

Congresso TRISOCIETARIO AIGO SIED SIGE TOSCANA Firenze 16 dicembre 2023

AIGO Toscana: Dott.ssa Francesca De Nigris STED Toscana: Dott.ssa Francesca Calella SIGE Toscana: Prof. Nicola de Bortoli

Appropriatezza e Innovazione in Gastroenterologia nell'era dell'open access

"APPROPRIATEZZA E INNOVAZIONE IN GASTROENTEROLOGIA NELL'ERA DELL'OPEN ACCESS"

Firenze, Sabato 16 dicembre 2023 Hotel Albani Firenze - Via Fiume, 12 Firenze

Esofagite eosinofila: nuove evidenze

Nicola de Bortoli

Associate Professor of Gastroenterology

Department of Translational Research and New Technologies in Medicine and Surgery

Head of Gastroenterology Training Program

University of Pisa



Disclosures:

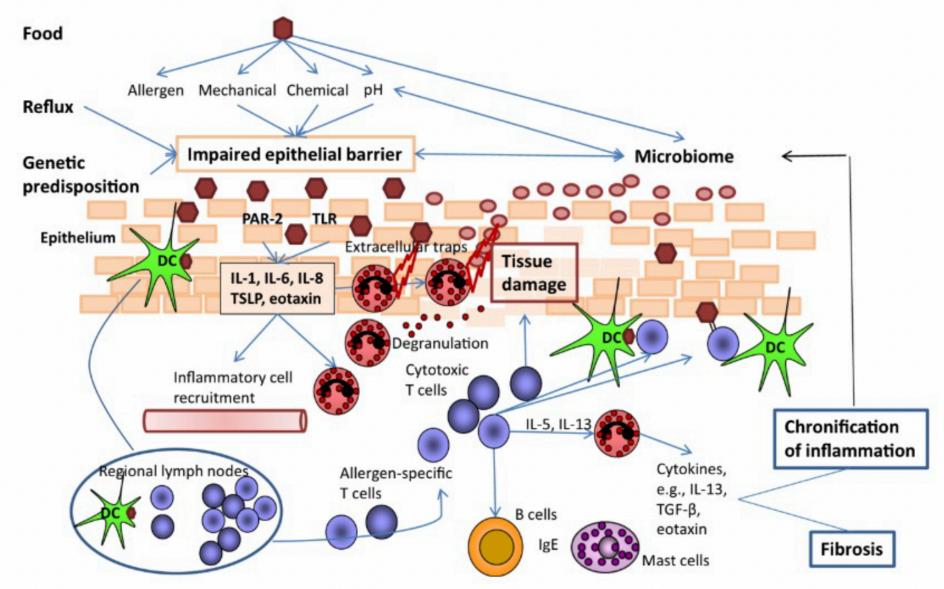
Conference Speech: Reckitt Benckiser; Malesci; Sofar; Dr Falk, PharmaLine, AlfaSigma,

Advisory Board: Dr Falk; Astra Zeneca; Sanofi Genzyme, AlfaSigma

EOSINOPHILIC ESOPHAGITIS: DEFINITION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by a peak eosinophil count (PEC) of ≥ 15 eosinophils per high power field (eos/HPF) (about 60 eos/mm2) in at least one esophageal biopsy, in the absence of other causes of esophageal eosinophilia.

IMMUNOPATHOGENESIS OF EOE



EOSINOPHILIC ESOPHAGITIS: EPIDEMIOLOGY

Impact of environmental factors on the epidemiology of eosinophilic esophagitis in southwestern Europe (2007-2020)

Check for updates

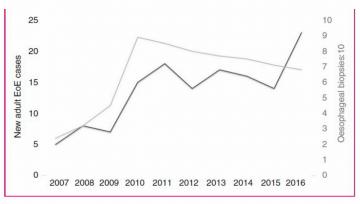
Alejandro Raúl Gratacós Gómez, MD,^a Sara Feo Ortega, MD,^b Alberto Palacios Cañas, MD,^a Francisco Feo Brito, PhMD, Jose Ramón Muñoz Rodriguez, PhMD,^c and Elisa Gomez Torrijos, PhMD^a Tomelloso, Ciudad Real, Spain

TABLE II. Incidence and prevalence of EoE per 100,000 habitats per year during 14 consecutive years and number of diagnoses of EoE per year

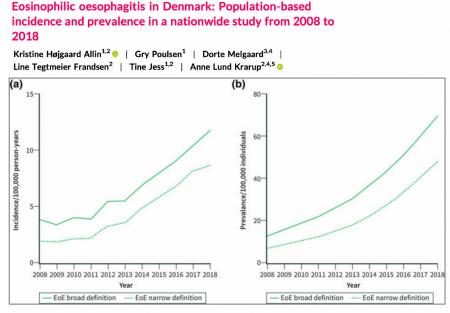
Year	Incidence (100,000/y)	Prevalence (100,000/y)	No. of EoE diagnoses
2007	0.455	0.455	1
2008	1.818	2.273	4
2009	5.455	7.728	12
2010	6.818	14.546	15
2011	11.364	25.91	25
2012	19.091	45.001	42
2013	16.818	61.819	37
2014	8.636	70.455	19
2015	17.727	88.182	39
2016	13.636	101.818	30
2017	12.727	114.545	28
2018	10.455	125	23
2019	24.545	149.545	54
2020	16.818	166.363	37
Average (2007-2020)	11.88	69.54	26.2

Rising incidence and prevalence of adult eosinophilic esophagitis in midwestern Spain (2007-2016)

Javier Molina-Infante^{1,2}, Pedro Luis Gonzalez-Cordero¹, Hal Cliff Ferreira-Nossa¹, Pilar Mata-Romero¹, Alfredo J. Lucendo^{2,3} and Angel Arias^{2,4}



