Controverses en Gastroentérologie

4 Février 2016

Oesophagite à éosinophiles: comment la traiter en 2016?

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Lausanne, Switzerland

Outline

- Definition
- Pathogenesis
- Therapeutic options
- Conclusions

Definition

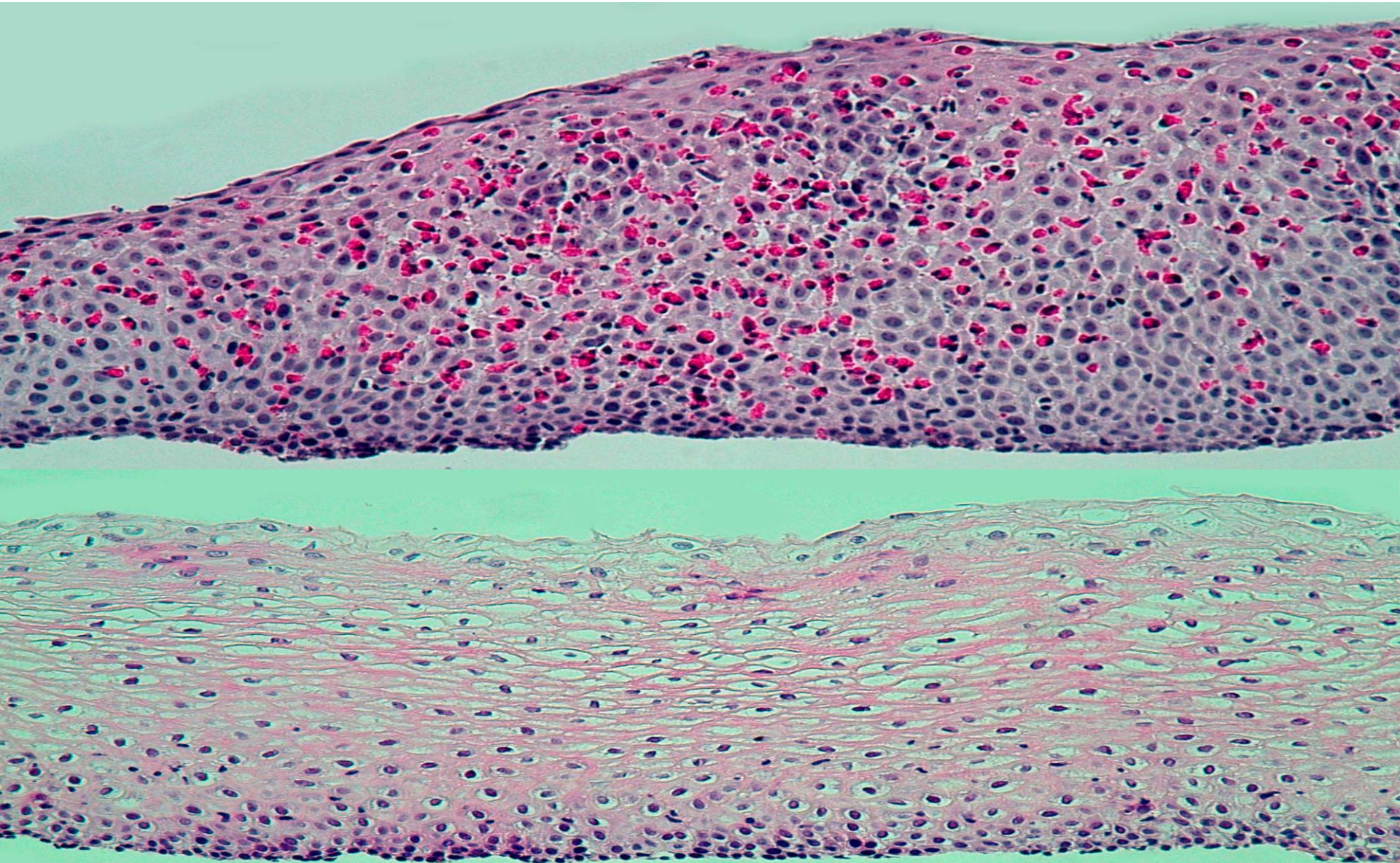
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

JACI 2011;128:3-20

Chris A. Liacouras, MD, Glenn T. Furuta, MD, Ikuo Hirano, MD, Dan Atkins, MD, Stephen E. Attwood, MD, FRCS, FRCSI, MCh, Peter A. Bonis, MD, A. Wesley Burks, MD, Mirna Chehade, MD, Margaret H. Collins, MD, Evan S. Dellon, MD, MPH, Ranjan Dohil, MD, Gary W. Falk, MD, MS, Nirmala Gonsalves, MD, Sandeep K. Gupta, MD, David A. Katzka, MD, Alfredo J. Lucendo, MD, PhD, Jonathan E. Markowitz, MD, MSCE, Richard J. Noel, MD, Robert D. Odze, MD, FRCP, Philip E. Putnam, MD, FAAP, Joel E. Richter, MD, FACP, MACG, Yvonne Romero, MD, Eduardo Ruchelli, MD, Hugh A. Sampson, MD, Alain Schoepfer, MD, Nicholas J. Shaheen, MD, MPH, Scott H. Sicherer, MD, Stuart Spechler, MD, Jonathan M. Spergel, MD, PhD, Alex Straumann, MD, Barry K. Wershil, MD, Marc E. Rothenberg, MD, PhD,* and Seema S. Aceves, MD, PhD* *Aurora and Denver, Colo, Milwaukee, Wis, Cincinnati, Ohio, Rochester, Minn, Philadelphia, Pa, Basel and Lausanne, Switzerland, Chapel Hill and Durham, NC, Boston, Mass, Chicago, Ill, San Diego, Calif, New York, NY, Indianapolis, Ind, Tomelloso, Spain, Greenville, SC, and North Shields, United Kingdom*

