

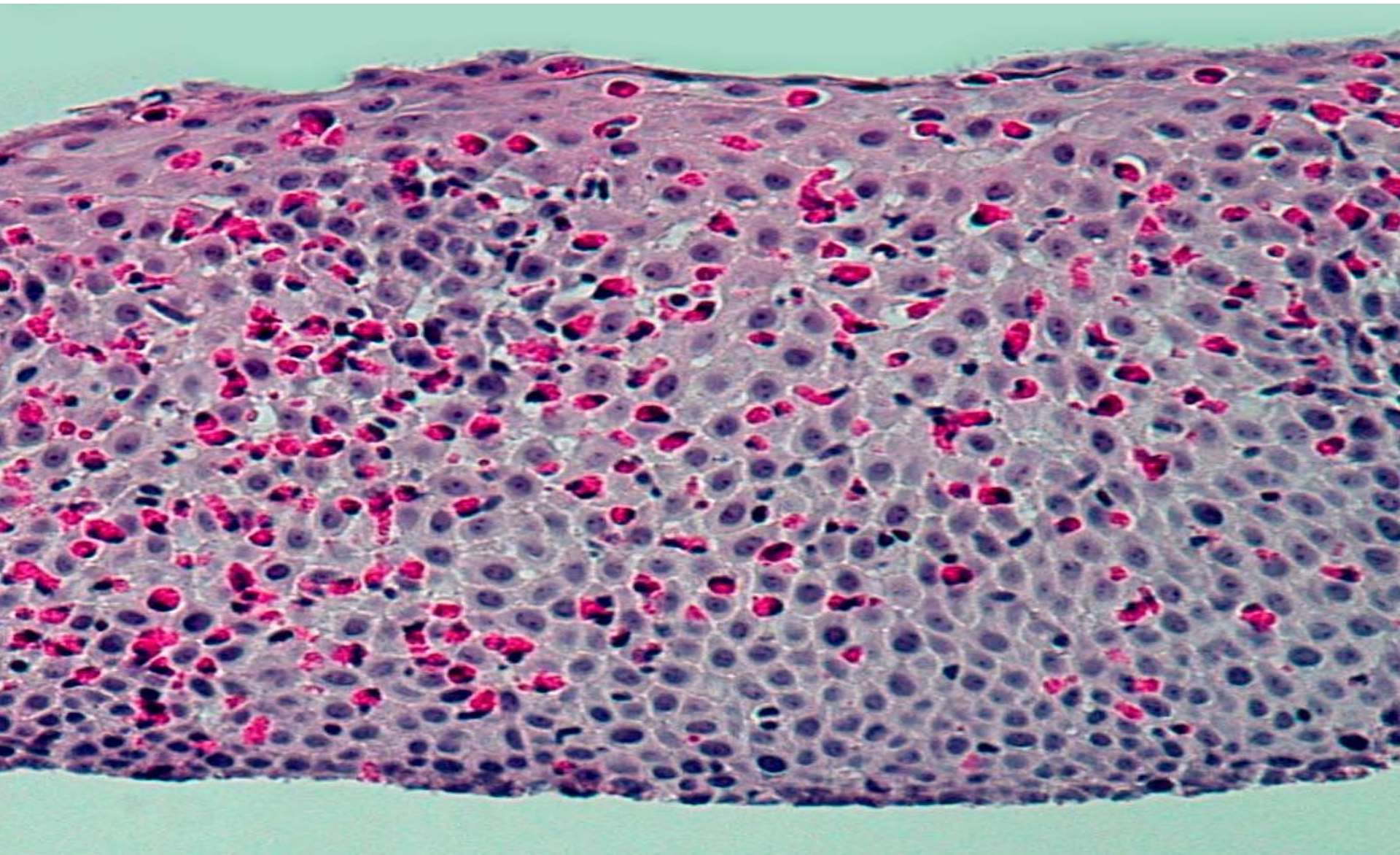
Journée d'Automne
CHUV, Octobre 19 2017

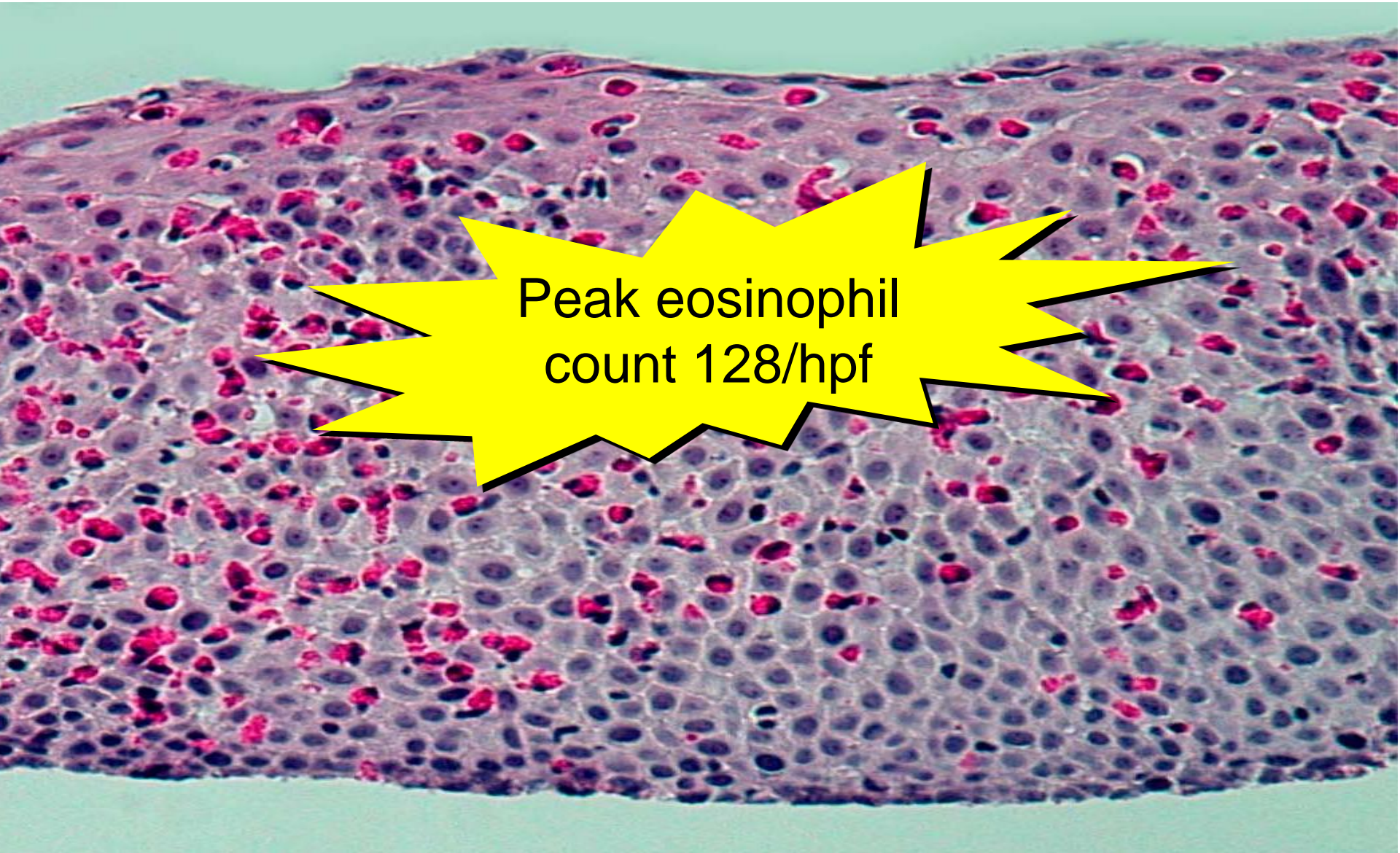
Eosinophilic Esophagitis

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Peak eosinophil
count 128/hpf

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

United European Gastroenterology Journal
0(0) 1–24

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DOI: 10.1177/2050640616689525

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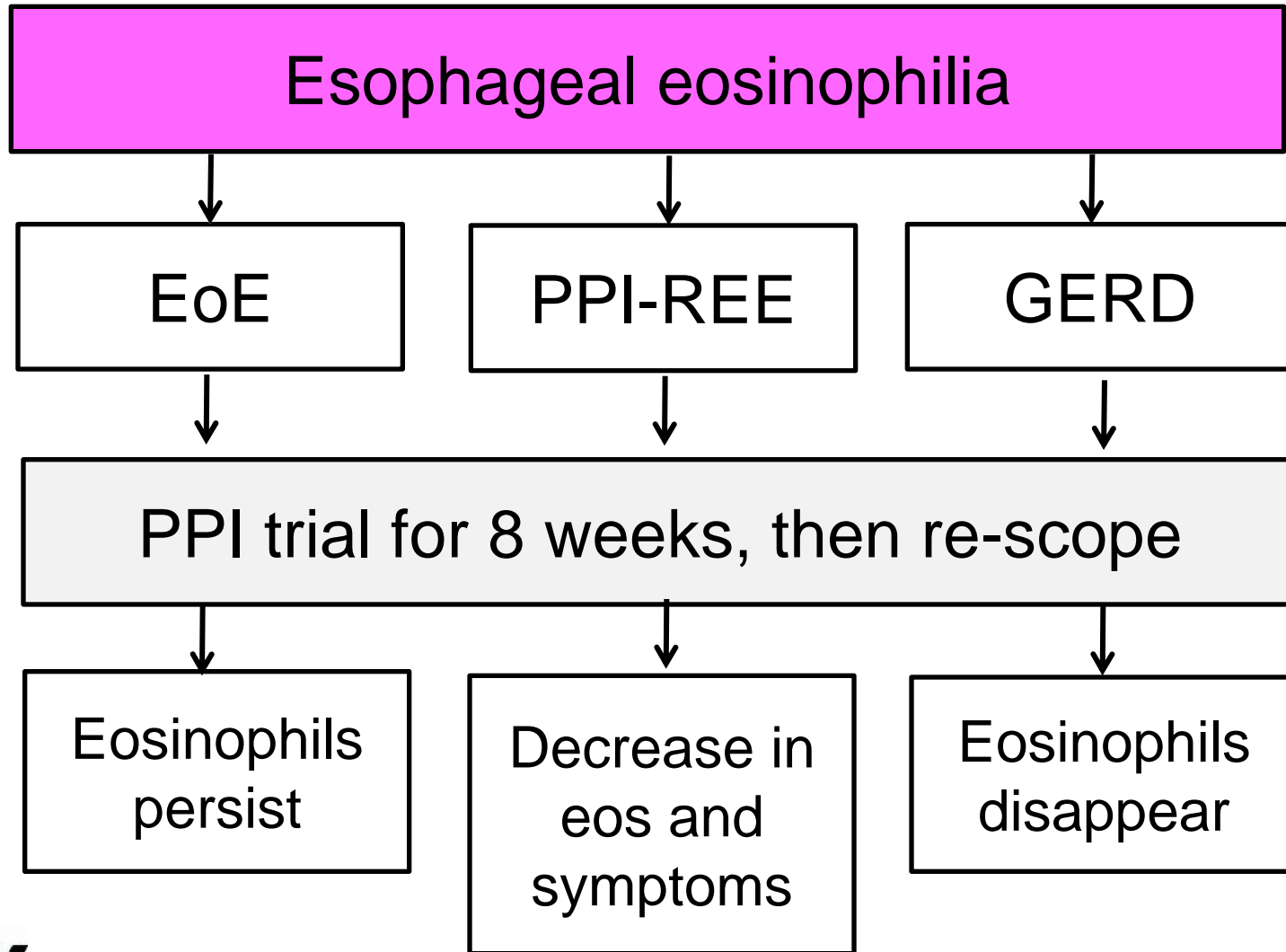


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Alain M Schoepfer¹⁷, Martin A Storr¹⁸, Ingrid Terreehorst¹⁹,
Alex Straumann²⁰ and Stephen E Attwood²¹

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



How to establish the diagnosis



How to establish the diagnosis

Esophageal eosinophilia

Under PPI: peak eos count 118/hpf
Symptom evolution (VAS): 7/10 => 6/10

PPI trial for 8 weeks, then re-scope

Eosinophils
persist

Decrease in
eos and
symptoms

Eosinophils
disappear

Summary and questions

- 24yr old male
- EoE diagnosis 8/2017
- peak eos cout 118/hpf under PPI
- normal esophageal caliber

Which therapy to choose?