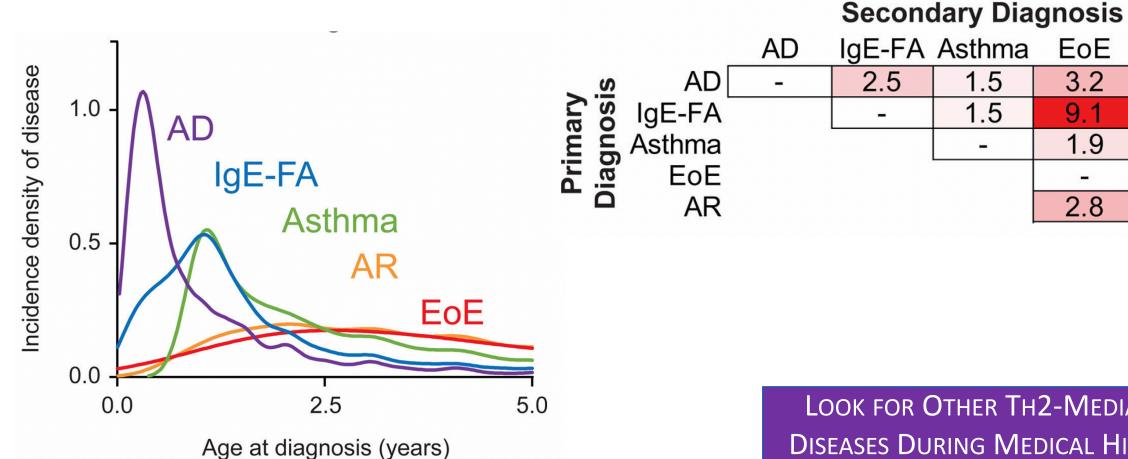
UEG Journal 2018, Vol. 6 29–37



UEG Journal 2022,10(7):640–50

- J Gastroenterol Hepatol 2023;
 - Incidence 12-15/100,000 inhabitants/year
 - Prevalence ranges between 0.5-0.8/1,000 inhabitants.
 - Males >>>Female (3:1), white ethnic origin, most often in those aged <50 years of age
 - Found in 2%-7% of patients undergoing upper endoscopy for any reason
 - Found in 12%-23% of patients undergoing endoscopy for dysphagia
 - Most common cause of bolus impaction

EOSINOPHILIC ESOPHAGITIS IS A LATE MANIFESTATION OF THE ALLERGIC MARCH



LOOK FOR OTHER TH2-MEDIATED DISEASES DURING MEDICAL HISTORY COLLECTION, EOE MIGHT BE BEYOND THE CORNER

AR

1.9

1.7

1.7

2.5

3.2

1.9

2.8

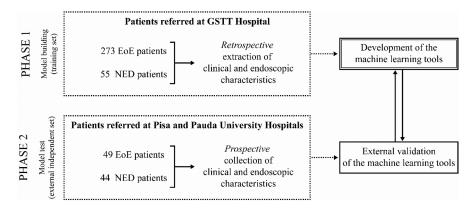
TITLE:

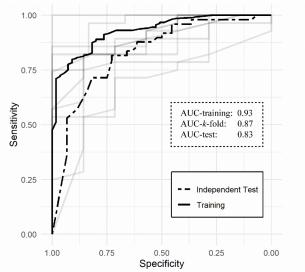
Machine Learning Tools for the Diagnosis of Eosinophilic Esophagitis in Adults Reporting

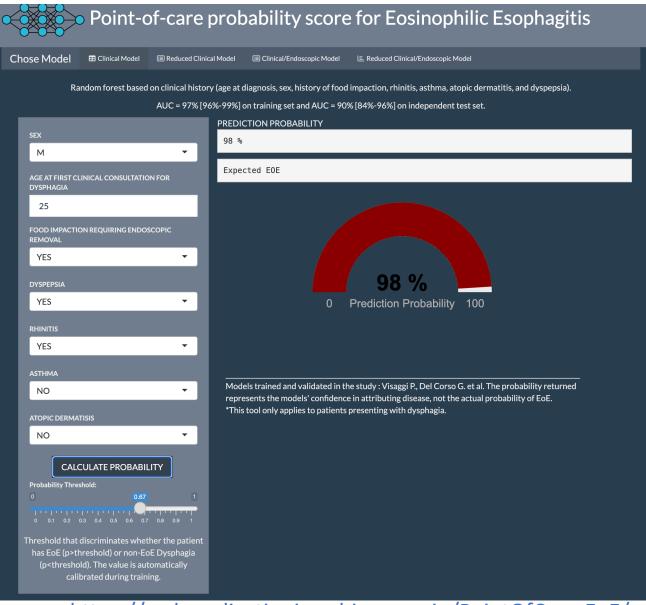
Dysphagia: Development, External Validation, and Software Creation for Point-of-Care Use

AUTHORS

Pierfrancesco Visaggi^{1,2,#}, Giulio Del Corso^{3,#}, Federica Baiano Svizzero¹, Matteo Ghisa⁴, Delio Stefani Donati¹, Arianna Venturini¹, Serena Bardelli⁵, Brigida Barberio⁴, Emanuele Marciano⁶, Massimo Bellini¹, Terry Wong², Nicola de Bortoli^{1,*}, Edoardo V. Savarino^{4,£} and Sebastian Zeki^{2, £}







https://webapplicationing.shinyapps.io/PointOfCare-EoE/

CLINICAL PRESENTATION

The main symptoms associated with EoE in adults are dysphagia and food bolus impaction. In children, symptoms are often non-specific and vary with age, including reflux-like symptoms, failure to thrive, dyspepsia, nausea, and vomiting.

Children*	Adults
Reflux-like symptoms Failure to thrive Food refusal Vomiting Abdominal pain Excessive mastication	Dysphagia Bolus impaction Chest pain Heartburn Regurgitation Abdominal pain
Atopic diathesis (allergic rhinitis, bronchial asthma, eczema)	
*Adolescents >13 years old have a similar clinical prese	ntation to adults

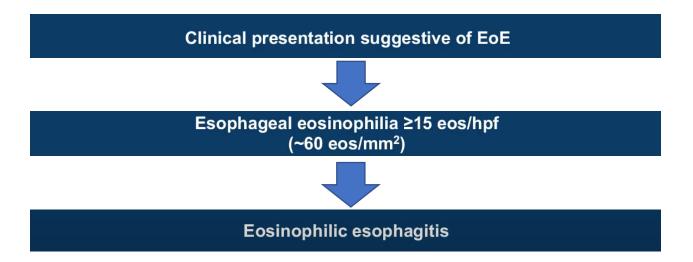


DIAGNOSIS

- a) A conclusive diagnosis of EoE requires a combination of symptoms of esophageal dysfunction and histology showing ≥15 eosinophils/high-power field (60 eosinophil/mm²) in at least one esophageal biopsy while off proton pump inhibitors.
- b) Proton pump inhibitors should be withdrawn at least 3-4 weeks prior to biopsy collection.
- c) Alternative causes of esophageal eosinophilia should be excluded.
- At least 6-8 biopsies from at least two different locations in the esophagus (distal, mid, proximal esophagus) due to a
 patchy distribution
- 7%–17% of patients with proven EoE may have a macroscopically normal appearance
- Biopsies targeted to areas of endoscopic abnormality.

