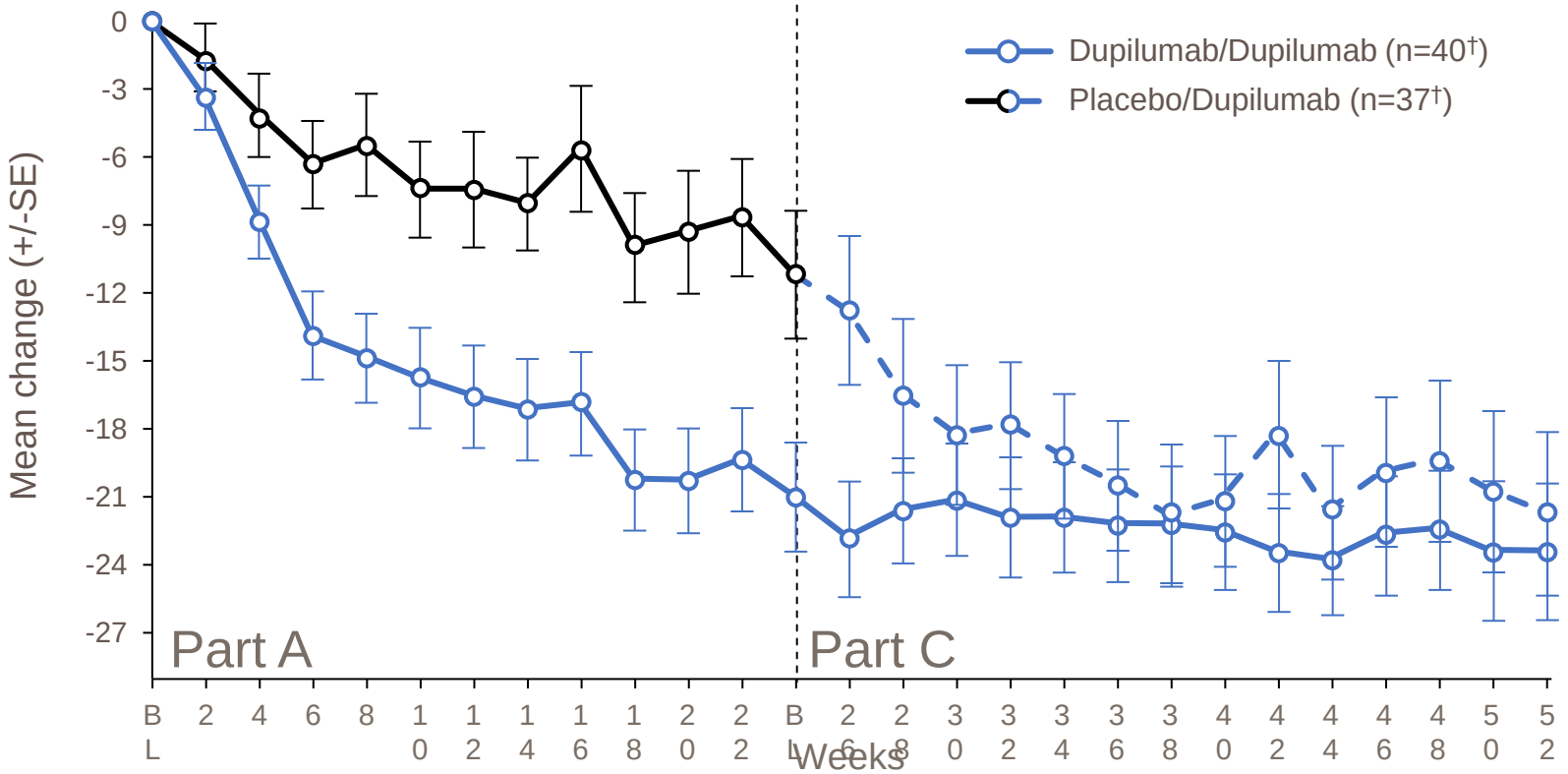
Dosing[1†]

- Dupilumab 300 mg SC QW



*Enrolment for Part B began immediately after the last patient was enrolled in Part A; patients who were enrolled in Part A were not eligible for Part B. Ineligible patients who did not enter Part C enter a 12-week follow-up period.[1]
†In Part B, patients who were randomly assigned to receive dupilumab 300 mg were given dupilumab 300mg either weekly or every 2 weeks. Only data from patients receiving dupilumab 300 mg weekly will be shown.
DSQ=Dysphagia Symptom Questionnaire; EoE=eosinophilic esophagitis; eos/hpf=eosinophils per high-power field; PPI=proton pump inhibitor; QW=weekly; SC=subcutaneous.
1. Dellon ES, et al. *N Engl J Med.* 2022;387(25):2317-2330. 2. Dupixent Summary of Product Characteristics October 2023. 3. Rothenberg ME, et al. *Lancet Gastroenterol Hepatol.* Published online 31 August 2023. doi: 10.1016/S2468-1253(23)00204-2.