Therapeutic Options 2017: DDD

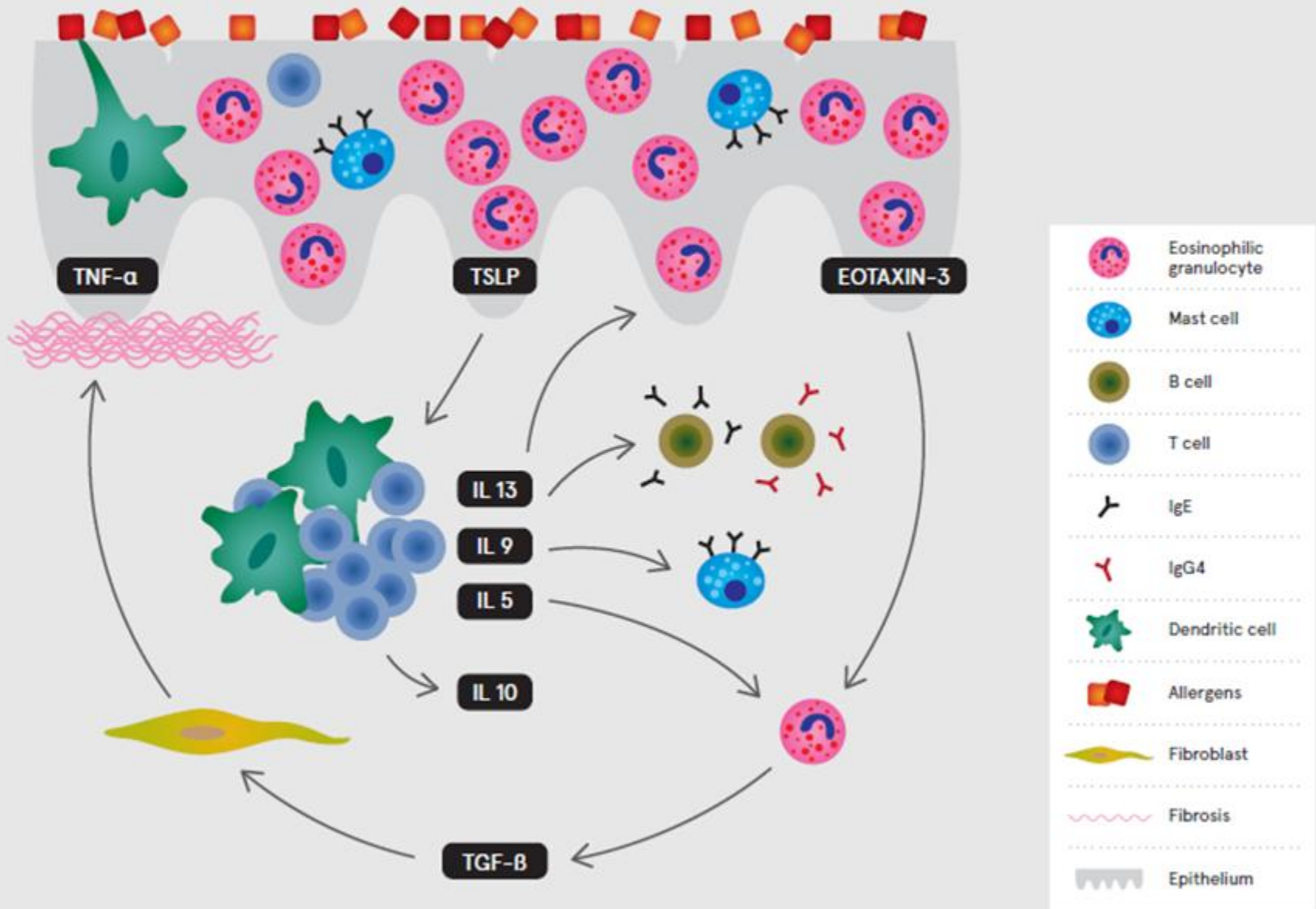
Drugs

- PPI
- Corticosteroids systemically (e.g. prednisone)
- Corticosteroids topically (e.g. budesonide, fluticasone)
- Anti-Allergens (Leukotriene-Antagonists)
- Biologicals (e.g. anti-IL5, anti-IL13, anti-IgE, CRTH2-blocker)
- Immunosuppressant's (e.g. azathioprine, 6-mercaptopurine)

Diet

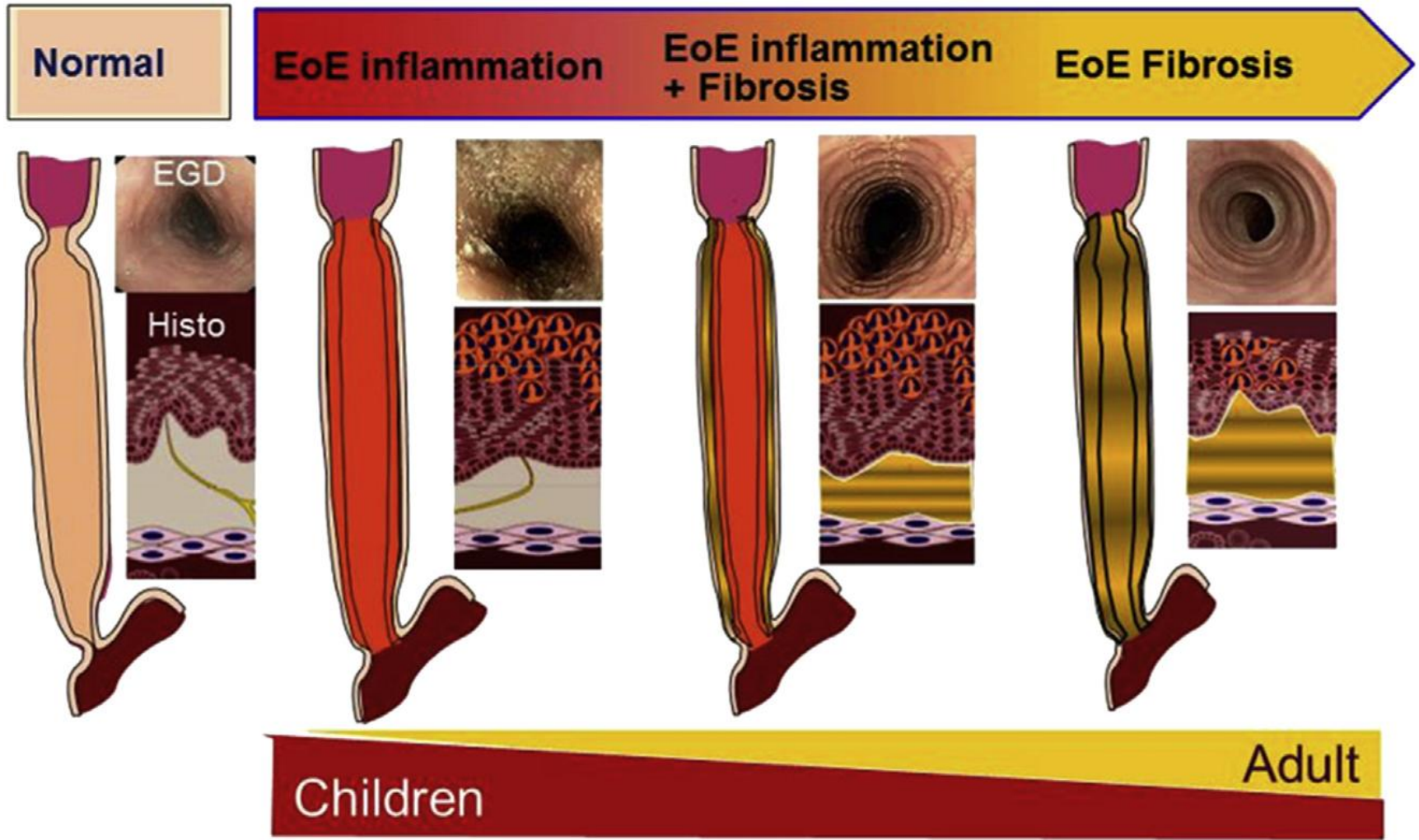
- Elemental Diet
- Elimination Diet (individually, allergy-testing based)
- Six-Food Elimination Diet