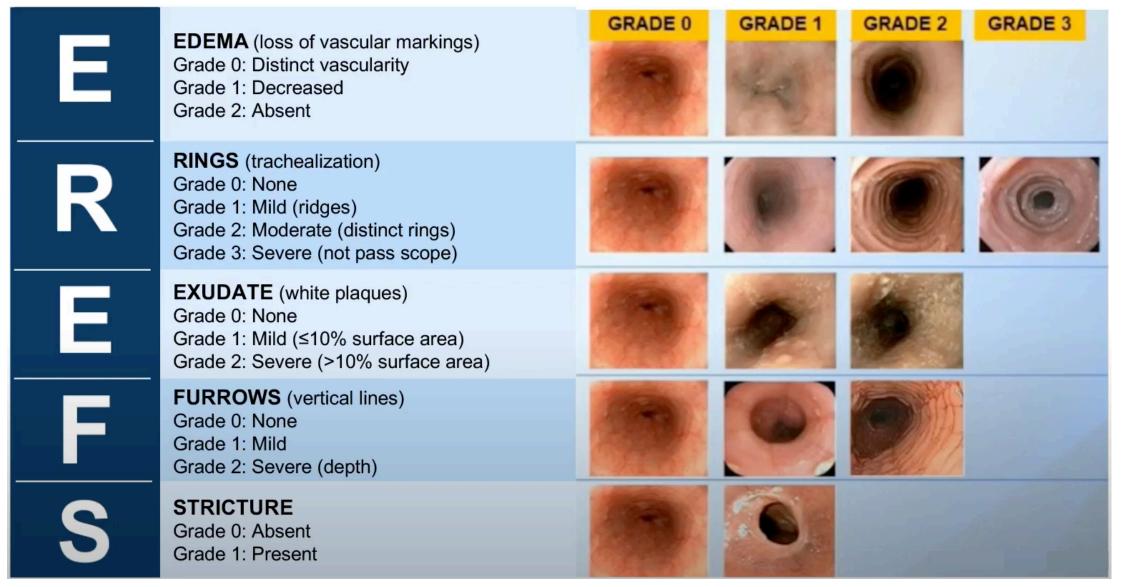
NO PPIs at least in the 3 weeks before endoscopy

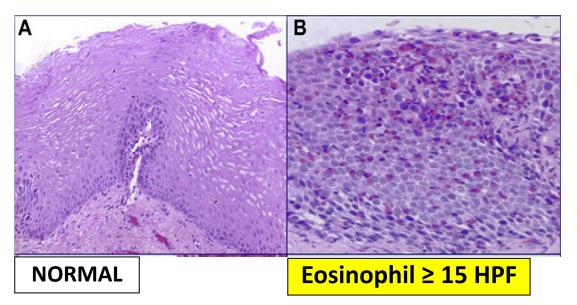
Gonsalves N et al Gastrointest Endosc 2006;64:313–319. Shah A, et al. Am J Gastroenterol 2009;104:716–721. Peery AF, et al. Clin Gastroenterol Hepatol 2011;9:475–480.



Dellon E GastroenteroL 2018; de Bortoli N et al. Dig Liv Dis 2017; Lucendo A, et al Unit Europ Gastroenterol J 2017; Dahr E, Gut 2022

EoE Endoscopic Reference Score (EREFS)

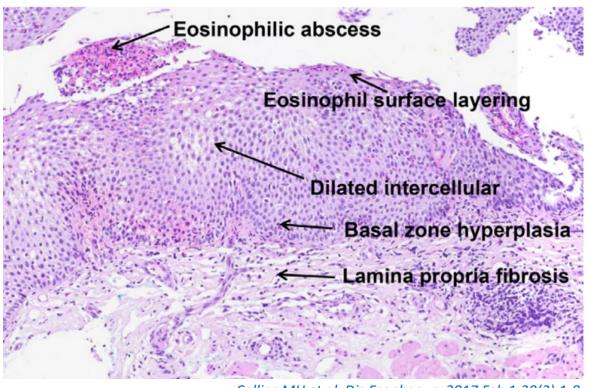




EoE Histologic Scoring System (EoEHSS):

- Grade (severity) & Stage (extent)
- 4-point scale
- Correlates with treatment status >> eosinophil count

HISTOLOGICAL FEATURES OF EOE



Collins MH et al. Dis Esophagus. 2017 Feb 1;30(3):1-8.

BSG and BSPGHAN join consensus guidelines

Mucosal eosinophilia should be accompanied by other histological features of eosinophilic oesophagitis. These include the presence of basal cell hyperplasia, oedema (spongiosis), eosinophil microabscesses, eosinophil layering, eosinophil degranulation and subepithelial sclerosis

Level of evidence: Moderate.

Strength of recommendation: Strong.

Level of agreement: 100%. Dhar A, et al. Gut 2022;0:1–29

Beyond mucosal eosinophilia, additional histologic features of eosinophilic esophagitis should be assessed for an accurate diagnosis and monitoring of disease activity. These include basal zone hyperplasia, eosinophil microabscesses, eosinophil surface layering, dilatated intercellular spaces, lamina propria fibrosis and papillary elongation.

KEY TREATMENT GOALS OF EOE INCLUDE REDUCTION IN ESOPHAGEAL EOSINOPHILIC INFLAMMATION AND IMPROVEMENT IN CLINICAL SYMPTOMS



Normalize and maintain esophageal histology

Eliminate disease symptoms

Normalize and maintain endoscopic appearance

Prevent symptom relapse

Resolve esophageal inflammation

Improve quality of life

Complete resolution of symptoms with a histologic and endoscopic normalization THE REAL GOAL of TREATMENT.

A relevant symptomatic improvement not always results in a histological improvement If Eos disappear from the tissue, it does not mean that symptoms disappear as well.