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

Squamous Epithelium with features of EoE compared with normal findings



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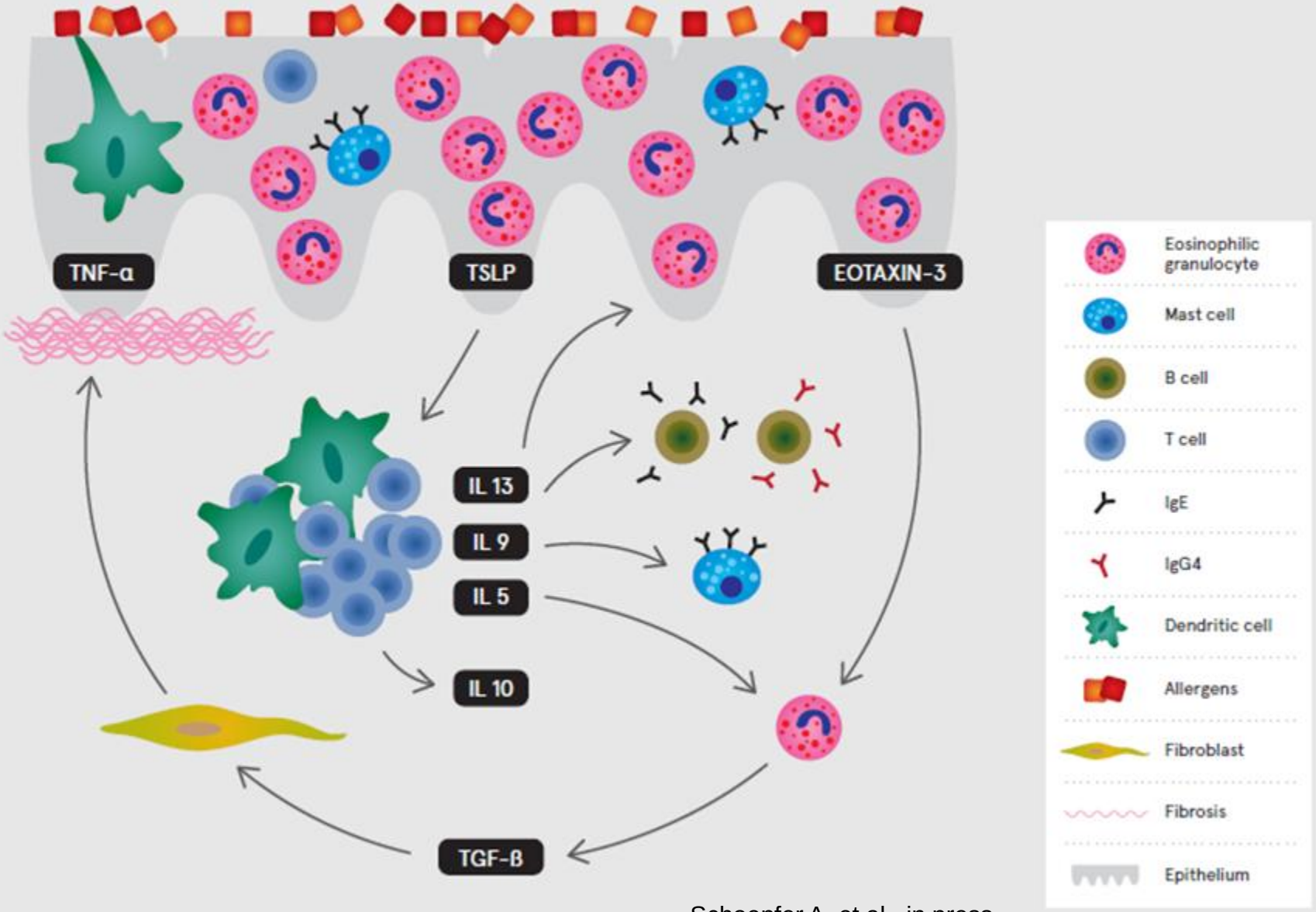
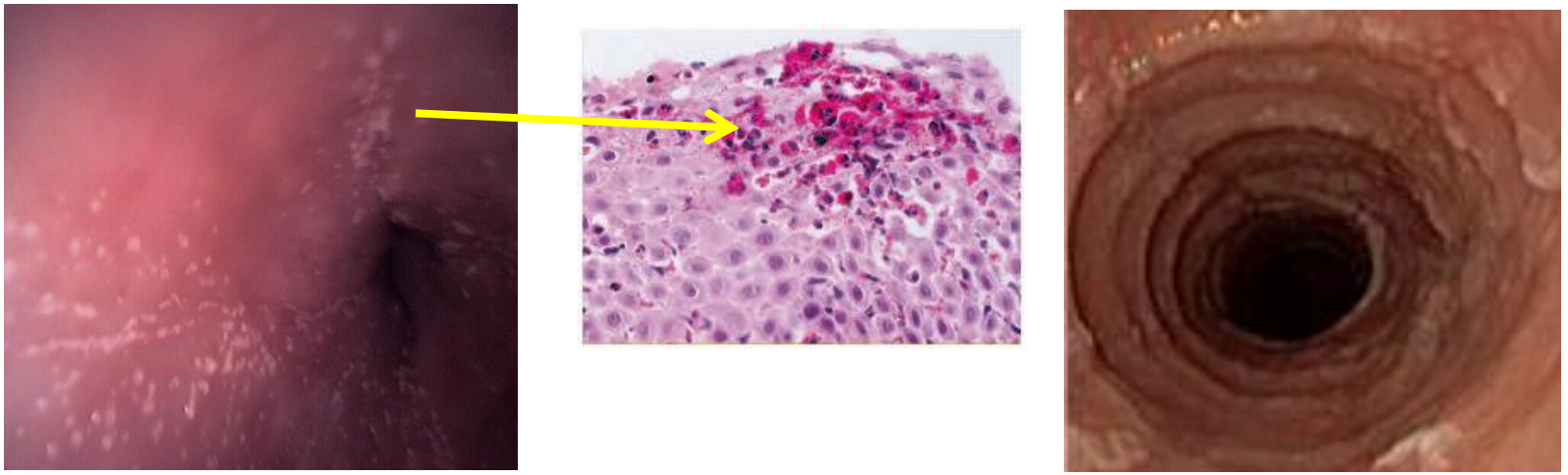