Dilation



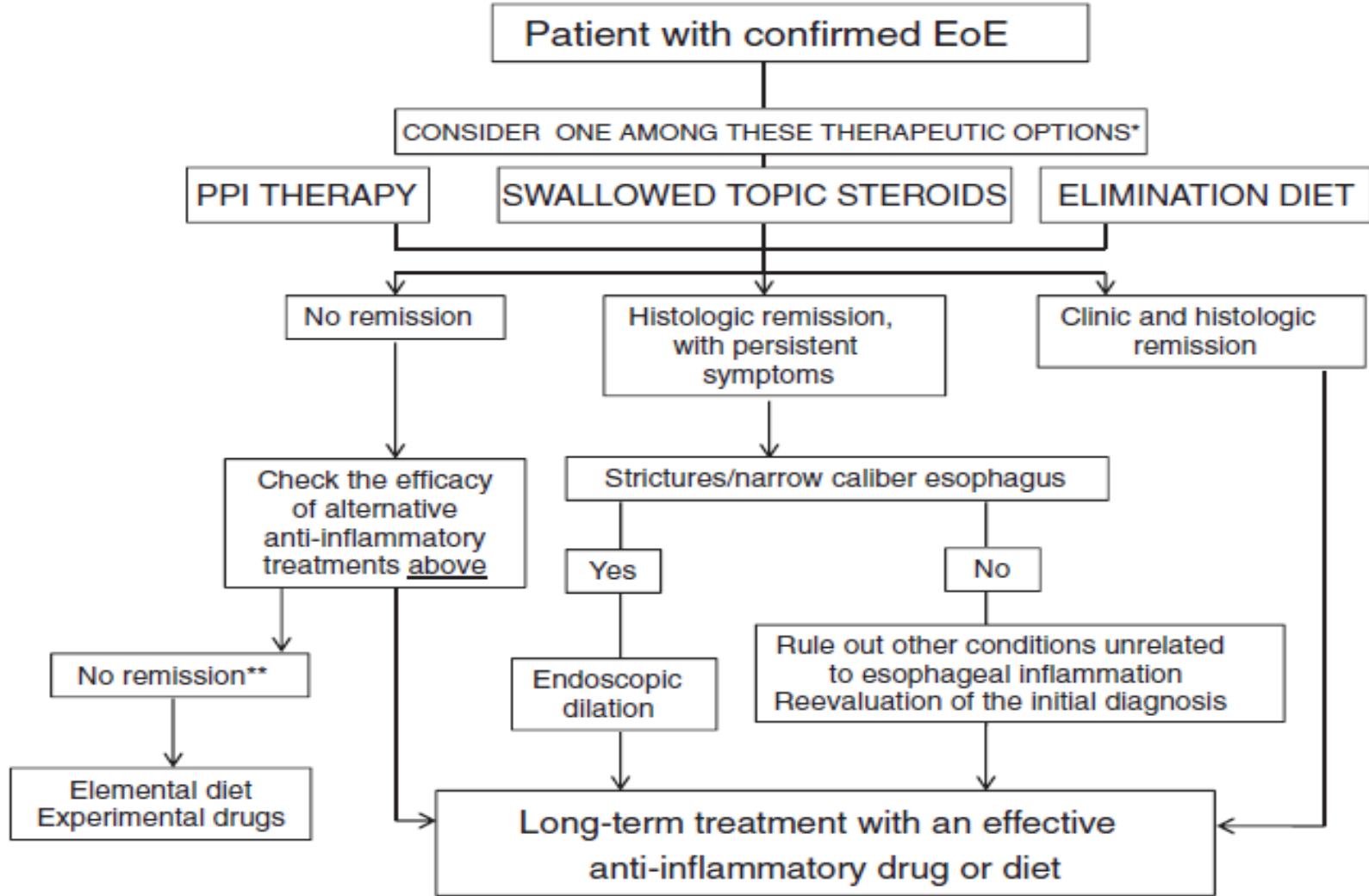
Schoepfer AM, et al. Dig Dis 2016

EoE Conceptual Model





Therapy algorithm 2017



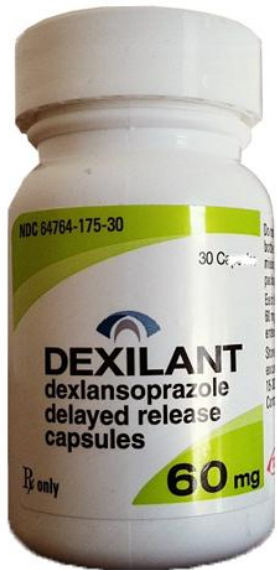
*In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered

** Refer the patient to an EoE center

Proton pump inhibitors

50%

Clinical and
histologic response



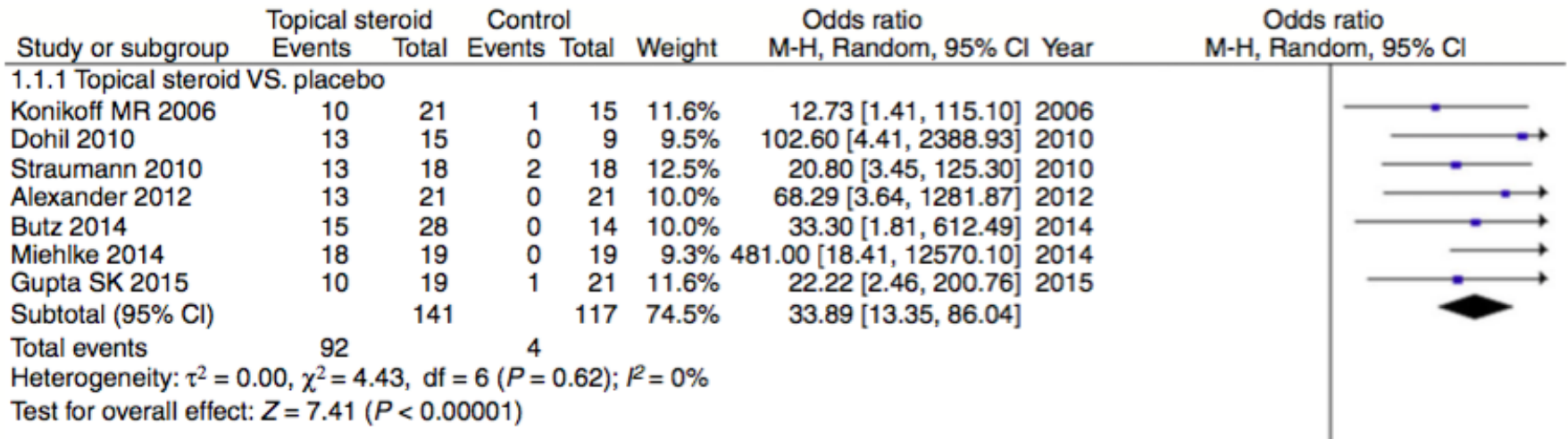
Lucendo AJ, et al. Clin Gastroenterol Hepatol 2016

Short-term Treatment with Topical Steroids in EoE Placebo-controlled Trials

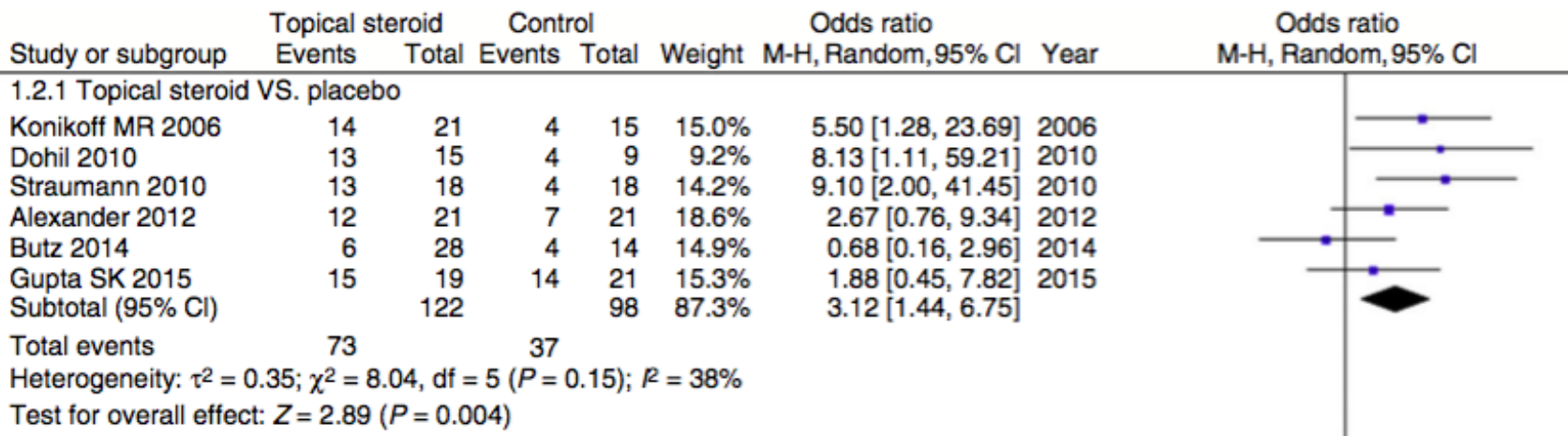
Publication	Pat. (n)	Mean age	Topical Steroid	Formulation	Dosage/day	Duration (weeks)
Konikoff et al. Gastro 2006	36	9,6	Fluticasone	Spray (swallowed)	2 x 400 ug	12
Straumann et al. Gastro 2010	36	36	Budesonide	Suspension	2 x 1 mg	2
Dohil et al. Gastro 2010	32	7,8	Budesonide	Suspension	1-2 mg body weight adapted	12
Alexander et al. CGH 2012	42	37,5	Fluticasone	Spray (swallowed)	2 x 880 ug	6
Butz et al. Gastro 2014	42	12,6	Fluticasone	Spray (swallowed)	2 x 880 ug	12
Miehlke et al. Gut 2016	76	39,7	Budesonide	Orodispersible Tablet, Suspension	2x1 mg /2x2 mg	2
Gupta et al. CGH 2016	81	9,1	Budesonide	Suspension	0,35 to 2,8 mg age-adapted	12
Dellon et al. Gastro 2017	93	21,5	Budesonide	Suspension	2 x 2 mg	12
Lucendo et al. DDW 2017	88	37,0	Budesonide	Orodispersible Tablet	2 x 1 mg	6

Metaanalyses of Topical Steroids in EoE

Histological Remission



Symptom Improvement



Safety of Topical Steroids in EoE

Autor, Year	Local Candidiasis (%)	
Konikoff 2006	1 / 21	4,8
Schäfer 2008	6 / 40	15
Straumann 2010	3 / 18	16,7
Dohil 2010	no data	
Alexander 2012	5 / 19	26
Peterson 2010	no data	
Dellon 2012	3 / 22	13,6
Moawad 2013	1 / 21	4,7
Butz 2014	no data	
Miehlke 2016	6 / 57	10,5
Gupta 2016	2 / 60	3,3
Dellon 2017	2 / 51	3.9
Lucendo 2017	3 / 59	5.1
TOTAL	32 / 368	8.7 %

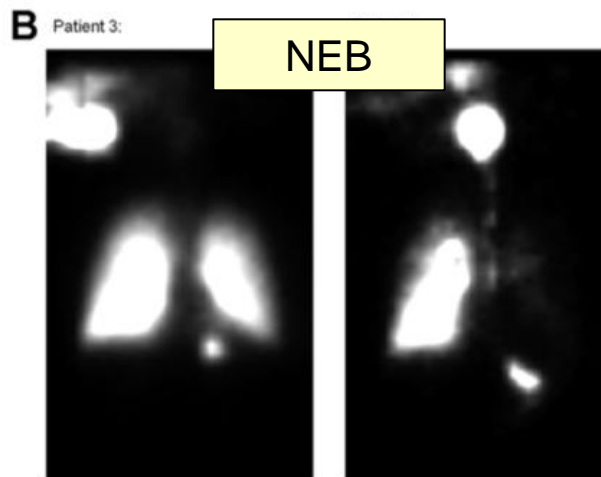
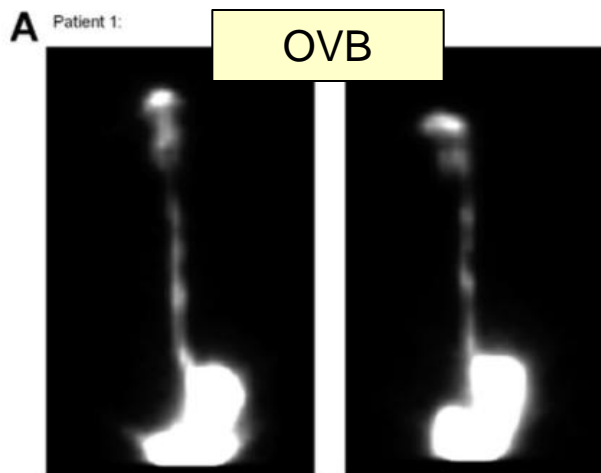
Topical Steroids in EoE are effective and safe, but ... formulation matters !