Long-Term Clinical Remission

Lack of EoE-attributed symptoms

Endoscopic Inflammatory Remission

EREFS < 2

Histological Inflammatory Remission

Peak eosinophilic count <15 eos/HPF

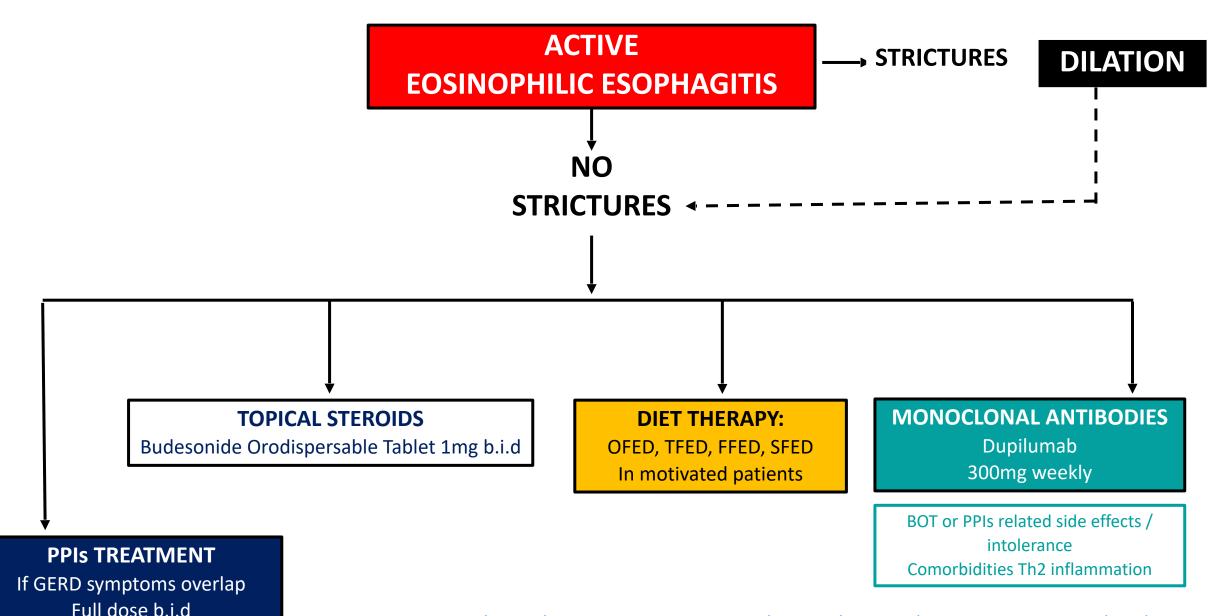
Deep Remission

Combination of clinical, endoscopic, and histological remission (Eos ≤1)

De Rooij WE, et al. *Drugs*. 2019;79(13):1419–1434. Lyons E, et al. *Gastroenterology*. 2019;157(2):275–277. Straumann A, Safroneeva E. *Curr Treat Options Allergy*. 2015;2:100–109. Greuter T, et al. *Am J Gastroenterol*. 2017;112(10):1527–1535. Dellon ES, Gonsalves N, Hirano I *Am J Gastroenterol*. 2013 May;108(5):679–692.

Gomez Torrijos E, et al. Front Med (Lausanne);2018;5:247.

THERAPEUTICAL APPROACH TO ACTIVE EOE



PROTON PUMP INHIBITORS

Table 1. Summary and dosage of PPIs and steroids in EoE patients.²⁹

Drug		Target population	Induction dose	Maintenance dose
PPIs	Omeprazole Pantoprazole Esomeprazole	Children	1–2 mg/kg daily	Not yet validated*
		Adults	20-40 mg bid	Not yet validated*
Topical steroids§	Fluticasone propionate	Children	880–1760 mcg/daily	440–880 mcg/daily
		Adults	1760 mcg/daily	880–1760 mcg/daily
	Budesonide	Children	1–2 mg/daily	1 mg/daily
		Adults	2–4 mg/daily	2 mg/daily#

^{*}It has been shown that children could be kept in remission with Esomeprazole 1 mg/kg daily and that adults could be kept in remission with Esomeprazole 20 mg daily.³⁰

PPI therapy should be given two times per day at least 8-12 weeks before control EGDS

[§]Topical steroids may be administered in single or split dose.²⁹

[#]Budesonide 0.5 mg daily could keep in remission for 50 weeks 36% of adults included in a randomized double-blind placebo-controlled trial.³¹

PPIs, proton pump inhibitors.

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§

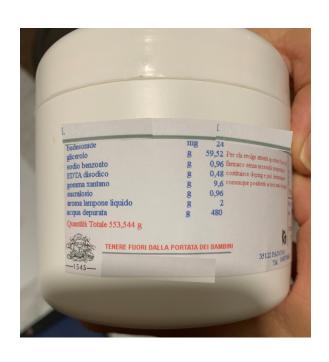
PPI therapy	Histologic remission (%)	n	l ²	Clinical response (%)	n	l ²
Overall	50.5 (42.2-58.7)	27	67.5	60.8 (48.38-72.2)	26	80.2
Adults	49.6 (40.1-59.2)	17	65.5	56.2 (41.4-70.4)	15	78.3
Children	54.1 (37.7–70)	11	69.6	64.9 (43.4-83.6)	11	83.8
Subgroups according to PPI used						
PPI unspecified	44.9 (33.9-56)	13	69.1	65.6 (46.6-82.4)	13	86.7
Omeprazole	53.5 (35.3-71.1)	4	59.9	55.7 (34.2-76.2)	5	66.6
Lansoprazole	70.2 (18.7-99.9)	3	57.1	44 (10.1-81.7)	3	23.2
Rabeprazole	72.3 (58.3-84.3)	3	0	72.3 (58.3-84.3)	3	0
Esomeprazole	46.8 (35.3-58.4)	5	2.6	33.3 (14.7-55.2)	3	31.2
Subgroups according to quality						
Medium/high	51.7 (43-60.3)	10	54.8	51.6 (34.4-68.5)	6	80.2
Low/low-medium	50.6 (37-64.2)	17	70	63 (46.9-77.7)	20	80.7
Subgroups according to type of publication						
Full text	49.7 (41.3-58)	23	62.3	56.4 (44.7-67.8)	24	77.7
Abstract	62.9 (27.1-92)	4	83.8	-	2	-
Subgroups according to doses						
Once daily	49.7 (28.9-54)	7	17.1	51.1 (29.3-72.7)	7	24.8
Twice daily	55.9 (46-65.6)	13	59.9	68 (51.5-82.5)	9	82.2
Subgroups according to design						
Prospective	52.6 (44.4-60.7)	11	52.8	59.1 (39.3-77.5)	7	87.4
Retrospective	39.1 (26.6-52.4)	8	66	59.9 (41–77.4)	12	84.3
Case report/case series	66.2 (34.7-91.3)	8	58.2	69 (40.7-91.1)	7	22.4
Subgroups according to pH monitoring						
Normal	49.3 (24.2-74.6)	7	82.7	-	-	_
Pathologic gastroesophageal reflux	65.4 (44.5-83)	6	61.7	_	_	_

DIFFERENT FORMULATIONS AVAIBLE FOR STS



Nebulized and swallowed

Should not be longer used



Oral Viscous Budesonide (OVB: mixed with sucralose, xylitol, xhantan gum, stevia, honey...