Schoepfer A, et al., in press

The story of two phenotypes



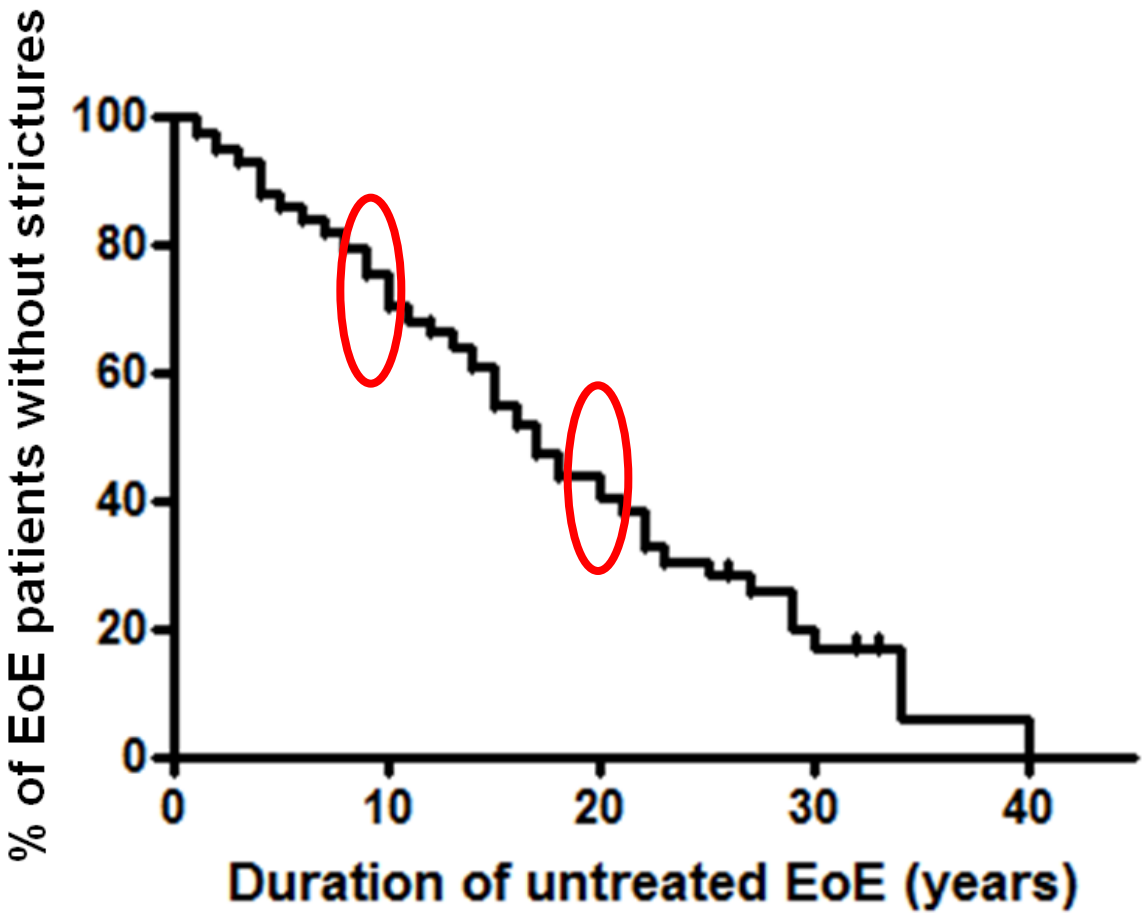
Inflammation → **Stenosis**

Schoepfer AM, et al. Am J Gastroenterol 2010;105:1062-70

Straumann A, et al. Clin Gastroenterol Hepatol 2008;6:598-600

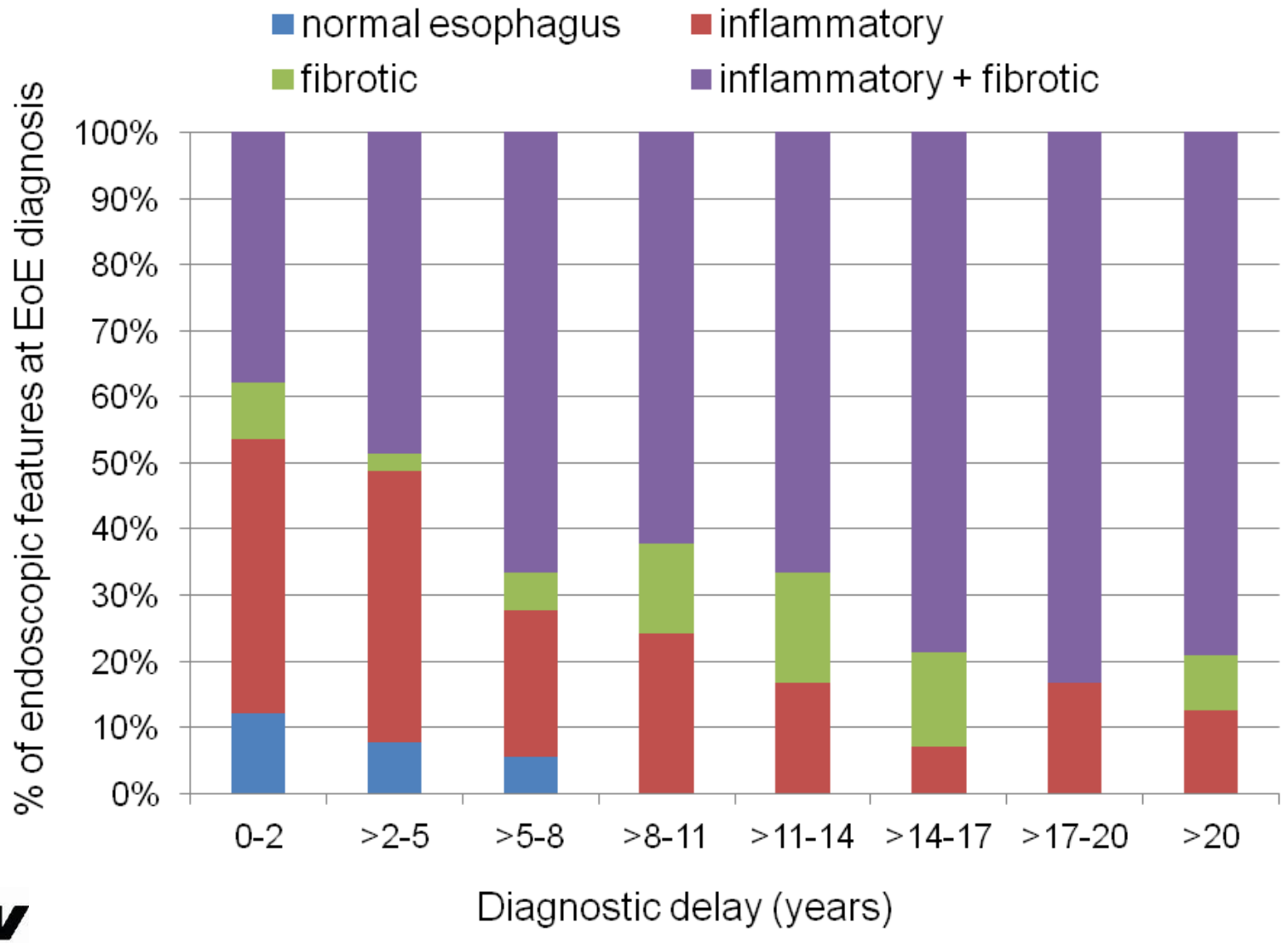
Straumann A, et al. Clin Gastroenterol Hepatol 2011;9:400-9