Improvements in Dysphagia Symptoms Were Rapid With Dupilumab as Early as Week 4 With Sustained Improvement Through Week 52[1,2]



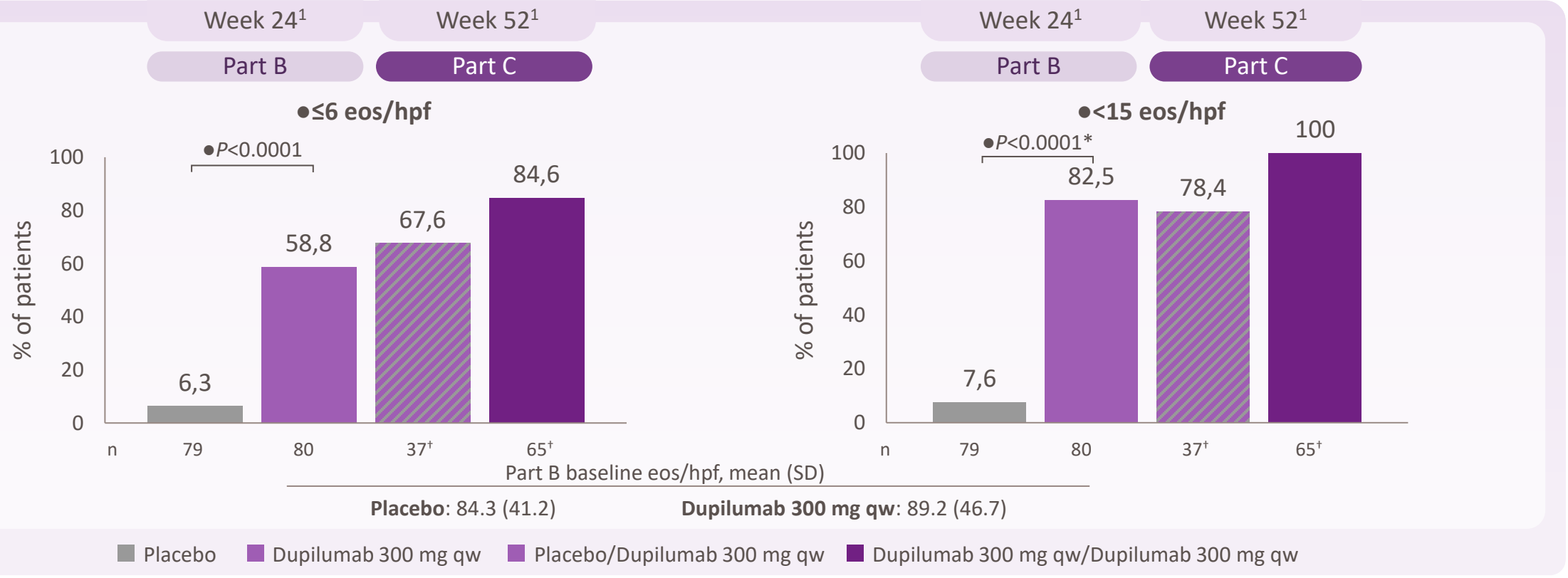
Dupilumab/Dupilumab (n=40)	40	40	39	38	36	38	40	32	34	36	33	35	32	29
Placebo/Dupilumab (n=37)	37	34	34	33	28	30	37	26	32	29	25	25	26	23

Up to 76% reduction in dysphagia symptoms from baseline through week 52 with dupilumab

Figure is Figure 9 in the Dupixent Summary of Product Characteristics. *The biweekly DSQ score ranges from 0 to 84, with higher scores indicating more frequent or more severe dysphagia.[1] †All observed values were used regardless of rescue treatment use.[1]
DSQ=Dysphagia Symptom Questionnaire; SE=standard error. 1. Dupixent Summary of Product Characteristics October 2023. 2. Dellon ES, et al. *N Engl J Med*. 2022;387(25):2317-2330.