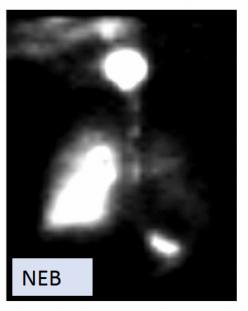
REMISSION **65%**

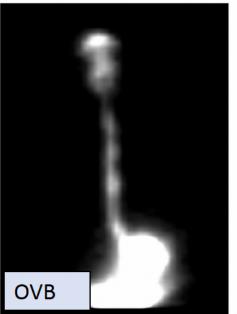


Orodispersible tablets

REMISSION **85%**

ORAL VISCOUS FORMULATION IS MORE EFFECTIVE THAN NEBULIZED





	NEB (n = 11)	OVB (n = 11)	p value
Primary outcomes			
Overall eosinophil counts (eos/hpf ± SD)			
Baseline maximum eosinophil count	101 ± 85	83 ± 89	0.62
Baseline mean eosinophil count	23 ± 20	20 ± 24	0.80
Post-treatment max eosinophil count *	89 ± 94	11 ± 23	0.02
Post-treatment mean eosinophil count *	31 ± 37	3 ± 7	0.02

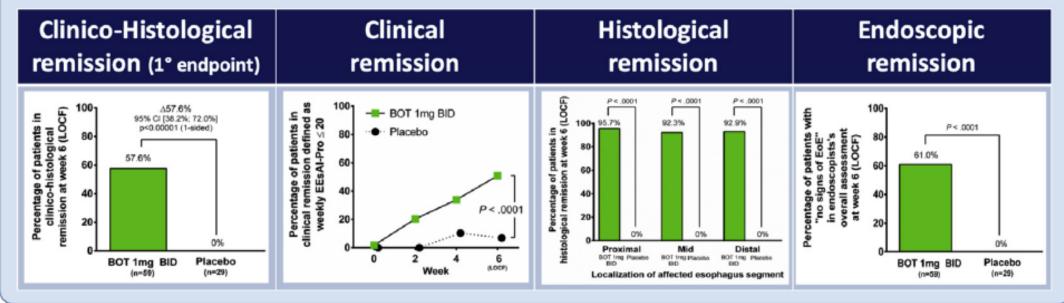
CONCLUSION: OVB was more effective than NEB in reducing numbers of esophageal eosinophils in patients with EoE. OVB provided a significantly higher level of esophageal exposure to the therapeutic agent, which correlated with lower eosinophil counts.

Budesonide Orodispersible induction RCT

Lucendo AJ et al. 2019

Active eosinophilic esophagitis

A 6-weeks twice daily treatment with Budesonide 1mg orodispersible tablets (BOT) was safe and highly effective for achieving:



Gastroenterology

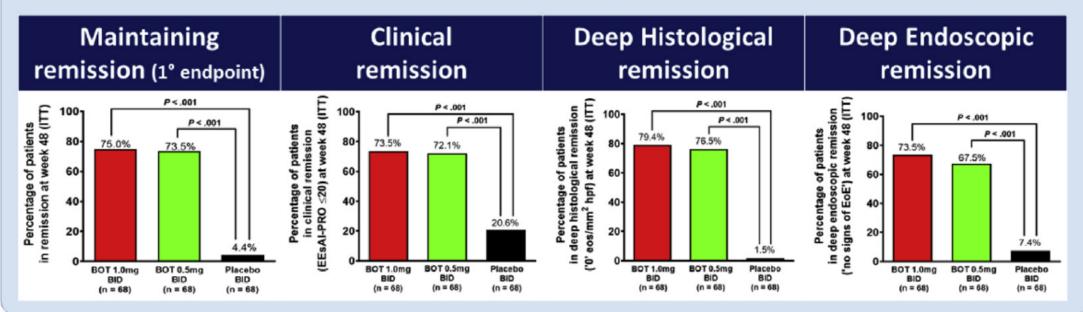
After 12 weeks, 85% of patients achieved remission

Budesonide Orodispersible maintenance RCT

Straumann A. et al. 2020

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:

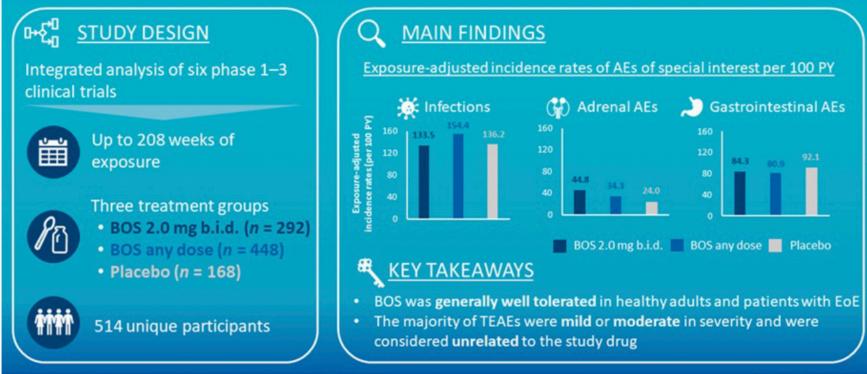


Persistent remission in 73.5% BOT 0.5 mg bid and 75% receiving BOT 1.0 mg bid

Only 4.4% of patients in the placebo group

Gastroenterology

Integrated safety analysis of an investigational formulation of budesonide (budesonide oral suspension [BOS]) for the treatment of eosinophilic oesophagitis (EoE)



AE, adverse event; b.i.d., twice daily; PY, participant-years; TEAE, treatment-emergent adverse event

Hirano I, et al. Aliment Pharmacol Ther. 2023



Editorial: safety of topical steroids designed specifically for eosinophilic oesophagitis—new data bring new questions