Stricture risk over time (n=200)



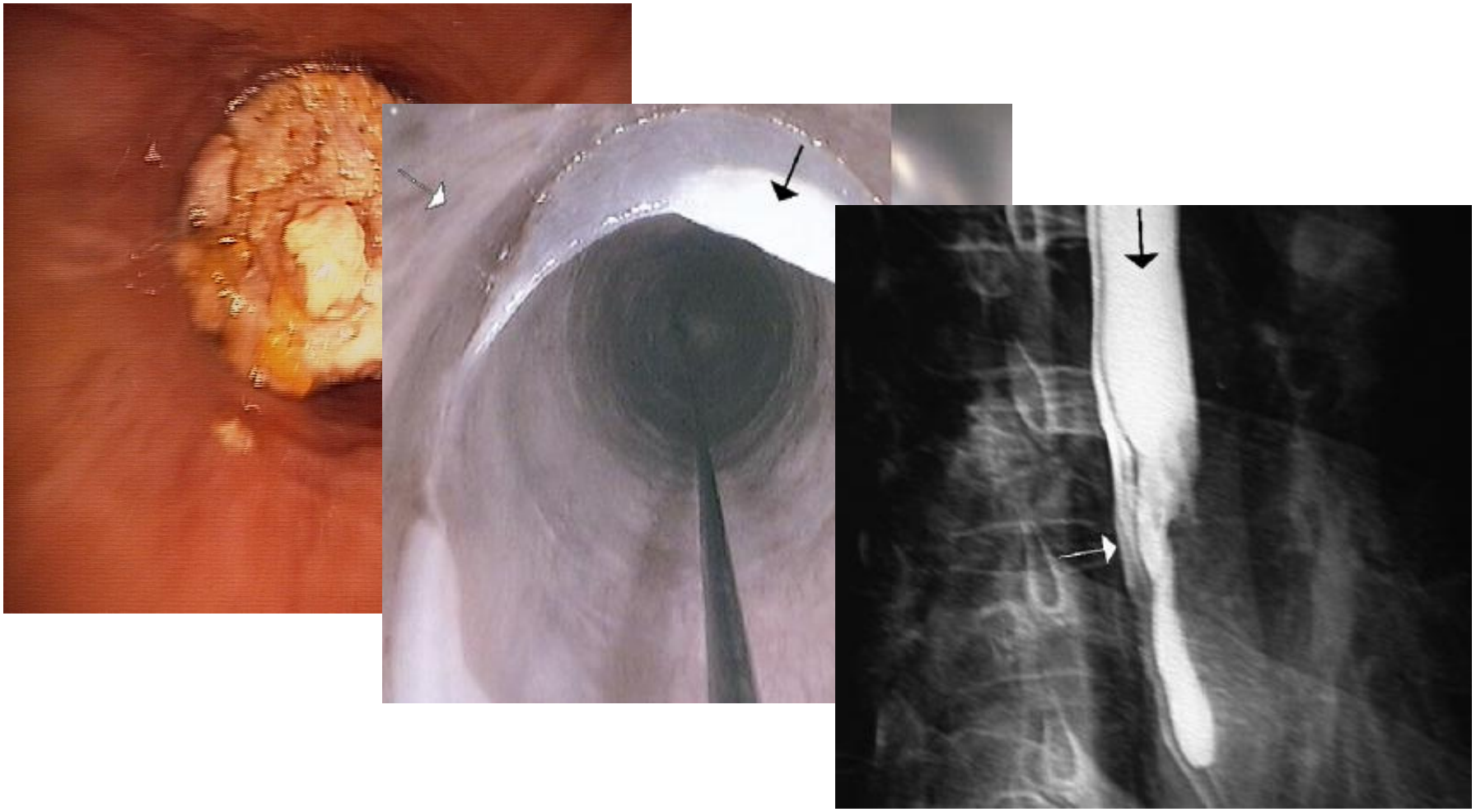
Schoepfer AM, et al, Gastroenterology 2013; 145:1230-1236

Endoscopic features at EoE Dx (n=200)



Schoepfer AM, et al, Gastroenterology 2013; 145:1230-1236

Consequences of remodeling



Straumann A, et al. Clin Gastroenterol Hepatol 2008;6:598-600

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Therapeutic Options 2016: 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

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

Results

Thirty-three studies (11 prospective studies) comprising 619 patients with symptomatic esophageal eosinophilia (188 children and 431 adults) were included. PPI therapy led to a clinical response in 60.8% (95% confidence interval, 48.38%–72.2%; I^2 = 80.2) and histologic remission in 50.5% (95% confidence interval, 42.2%–58.7%; I^2 = 67.5) of patients.