Viscous Topical Is More Effective Than Nebulized Steroid Therapy for Patients With Eosinophilic Esophagitis

EVAN S. DELLON,^{*,‡} ARIF SHEIKH,[§] OLGA SPECK,^{||} KIMBERLY WOODWARD,^{||} ANN B. WHITLOW,[§]
 JESSICA M. HORES,^{*} MARIJA IVANOVIC,[§] ALLEN CHAU,[§] JOHN T. WOOSLEY,^{||} RYAN D. MADANICK,^{*,‡}
 ROY C. ORLANDO,^{*,‡} and NICHOLAS J. SHAHEEN^{*,‡}

n=25 randomized, Budesonide 2x1 mg/d, 8 weeks
 Oral Viscous Suspension versus Nebulized (& swallowed)



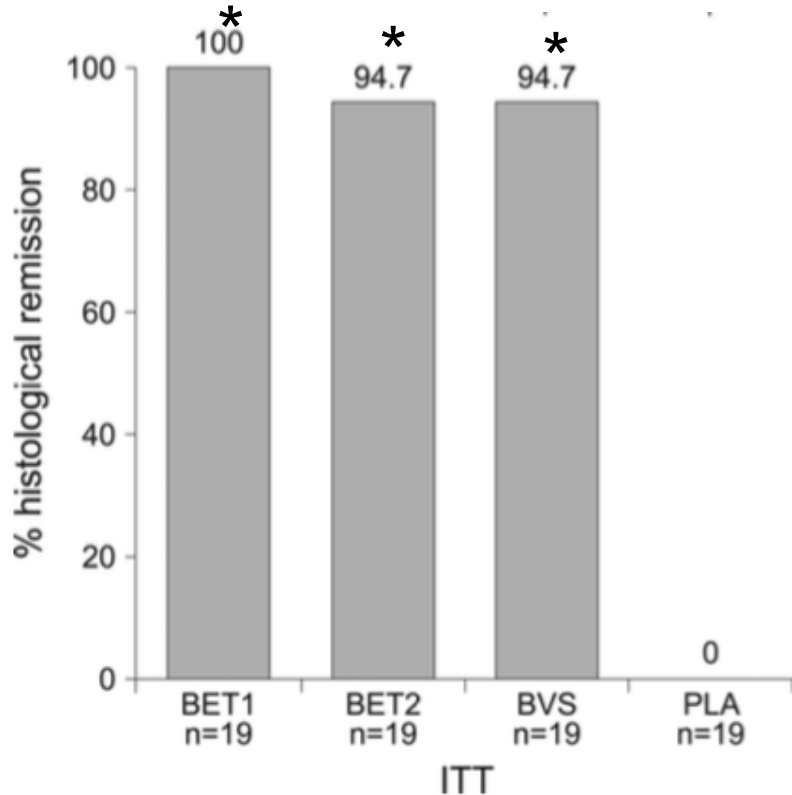
	OVB n=11	NEB n=11	p
Eosinophil counts	83 -> 11	101 -> 89	.02
Mucosal medication contact time	48.9	19.2	.005
Inverse correlation R 0.67; p=0.001			
EGD improved	91	45	.02

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

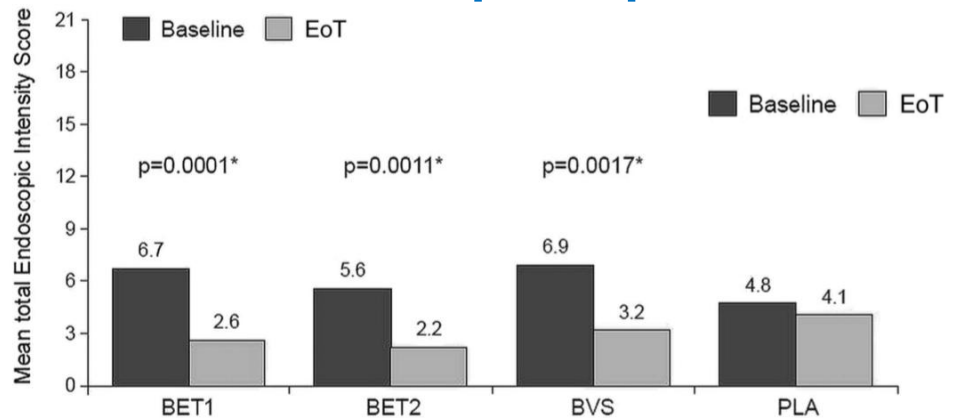
Phase 2, rx, db, pc, double-dummy, 76 adults, 2 weeks

Budesonide orodispersible tablet (2x1 mg) vs. viscous suspension (2x1/2x2 mg) Endoscopic Improvement

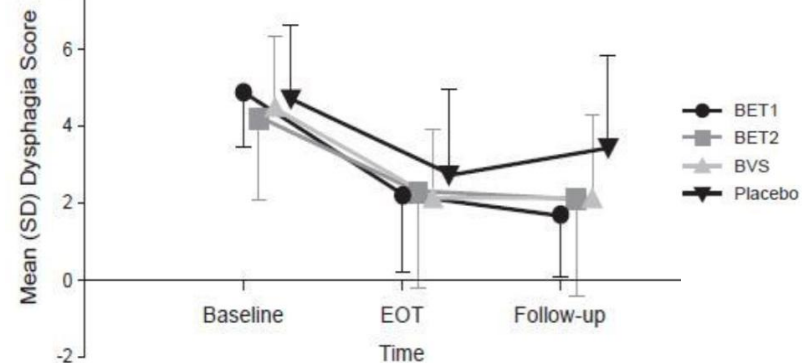
Histological Remission



* p<0.0001 vs. placebo



Symptom Improvement

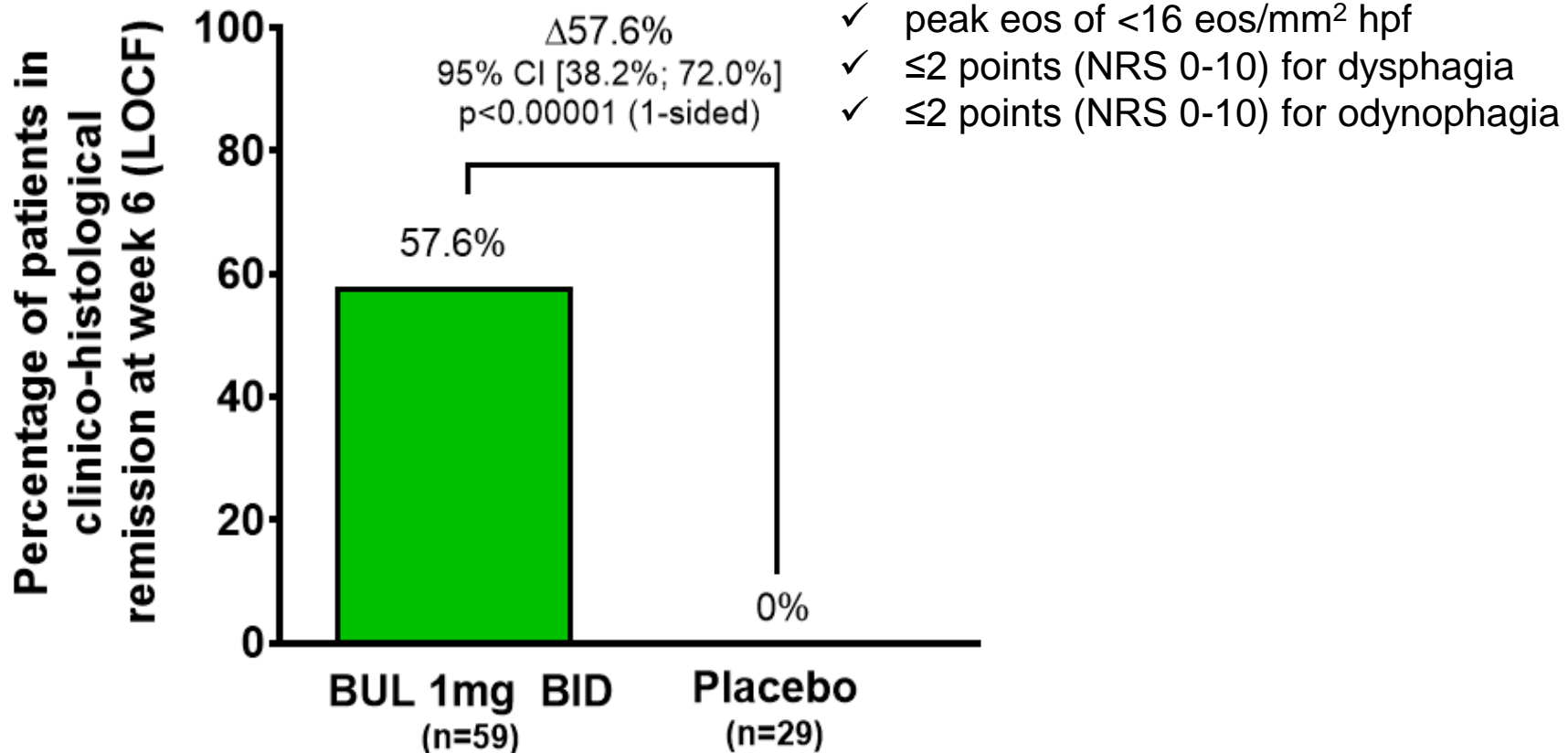


Budesonide Orodispersible Tablets for Active EoE

Phase 3: rx, db, pc, mc, budesonide 2 x 1m g/d, 6 weeks, n= 88

Primary Endpoint: Clinico-histological

Remission



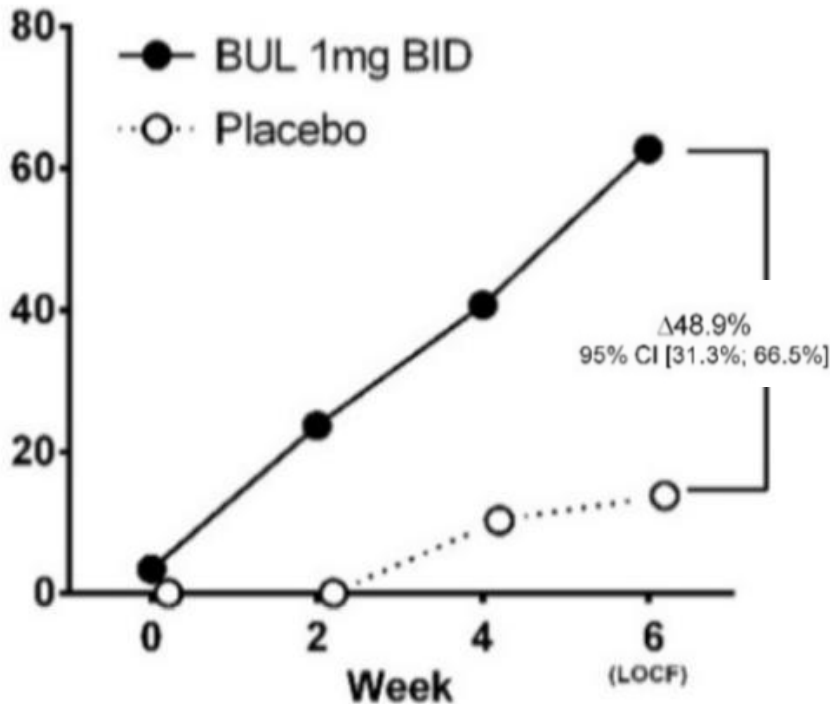
Lucendo et al. DDW 2017; Miehlke et al, EAACI & DGVS 2017, Straumann et al. UEGW 2017, Straumann et al. SGG 2017