Dupilumab Improved Histologic Response at Weeks 24 and 52 in Part B/C

LIBERTY EoE TREET



Substantial improvement in histologic endpoints observed at Week 24 in Parts A and B, regardless of history of prior STC use[2]

Dupilumab Phase 3 Safety Results

PART A/C

Event, n (%)	Part A (24 weeks)		Part C (Patients from Part A, at 52 weeks)	
	Placebo (n=39)	Dupilumab 300 mg qw (n=42)	Placebo/ Dupilumab 300 mg qw (n=37)	Dupilumab 300 mg qw/ Dupilumab 300 mg qw (n=40)
Deaths	0	0	0	0
TEAEs	32 (82.1)	36 (85.7)	27 (73.0)	24 (60.0)
Treatment-emergent SAEs	0	2 (4.8)*	1 (2.7)‡	0
TEAEs leading to discontinuation	0	1 (2.4)†	2 (5.4)§	0
TEAEs occurring in ≥10% of patients in any group				
Injection site reaction (PT)	4 (10.3)	7 (16.7)	8 (21.6)	4 (10.0)
Nasopharyngitis	4 (10.3)	5 (11.9)	3 (8.1)	1 (2.5)
Injection site erythema	5 (12.8)	3 (7.1)	5 (13.5)	4 (10.0)
Headache	4 (10.3)	2 (4.8)	2 (5.4)	3 (7.5)
Rash	4 (10.3)	0	0	1 (2.5)

*Abdominal pain and uterine polyp—assessed as not related to study medication. †Arthralgia. ‡Shortness of breath and diaphoresis. §Arthralgia and systemic inflammatory response syndrome.
EoE, eosinophilic esophagitis; PT, Medical Dictionary for Regulatory Activities (MedDRA) preferred term; qw, weekly; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Dellon ES, et al. Presented at: the United European Gastroenterology Week Virtual Congress; October 3-5, 2021; Abstract LB10.

PART B/C

Event, n (%)	Part B (Weeks 0 to 24)		Part C (Patients from Part B, Weeks 24 to 52)	
	Placebo (n=78)	Dupilumab 300 mg qw (n=80)	Placebo/ Dupilumab 300 mg qw (n=37)	Dupilumab 300 mg qw/ Dupilumab 300 mg qw (n=74)
Deaths	0	0	0	0
TEAEs	55 (70.5)	67 (83.8)	23 (62.2)	51 (68.9)
Treatment-emergent SAEs	1 (1.3)*	5 (6.3)†	2 (5.4)‡	3 (4.1)§
TEAEs leading to discontinuation	2 (2.6)	2 (2.5)	0	0
TEAEs (MedDRA preferred term) occurring in ≥10% of dupilumab-treated patients				
Injection site reaction	16 (20.5)	16 (20.0)	4 (10.8)	10 (13.5)
COVID-19	0	4 (5.0)	4 (10.8)	7 (9.5)
Nasopharyngitis	3 (3.8)	2 (2.5)	4 (10.8)	3 (4.1)
Injection site erythema	9 (11.5)	8 (10.0)	1 (2.7)	6 (8.1)
Injection site swelling	2 (2.6)	10 (12.5)	0	2 (2.7)

*Mental status changes. †Depression suicidal, *Campylobacter* colitis, blood creatine phosphokinase abnormal, breast cancer, pneumonia aspiration. ‡Vomiting, cellulitis. §Diarrhea, rectal tenesmus, enterocolitis infectious, chest pain.
EoE, eosinophilic esophagitis; qw, weekly; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Dellon ES, et al. Presented at the Annual Scientific Meeting of the American College of Gastroenterology; Charlotte, North Carolina, USA; October 21–26, 2022; Abstract 52.

Key messages

- The prevalence of EoE is skyrocketing
- Multiple esophageal biopsies are mandatory to diagnose EoE
- An Early EoE diagnosis and treatment is key to stop its natural history
- PPIs, STCs and elimination diets are three effective and safe treatments for EoE
- Orodispersible budesonide has the highest efficacy
- PPIs remain a valid options thanks to their ease of intake, safety and efficacy
- Dietary regimens should be considered only in highly motivated patients and considering a step-up approach
- Dupilumab is effective for treating Type 2 inflammatory disorders, including EoE regardless its severity
- With the expansion of therapeutic options, there is a growing need to characterize and stratify patients based on their risk of developing fibrotic complications

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