No differences were observed regarding the study population (children vs adults), the type of publication, or its quality.

A significant publication bias in favor of studies reporting histologic responses to PPIs was observed.

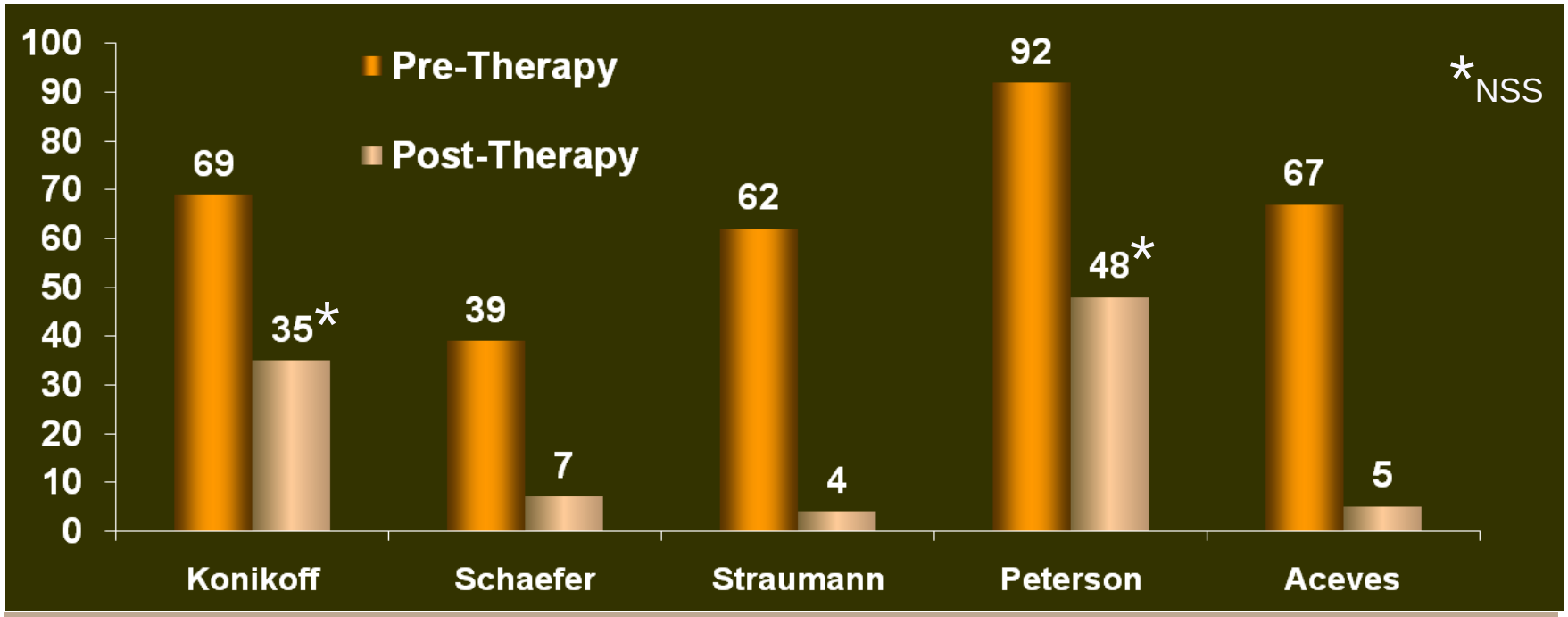
Conclusions

PPI therapy induces clinicohistologic remission in half of patients with symptomatic esophageal eosinophilia. This finding should be interpreted with caution because of poor-quality evidence, heterogeneity, and publication bias.