Budesonide Orodispersible Tablets for Active EoE

Phase 3: rx, db, pc, mc, budesonide 2 x 1m g/d, 6 weeks, n= 88

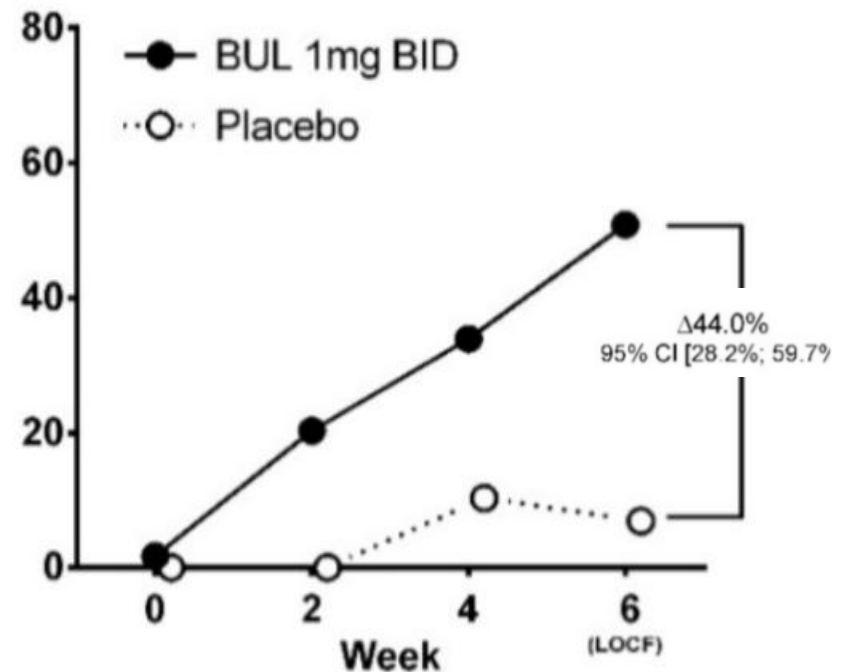
Resolution of Dysphagia (% patients)

Percentage of patients with resolution of dysphagia



Clinical Remission (EESAI-PRO ≤ 20)

Percentage of patients in clinical remission defined as weekly EEsAI-Pro ≤ 20

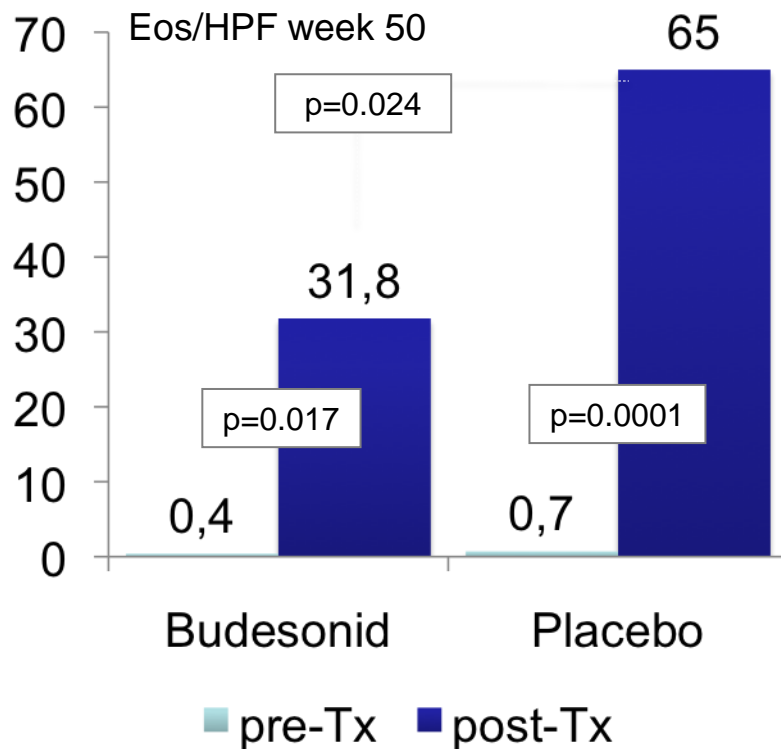


Long-term Therapy of EoE with Budesonide Suspension

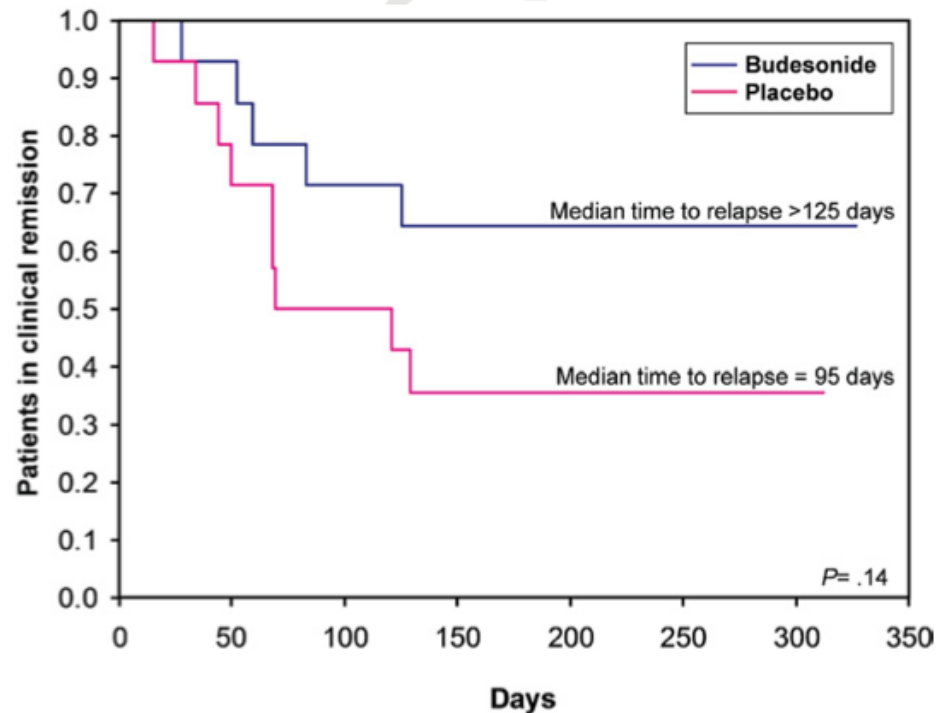
rx, db, pc, n=28

Budesonide Suspension 2 x 0,25 mg / day or Placebo, 50 weeks

Eosinophil counts Week 50



Clinical Remission



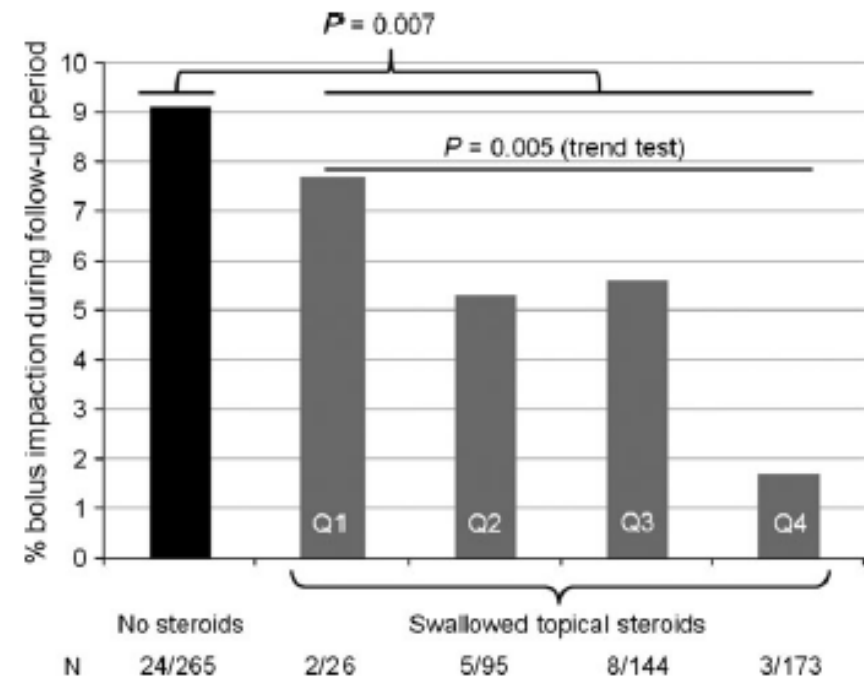
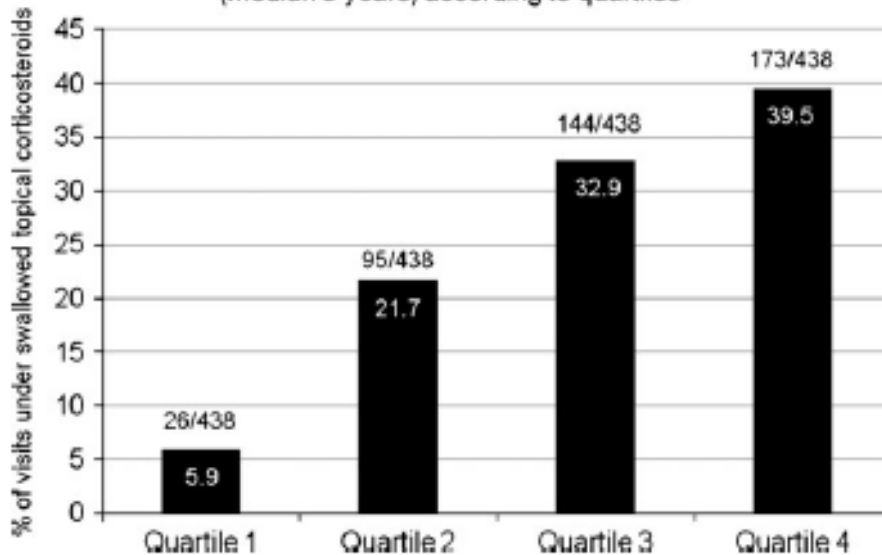
ORIGINAL ARTICLE

GASTROINTESTINAL DISEASES

Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis

T. Kuchen^{1,*}, A. Straumann^{2,3,*}, E. Safroneeva⁴, Y. Romero^{5,6}, C. Bussmann⁷, S. Vavricka^{1,8}, P. Netzer⁹, A. Reinhard¹⁰, S. Portmann¹¹ & A. M. Schoepfer¹²

Use of swallowed topical corticosteroids during the follow-up period (median 5 years) according to quartiles