DIET THERAPY

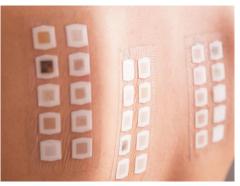


EMPIRIC ELIMINATION

REMISSION

55%





TARGET ELIMINATION

Low sensitivity and specificity

30%

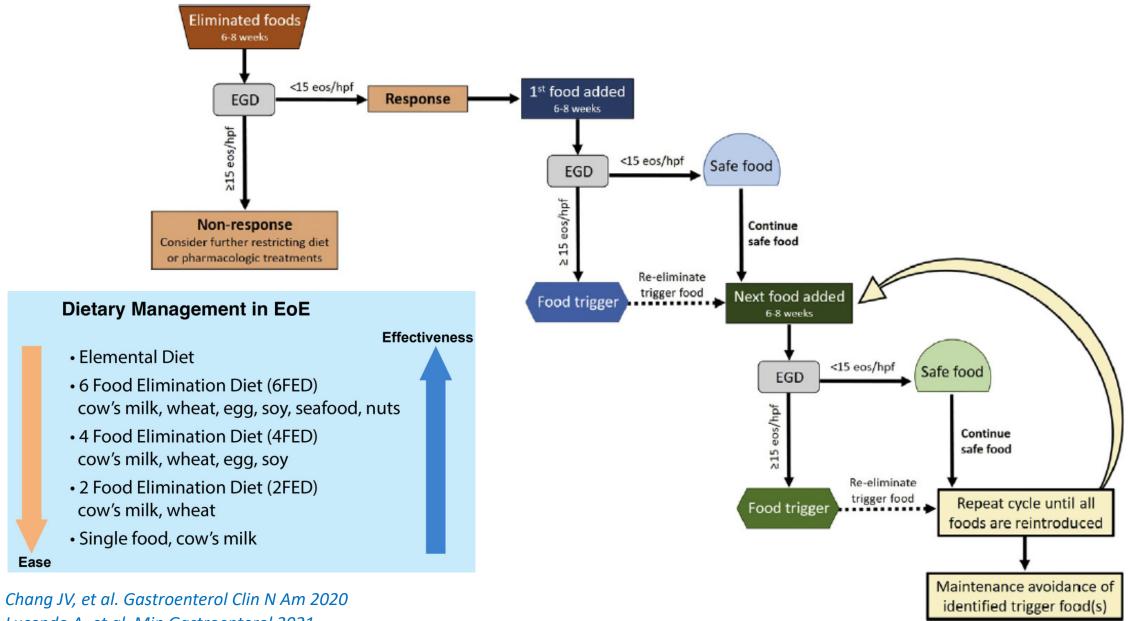


ELEMENTAL FORMULA

REMISSION 80%

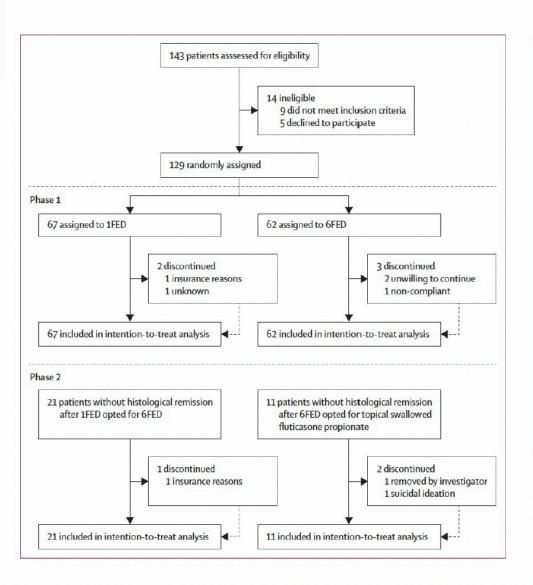
Poor tasting
Scarce compliance
High costs
Rescue therapy or bridge therapy

ELIMINATION DIET PROCESS: SFED, FFED, TFED, OFED



Lucendo A, et al. Min Gastroenterol 2021

ONE-FOOD VERSUS SIX-FOOD ELIMINATION DIET THERAPY FOR THE TREATMENT OF EOSINOPHILIC OESOPHAGITIS: A MULTICENTRE, RANDOMISED, OPEN-LABEL TRIAL



	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.

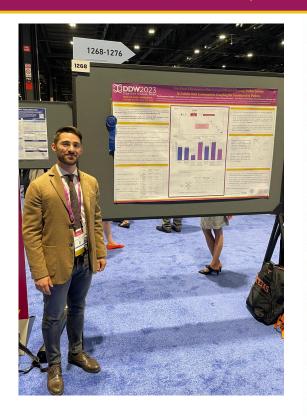
Table 2: Proportion of patients in histological remission (intention-to-treat population)

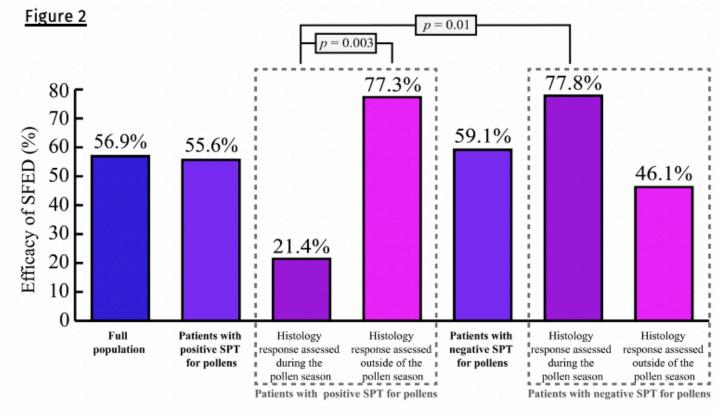


Six-Food Elimination Diet is Less Effective During Pollen Season in Adults with Eosinophilic Esophagitis Sensitized to Pollens

MAY 6-9, 2023 | CHICAGO, IL EXHIBIT DATES: MAY 7-9, 2023

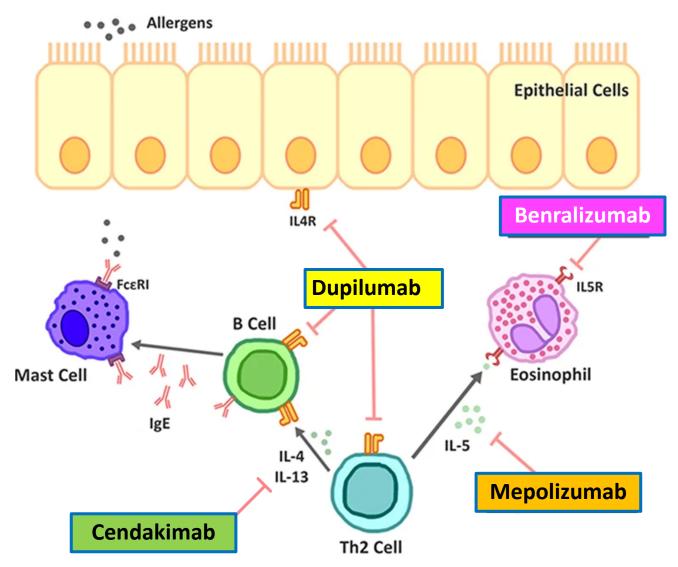
Pierfrancesco Visaggi^{1,2}, Edoardo Savarino³, Giulio Del Corso⁴, Hannah Hunter⁵, Federica Baiano Svizzero¹, Jason Dunn², Terry Wong², Nicola de Bortoli¹, Sebastian Zeki² 1 Gastroenterology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; 2 Centre for Esophageal Diseases, Guy's and St. Thomas Hospital, Westminster Bridge Road, London, UK; 3 Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy 4 Institute of Information Science and Technologies "A. Faedo", National Research Council of Italy (CNR), Pisa, Italy 5 Department of Dietetics, Guy's and St Thomas' NHS Foundation Trust, London, UK;





Conclusions: Pollens may have a role in sustaining esophageal eosinophilia in sensitized adults with EoE despite avoidance of trigger foods. The SPT for pollens may identify patients less likely to respond to the diet during the pollen season.