Lucendo AJ, et al. Clin Gastroenterol Hepatol, in press

Topical Corticosteroids in EoE

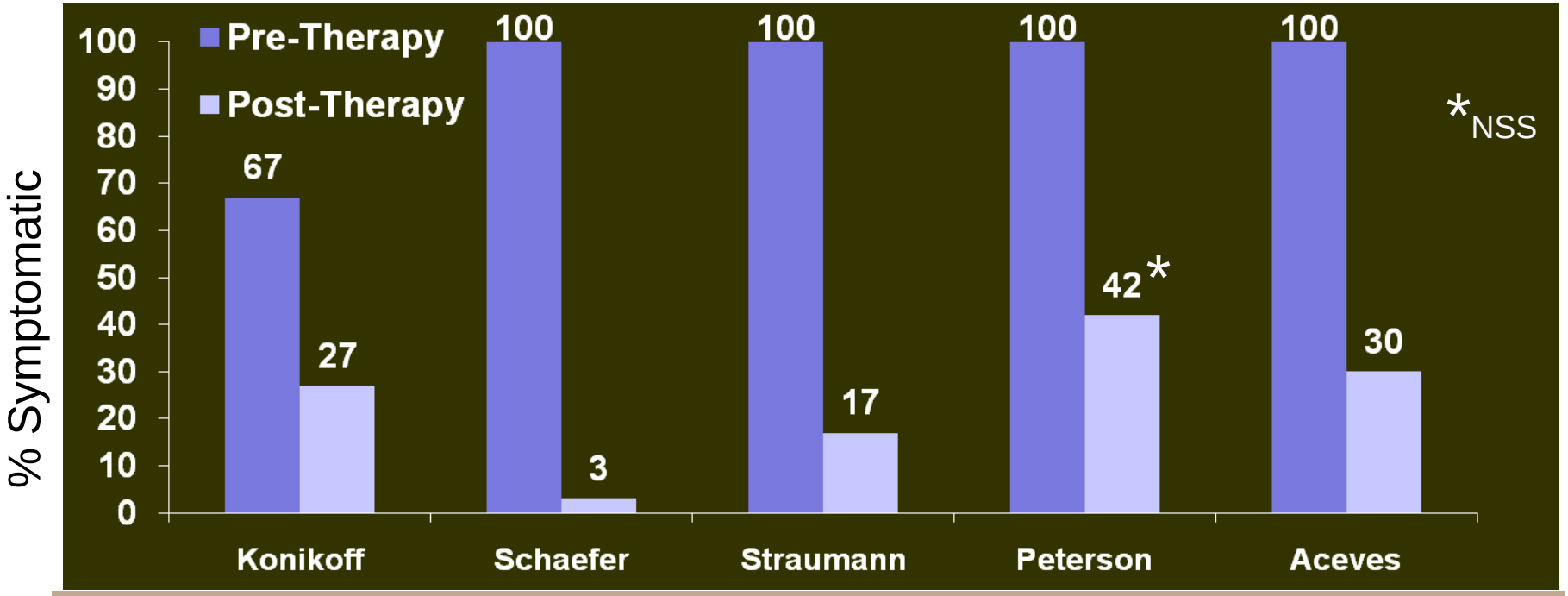
Esophageal Eosinophilia



Year	2006	2008	2008	2009	2010
Cohort	36 Peds	80 Peds	36 Adults	30 Adults	24 Peds
Tx	Fluticasone 440 mcg BID	Fluticasone 220-440 mcg QID	Budesonide 1 mg BID	Fluticasone 440 mcg BID	Budes. 1-2 mg QD
Tx Period	3 mts	4 weeks	15 days	8 weeks	3 mts
Control	Placebo	Prednisone	Placebo	Esomeprazole	Placebo

Topical Corticosteroids in EoE

Symptom Response



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Swallowed topical steroids: what form is best?

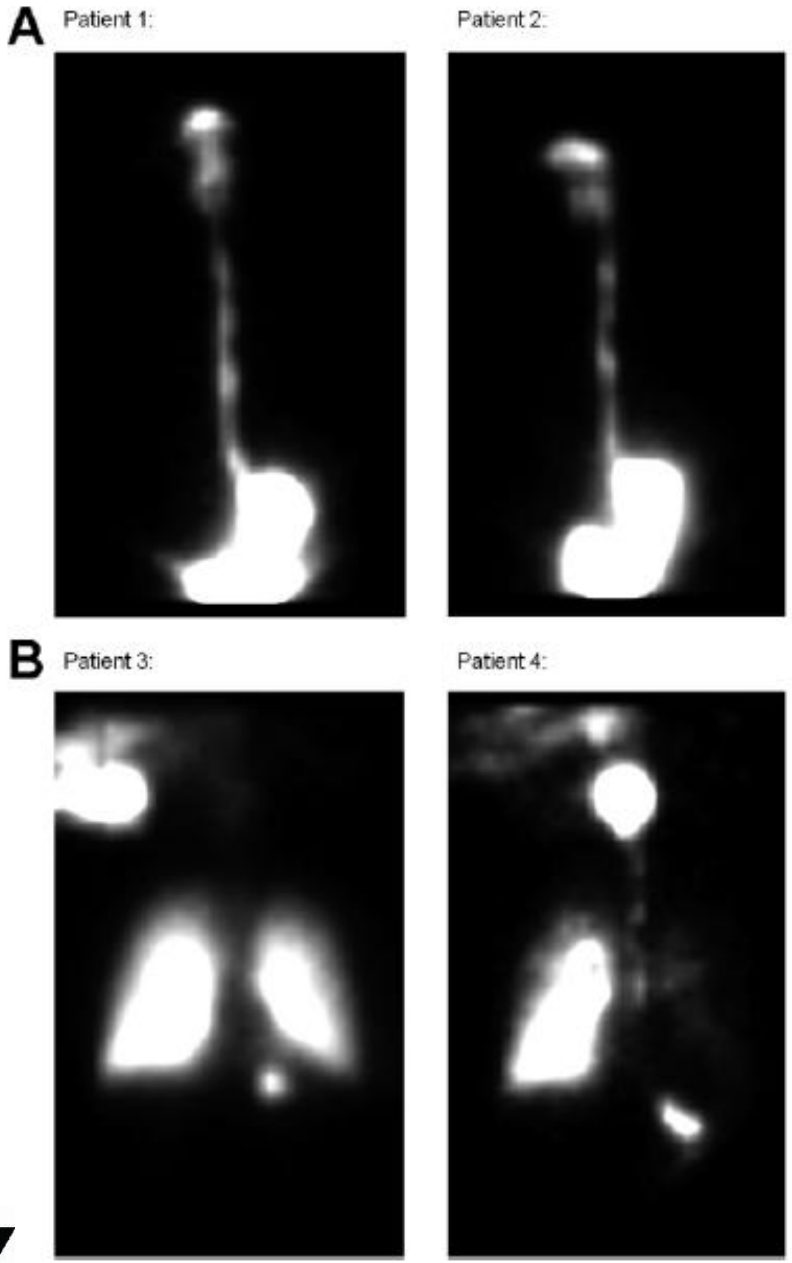
Viscous Topical Is More Effective Than Nebulized Steroid Therapy for Patients With Eosinophilic Esophagitis

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*,‡

*Center for Esophageal Diseases and Swallowing and ‡Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, §Division of Nuclear Medicine, Department of Radiology, and ‖Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

	Spray (NEB)	Syrup (OVB)	P-value
Number of patients	11	11	
Peak eos count before treatment	101±85	83±89	0.62
Peak eos count after treatment	89±94	11±23	0.02
Mean eos count after treatment	21±37	3±7	0.02