Median follow-up time 5 years

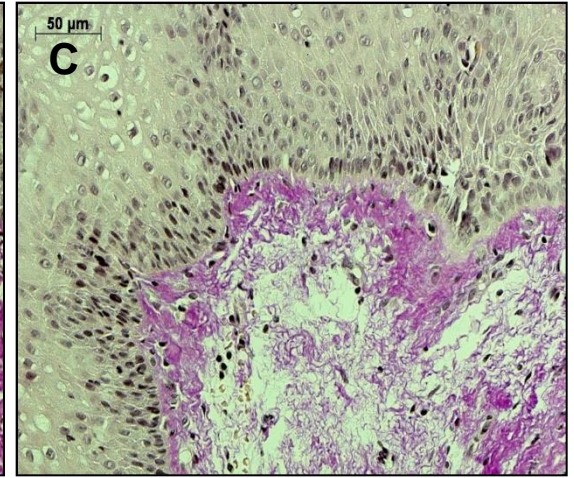
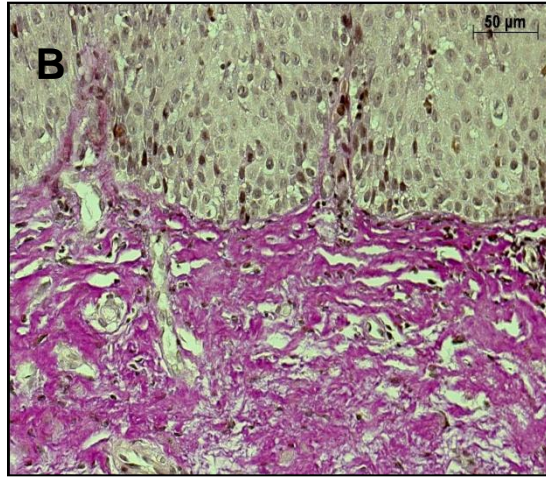
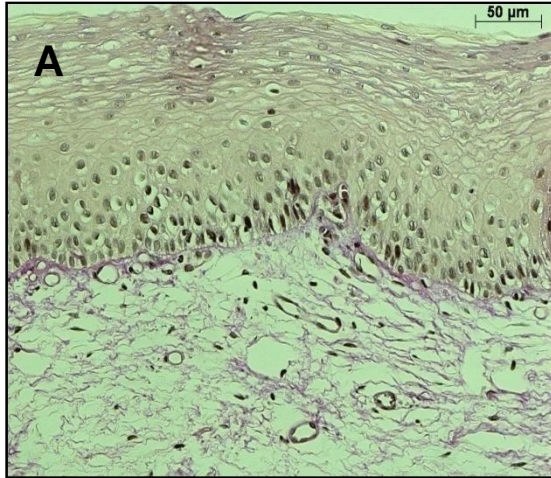
Swallowed budesonide can reduce subepithelial fibrosis

Control
(esophagus healthy)

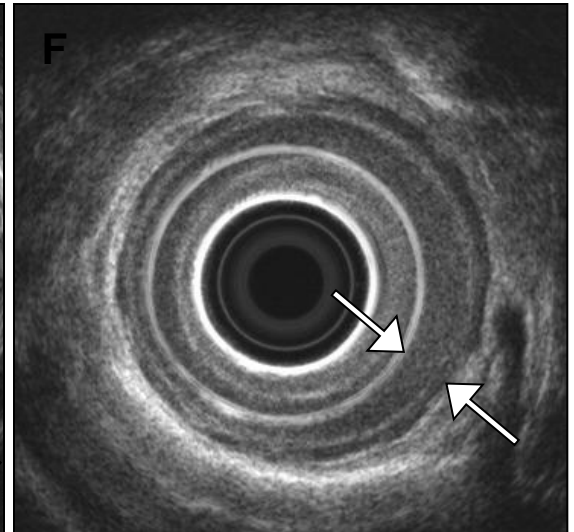
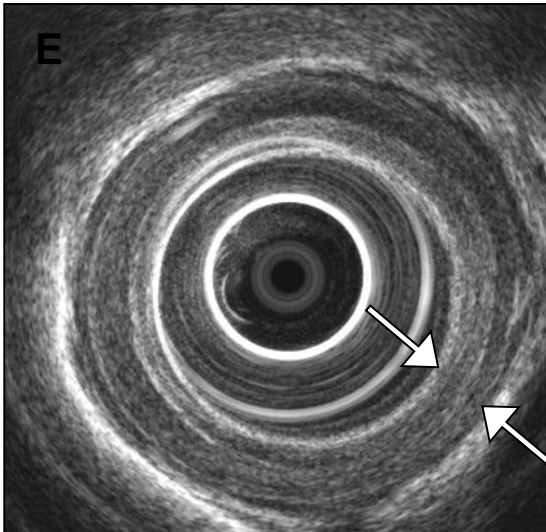
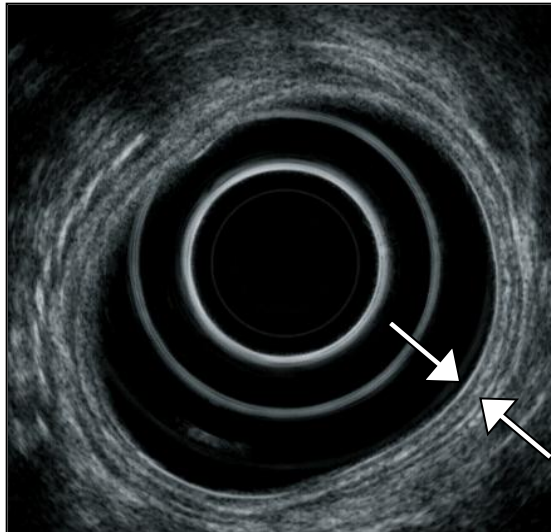
EoE Patient
Pre-treatment

EoE Patient
Post-treatment

EvG



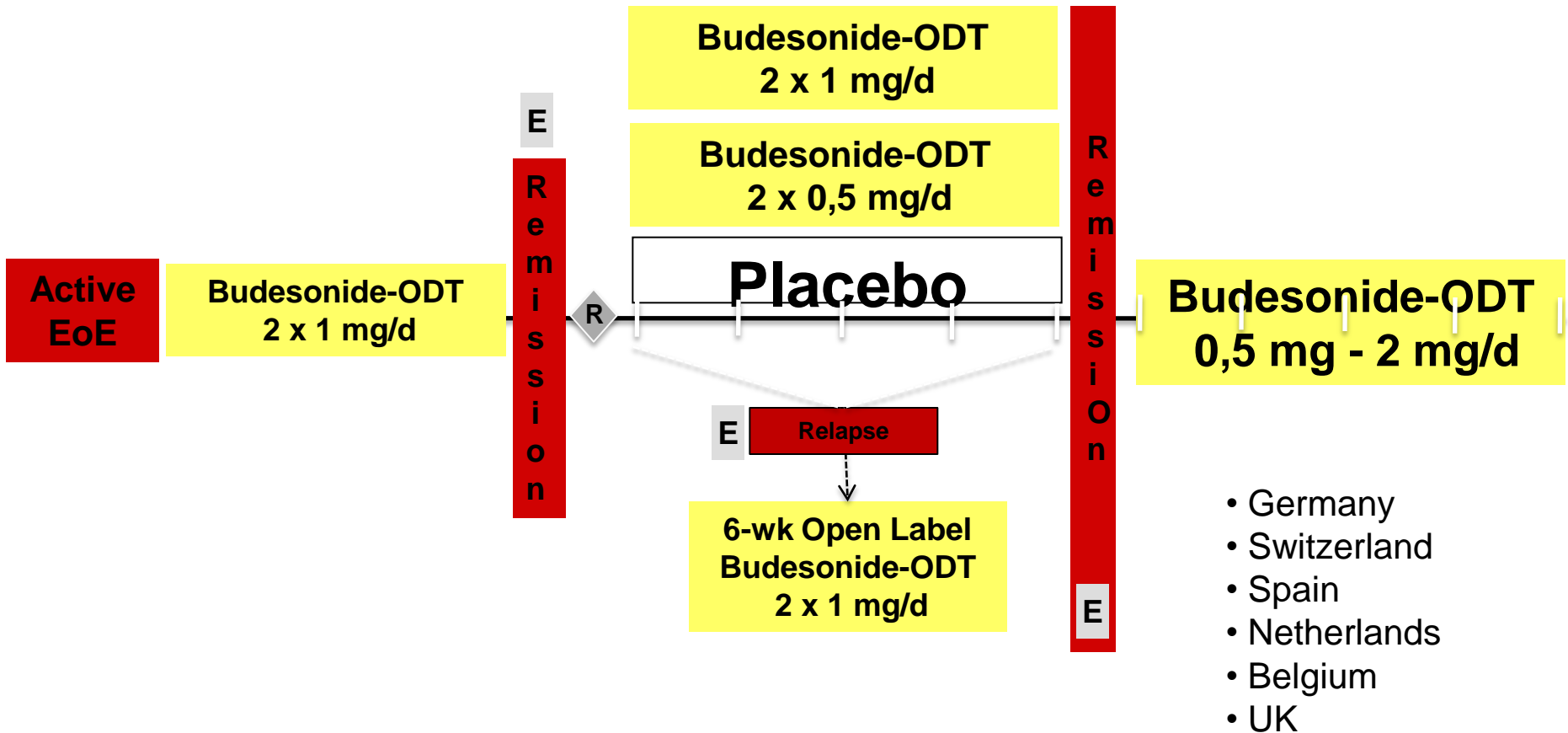
EUS



Long-term Maintenance Therapy of Active EoE in Adults with Budesonide Orodispersible Tablet (BUL-2/EER)