MONOCLONAL ANTIBODIES

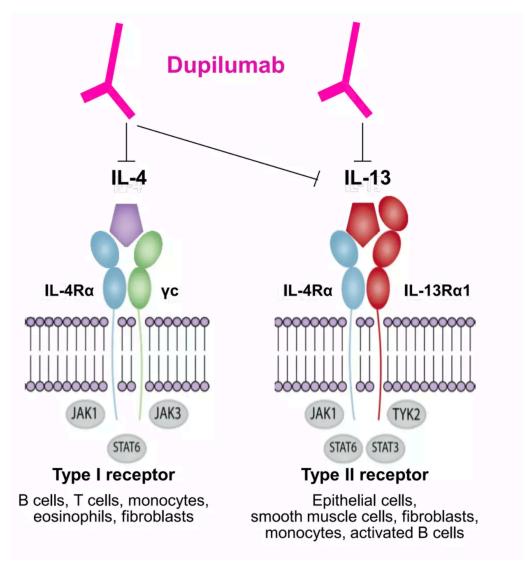


Dupilumab: An Il-4/IL-13 Monoclonal Antibody Targeting

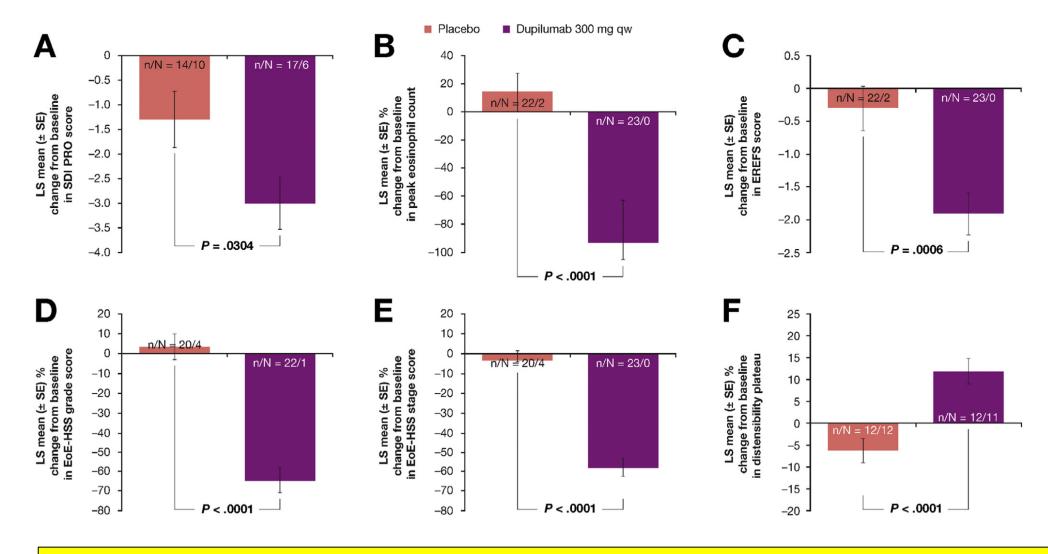
Type 2/Type 2 Pathway

Dupilumab is a fully human monoclonal antibody directed against il IL-4R α subunit of the IL-4 and IL-13 receptors.

It is used for the treatment of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis.



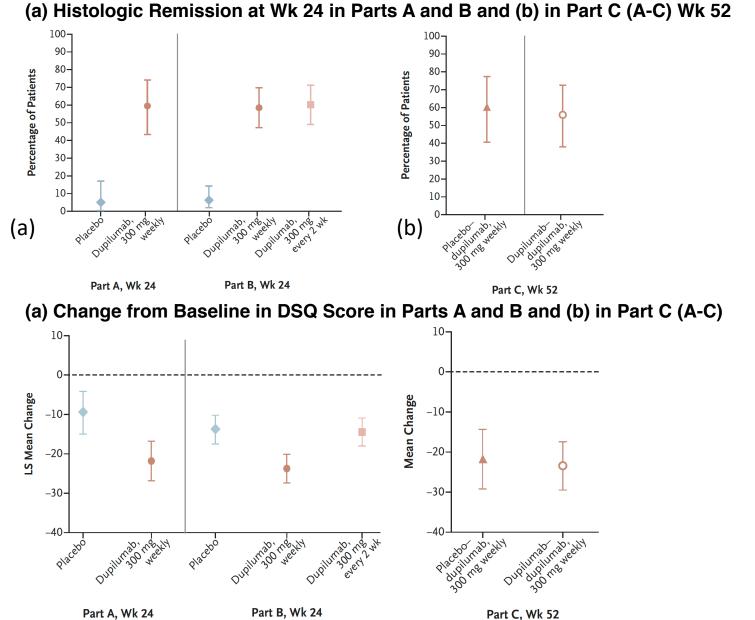
DUPILUMAB (against IL4 and IL13) IN ADULTS WITH ACTIVE EOE – PHASE 2 TRIAL

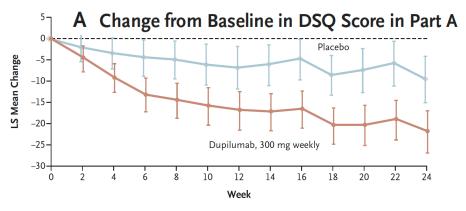


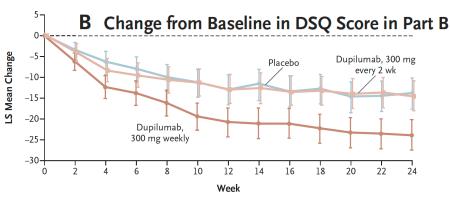
Reduced dysphagia, peak eosinophil count, EoEHSS, EREFS score, and improved distensibility vs placebo

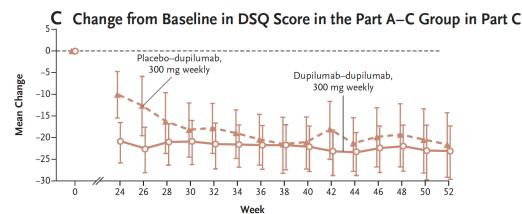
Dupilumab (Against II4 And II13) In Adults And Adolescents With Active EoE - Phase 3 Trial