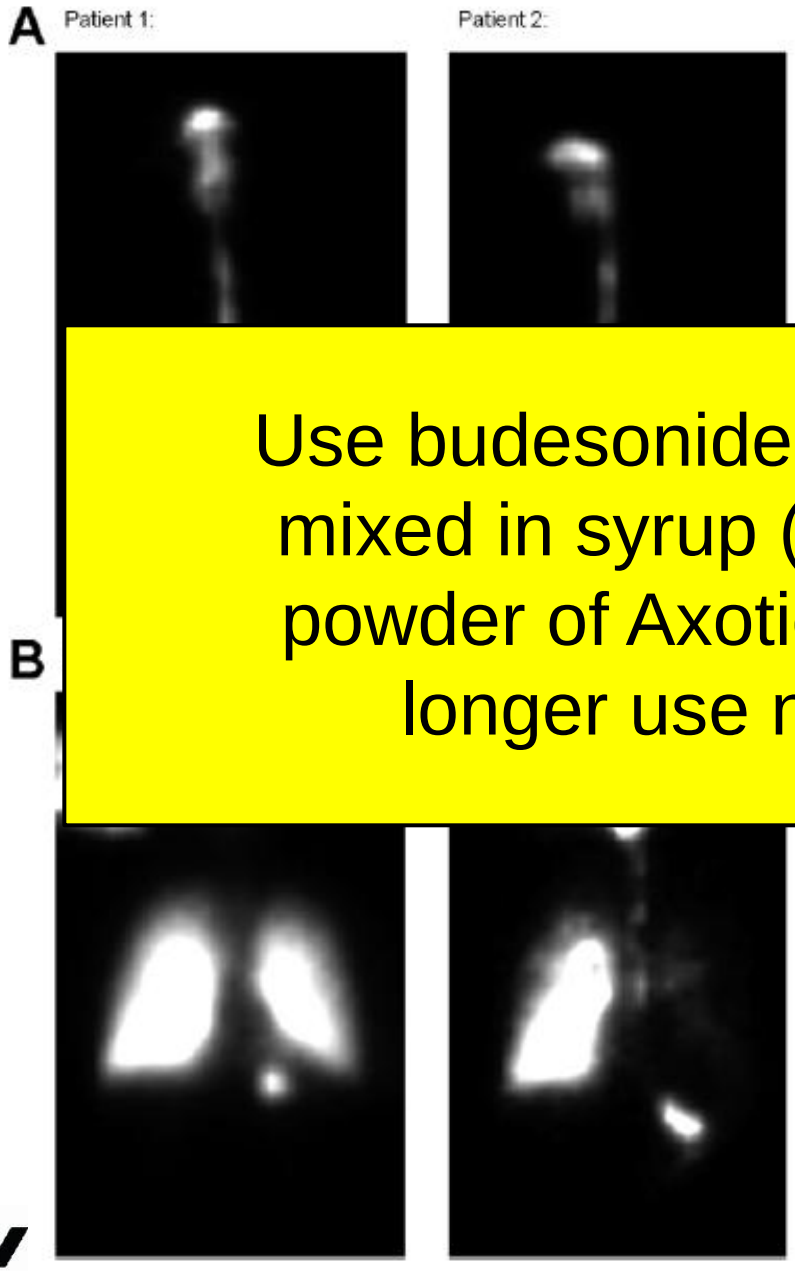
Gastroenterology 2012;321-4



Oral viscous budesonide (syrup)

Nebulized budesonide (spray)

Dellon ES, et al. Gastroenterology 2012;321-4



Oral viscous budesonide

Use budesonide or fluticasone mixed in syrup (sucralose) or powder of Axotide discus, no longer use nebulizers

budesonide (spray)