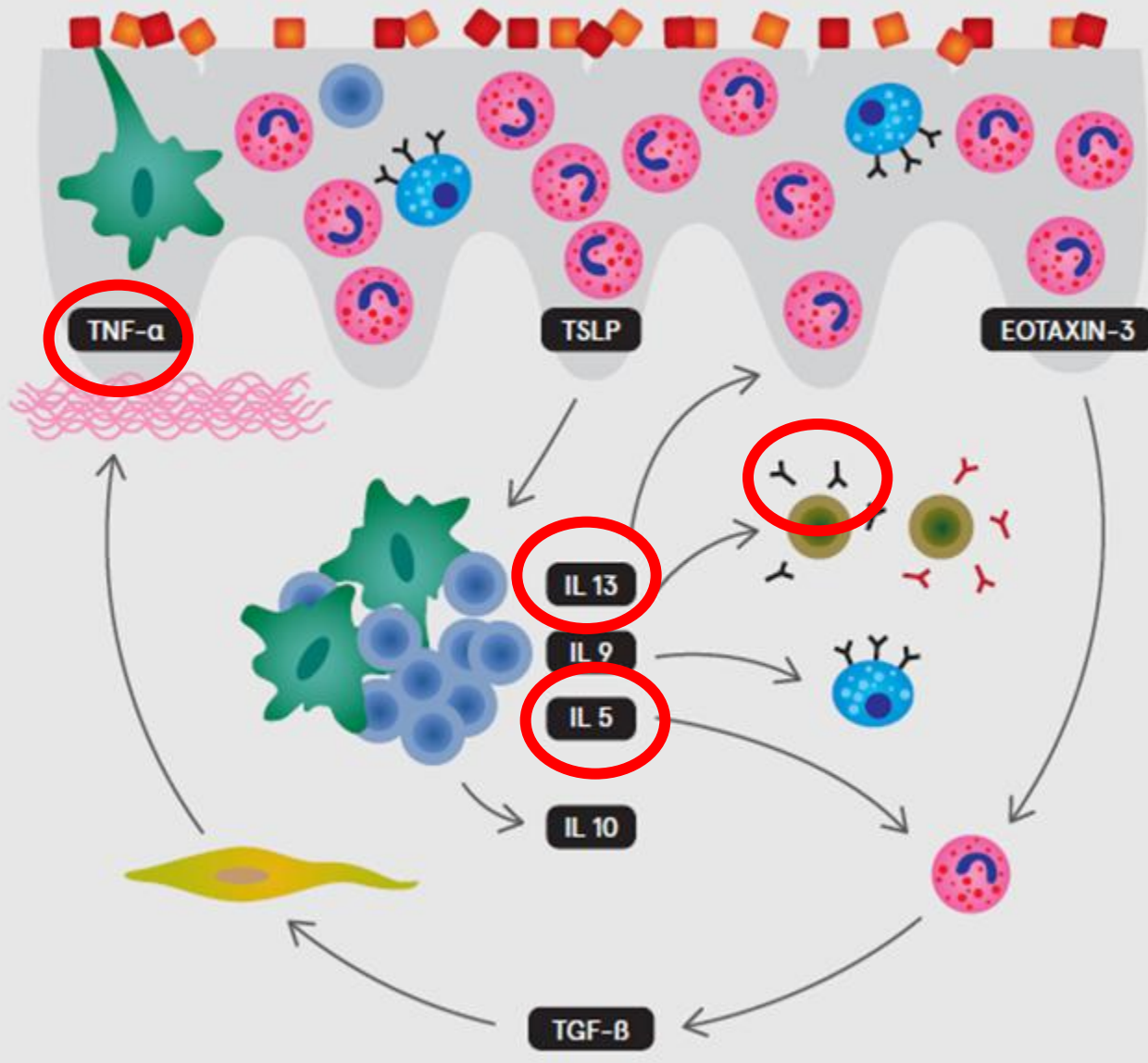
Double-blind
48 weeks












Open-Label
48 weeks



Is there anything beyond Steroids ?





-  Eosinophilic granulocyte
-  Mast cell
-  B cell
-  T cell
-  IgE
-  IgG4
-  Dendritic cell
-  Allergens
-  Fibroblast
-  Fibrosis
-  Epithelium

Biologicals in EoE

Publication	Study Design	Monoclonal Antibody	Symptom Response	Reduction of Esophageal Eosinophilia
Straumann, Gut 2010 Assa'ad, Gastro 2011 Spergel, JACI 2012	rx, db, pc	Anti-IL5 Mepolizumab Reslizumab	none	modest
Rothenberg, JACI 2015	rx, db, pc	Anti-IL-13 QAX576	none	modest
Clayton, Gastro 2014	rx, db, pc	Anti-IgE Omalizumab	none	none
Straumann, JACI 2008	Case series (n=3)	Anti-TNF Infliximab	none	none

HEROES study



OP325 - A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF A NOVEL RECOMBINANT, HUMANISED, **ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY (RPC4046)** IN PATIENTS WITH ACTIVE EOSINOPHILIC OESOPHAGITIS: RESULTS OF THE **HEROES STUDY**, Hirano I, et al. USA and Switzerland

phase II RCT - efficacy and safety

RPC4046 (180 mg, 360 mg IV, then sc. weekly) vs. **PBO** [1:1:1]

Primary endpoint: histology Wk 16 / secondary end. : symptoms , safety.

Results: 90 patients, Eo mean count significantly reduced at wk 16 for both RPC4046 doses compared to PBO .

(mean change: PBO -4.4, LD -94.8, and HD -99.9 [both $p < 0.0001$ vs PBO]).
Dysphagia improvement (NS), adverse events (AEs) : 65% PBO/LD, 85% HD.

RPC4046 significantly reduces esophageal eosinophilic inflammation and improves endoscopic features at both dose levels.

symptom improvement: **HD > LD. → phase 3**

DIETS



Most common food allergens

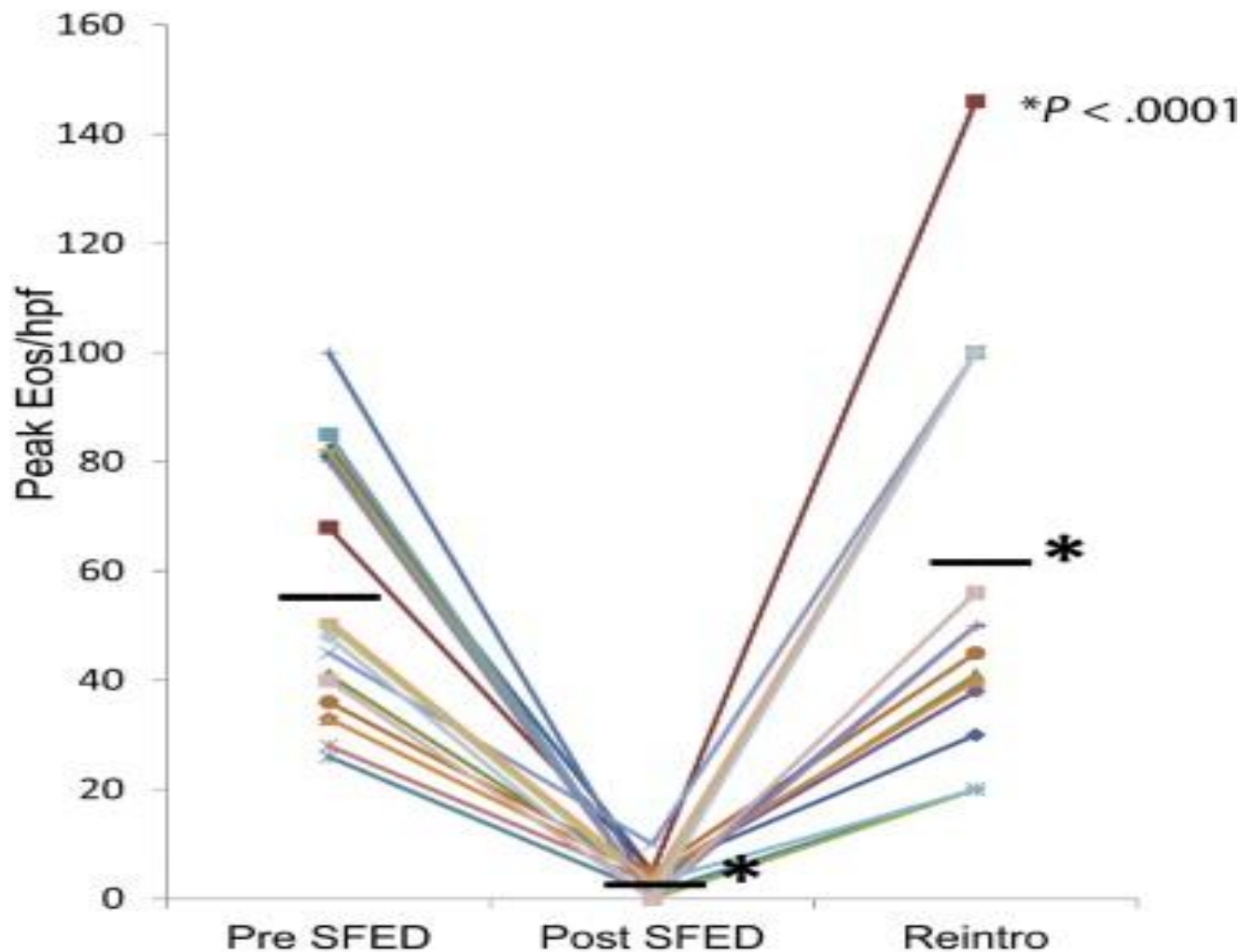
90% of IgE mediated allergies in young adults are caused by

- Cow's milk
- egg
- soy
- peanut / tree nuts
- wheat
- seafood



Sicherer SH, et al. JACI 2006;117:470

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors



Gonsalves N, et al. Gastroenterology Volume 142, Issue 7 2012 1451 - 1459.e1



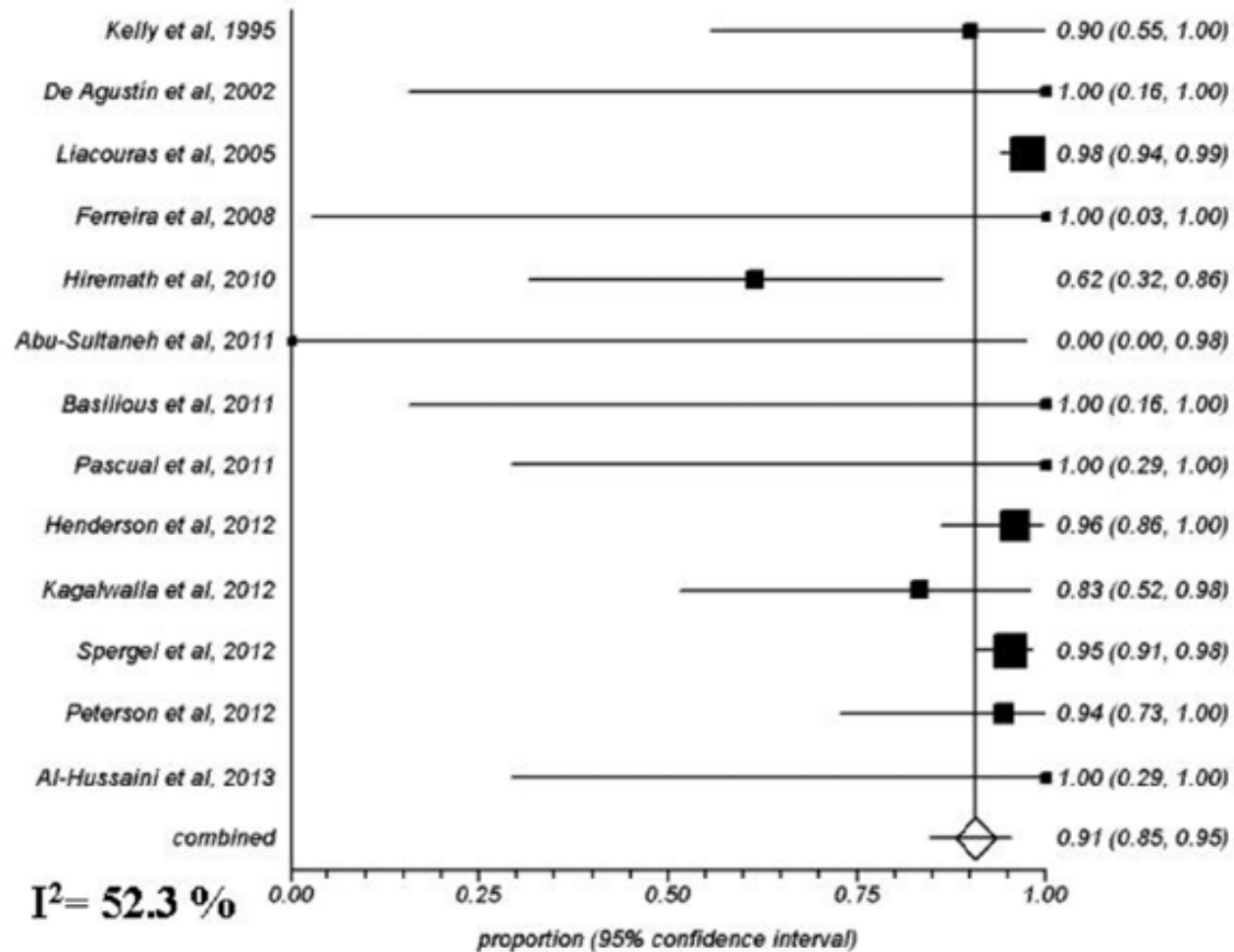
Which is the best diet?