Dellon ES & Rothenberg ME et al. NEJM 2022



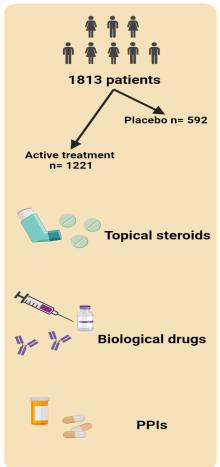


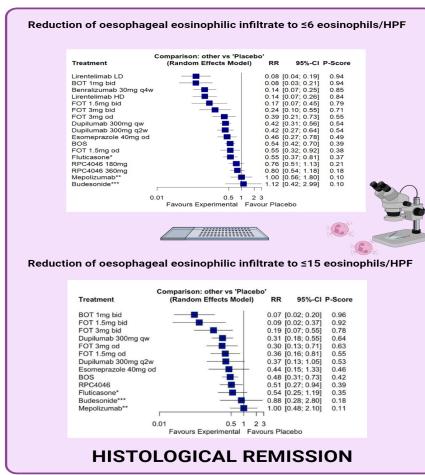




Comparison of drugs for active eosinophilic oesophagitis: systematic review and network meta-analysis

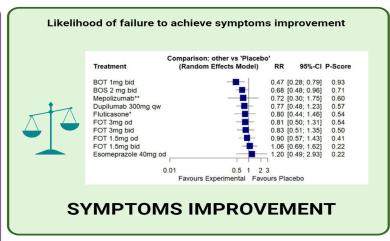
Pierfrancesco Visaggi , ¹ Brigida Barberio, ² Giulio Del Corso, ³ Nicola de Bortoli , ¹ Christopher J Black , ⁴ Alexander C Ford , ⁵ Edoardo Savarino , ⁶

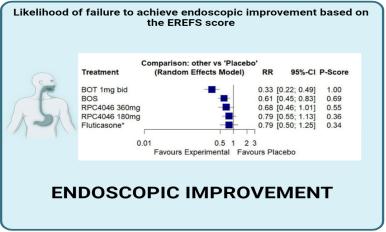




Box 1 Eligibility criteria

- ⇒ Randomised controlled trials.
- ⇒ Adults and adolescents ≥12 years of age with active eosinophilic oesophagitis.
- ⇒ Compared oral corticosteroids, proton pump inhibitors or biological drugs with each other, or with placebo.
- ⇒ Minimum duration of therapy of 6 weeks.
- ⇒ Assessment of failure of clinical response or histological remission at the last time point of assessment in the trial.

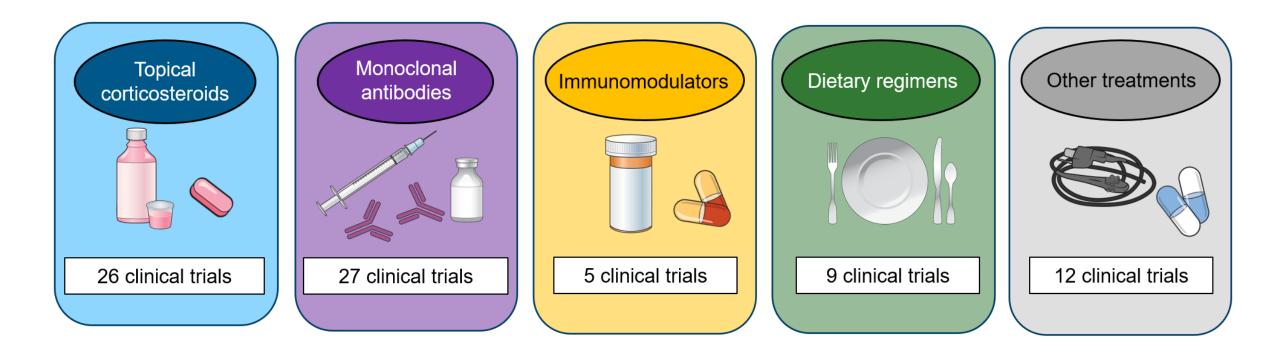




Treatment Trends for Eosinophilic Esophagitis and the Other Eosinophilic Gastrointestinal Diseases: Systematic Review of Clinical Trials

Pierfrancesco Visaggi^{a,1}, Matteo Ghisa^{b,1}, Brigida Barberio^b, Daria Maniero^b, Eliana Greco^b, Vincenzo Savarino^c, Christopher J. Black^d, Alexander C. Ford^{d,e}, Nicola de Bortoli^{a,2}, Edoardo Savarino^{b,2,*}

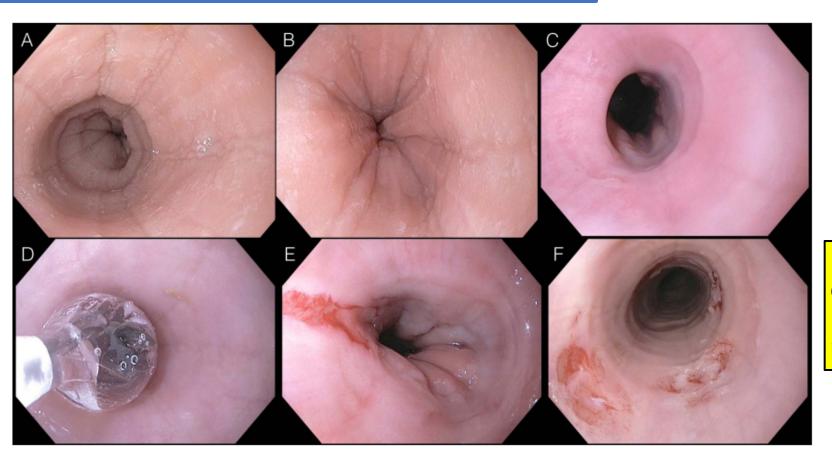
66 studies



Statement 13. Endoscopic esophageal dilation may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy and in patients with severe esophageal stenosis, endoscopically documented at onset of symptoms.

(Recommendation: strong; Evidence: moderate)

Dig Liver Dis. 2017



ESOPHAGEAL DILATION

845 patients → 1820 dilations:

- 0,038 % perforations
- 0,05% haemorrhage
- 9,3% chest pain
- NO deaths
- Through the scope balloon
- Wire guided bougie
- Simple bougie

Mucosal lacerations are not actually complications but outcome of dilation. Patients may not experience clinical improvement unless a tear develops.

TAKE HOME MESSANGES

- EoE is an emerging disorder characterized by the presence of esophageal symptoms (dysphagia and bolus impaction) due to a chronic infiltration of eosinophils in the mucosa.
- In a young male with a Th2 related disorder and dysphagia o bolus impaction
 6-8 biopsies should be collected even if endoscopy looks normal.
- The therapeutic landscape of these diseases is evolving.
- BOT is considered the first line treatment in Europe
- Dupilumab is first line therapy in US and it would be suggested if BOT fails or results intolerant or even in patients with serious different Th2 related disorders.
- Several other molecules are currently being tested in RCT.



Università di Pisa

K THANKS