Table 2 Characteristics of the available dietary modalities for treating eosinophilic oesophagitis

Item	Type of dietary therapy		
	Elemental diet	Targeted elimination diet	Empirical elimination diet
Clinicopathological success rate	>80%	Children 50–70% Adults 20–30%	50–70%
Number of eliminated foods	All food groups eliminated	Typically <6 foods eliminated	≤6 foods eliminated
Common food triggers identified	Not applicable	Milk, wheat, egg, soy	Milk, wheat, egg
Number of endoscopies required	Multiple (one endoscopy per reintroduced food group)	Multiple (one endoscopy per reintroduced food group)	Multiple (one endoscopy per reintroduced food group)
Drawbacks	Costly May require feeding tube May impact QoL	May impact QoL	May impact QoL

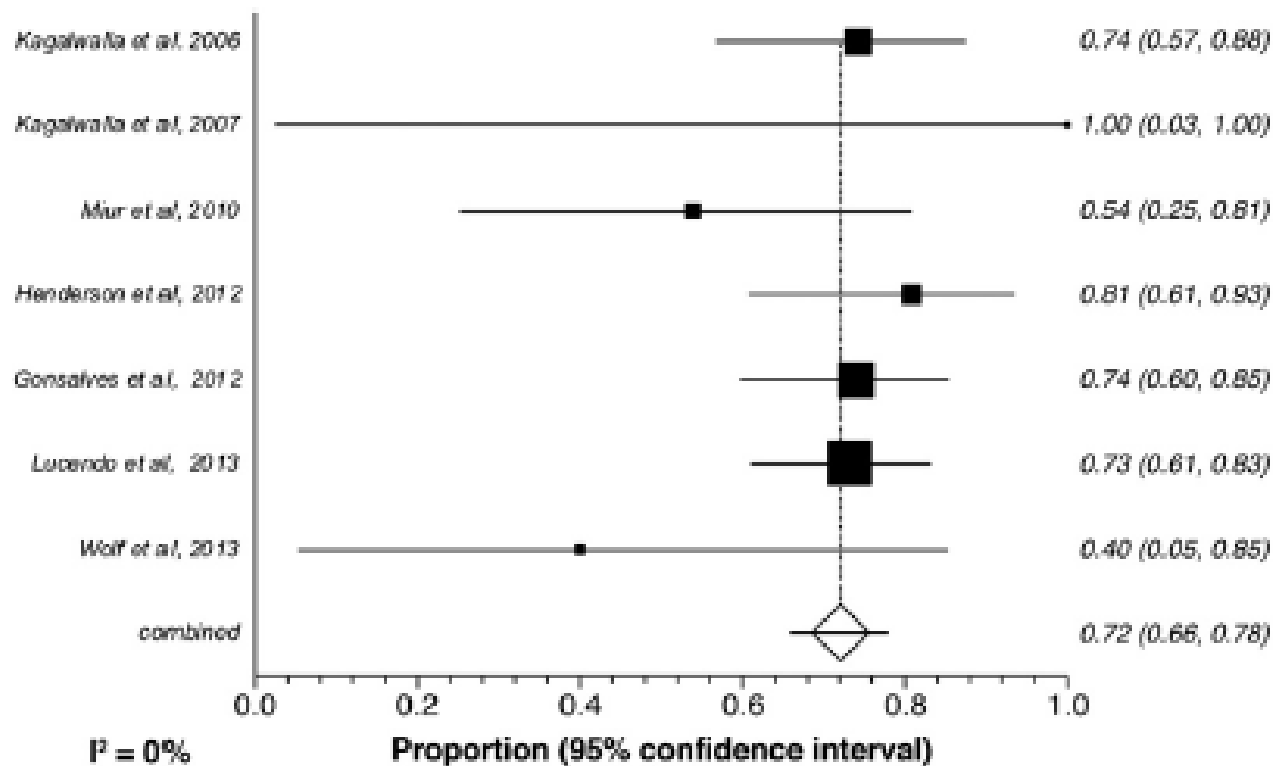
QoL, quality of life.

Efficacy of Elemental Diet: 91%



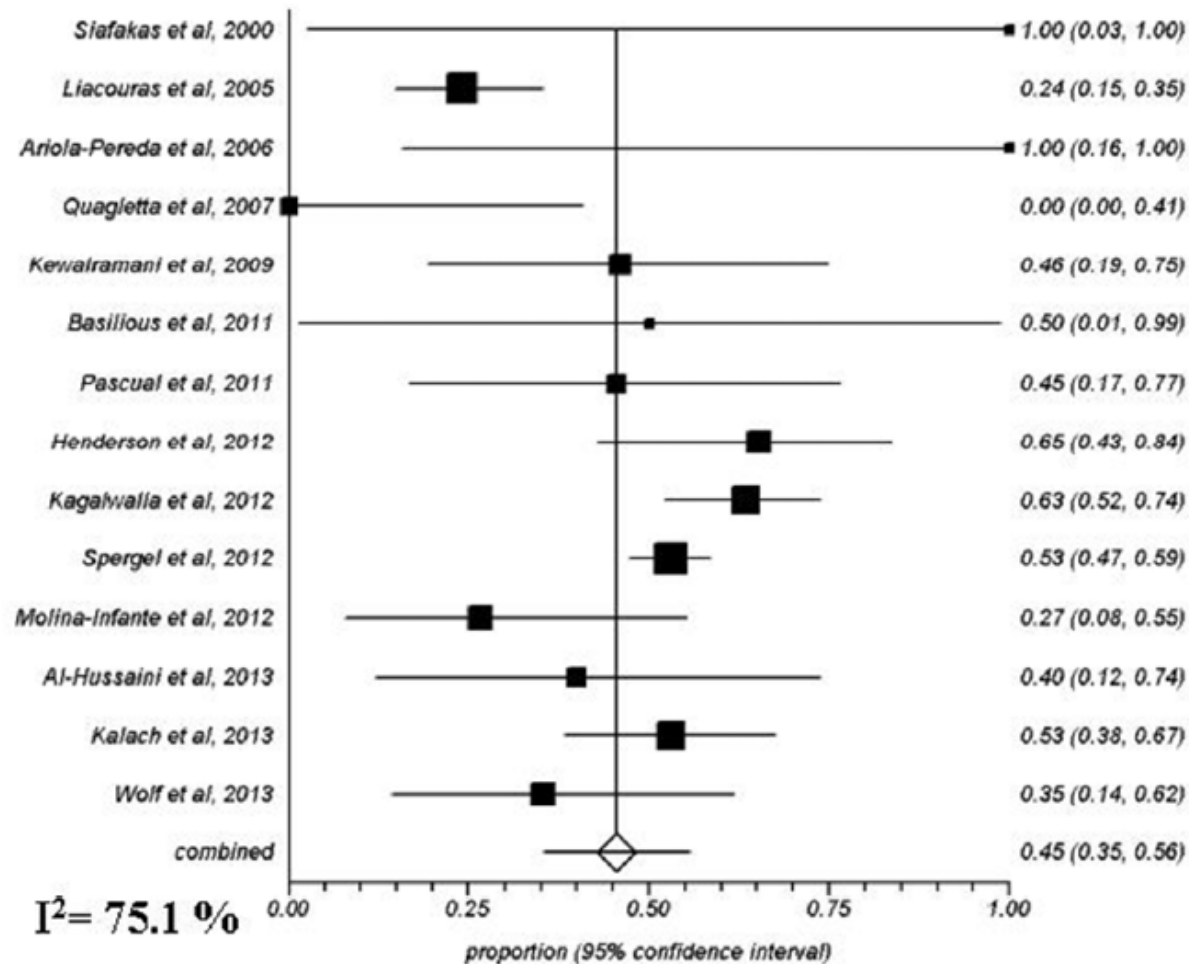
Outcome: histologic remission

Efficacy of 6-food elimination: 72%



Outcome: histologic remission

Efficacy of targeted food elimination: 45%



Outcome: histologic remission

REVIEW

Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity[§]

D. Simon^{1,*}, A. Cianferoni^{2,3,*}, J. M. Spergel^{2,3}, S. Aceves⁴, M. Holbreich⁵, C. Venter^{6,7}, M. E. Rothenberg⁶, I. Terreehorst⁸, A. Muraro⁹, A. J. Lucendo¹⁰, A. Schoepfer¹¹, A. Straumann¹² & H. U. Simon¹³

Measuring specific IgE levels and/or skin prick tests is not sufficient to identify foods that cause EoE.

Elimination diets exclusively based on results of IgE-mediated sensitization to foods do not improve EoE in a significant number of patients.

[Allergy 2016;71\(5\):611-20.](#)

OP323 - STEP-UP EMPIRIC ELIMINATION DIET FOR PEDIATRIC AND ADULT EOSINOPHILIC ESOPHAGITIS: THE 2-4-6 STUDY. Molina-Infante J, et al. Spain

6 – Food elimination diet = high level of dietary restriction → 4 Food → 2 Food E-Diet ?

Pop: 93 EoE adults and children in 12 spanish hospital with lack of PPI response.

2 Food elimination diet = animal milks and gluten-containing cereals

Reponse : symptom improvement and < 15 eos/HPF, If non responders = > 4 FED => 6 weeks reintroduction – histologic reevaluation.

Results : 2-Food – 40% remission (38 patients), 4- food = 52% , 6 –food 65%

35% recuction of endoscopic procedures

A **step-up empiric diet strategy (2-4-6)** might be a cost-effective dietary strategy for EoE. **2 Food elimination diet (milk & Gluten) = 40% remission / 35% less endoscopies**

Pro / Cons of different therapies

Modality	Advantages	Shortcomings
Drugs - STC - Biologic therapies	<ul style="list-style-type: none">• Effective• No dietary restriction • Favorable safety profile	<ul style="list-style-type: none">• No FDA-approved drugs yet on the market• Long-term side effects / safety unknown• Costs, availability, limited clinical efficacy
Diets	<ul style="list-style-type: none">• Non-pharmacologic, effective treatment option• Antifibrotic	<ul style="list-style-type: none">• Repetitive EGDs may be necessary (up to 10x)• Needs motivated patient
Dilation	<ul style="list-style-type: none">• Long-lasting symptom improvement	<ul style="list-style-type: none">• No influence on underlying inflammation• Post-dilational pain• (safety)

Key points on EoE therapy

- therapeutic goals:
 - restore swallowing,
 - avoid impactions
- therapy options: drugs, diets, dilations
- budesonide tablets will probably be on Swiss market in 2018

Thank you