Dellon ES, et al. Gastroenterology 2012;321-4

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

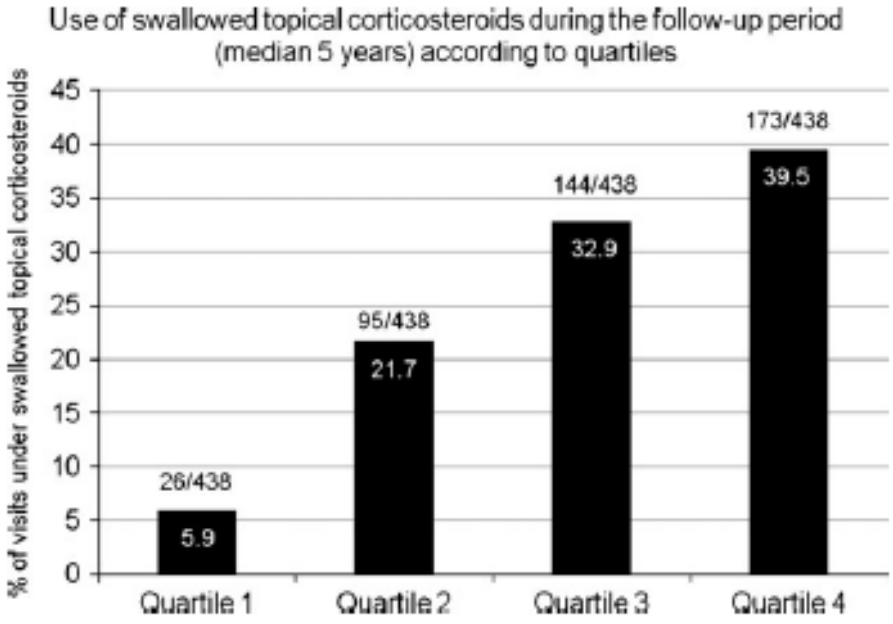
EAACI

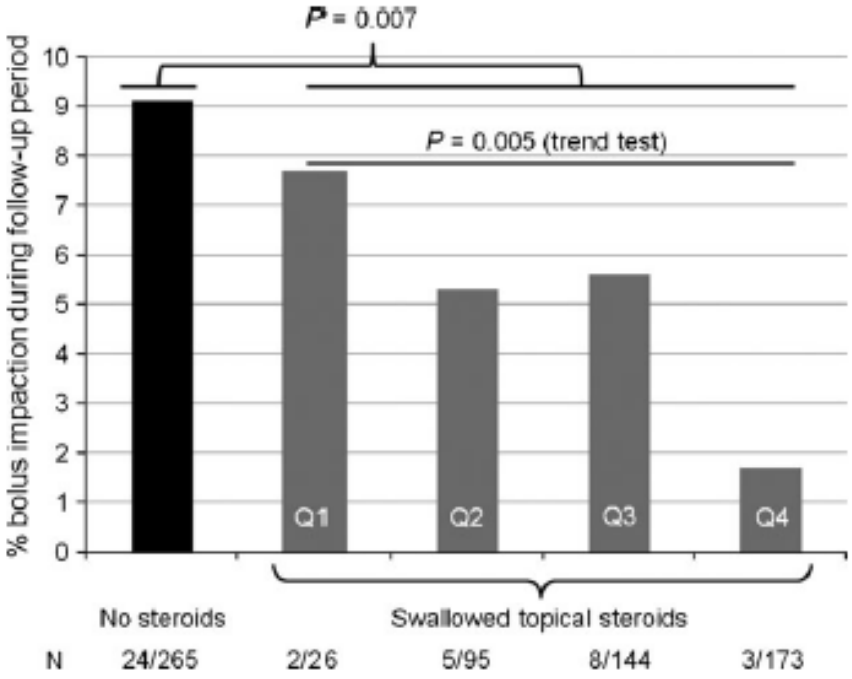
Allergy

ORIGINAL ARTICLE GASTROINTESTINAL DISEASES

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

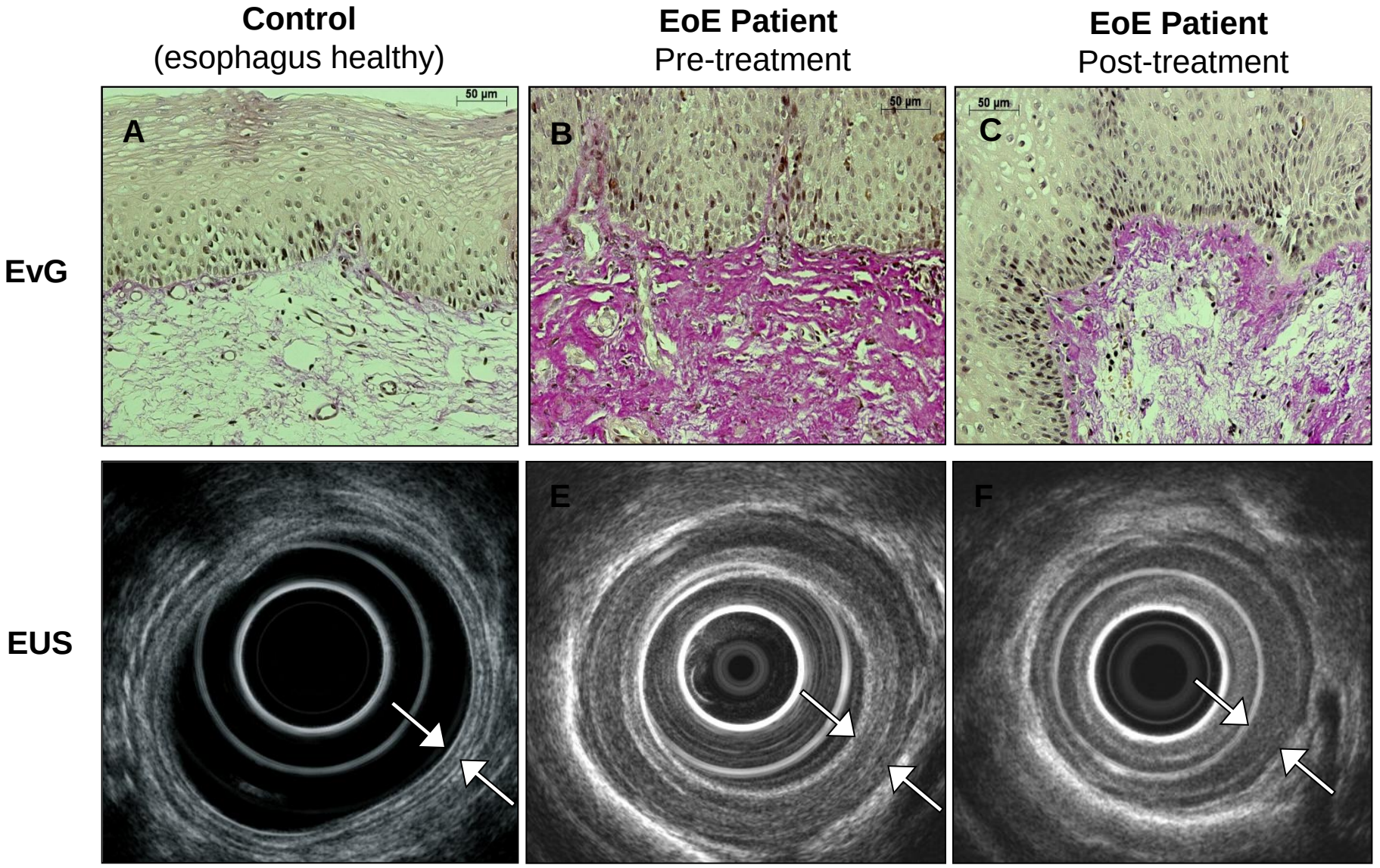
T. Kuchen[1,*], A. Straumann[2,3,*], E. Safroneeva[4], Y. Romero[5,6], C. Bussmann[7], S. Vavricka[1,8], P. Netzer[9], A. Reinhard[10], S. Portmann[11] & A. M. Schoepfer[12]



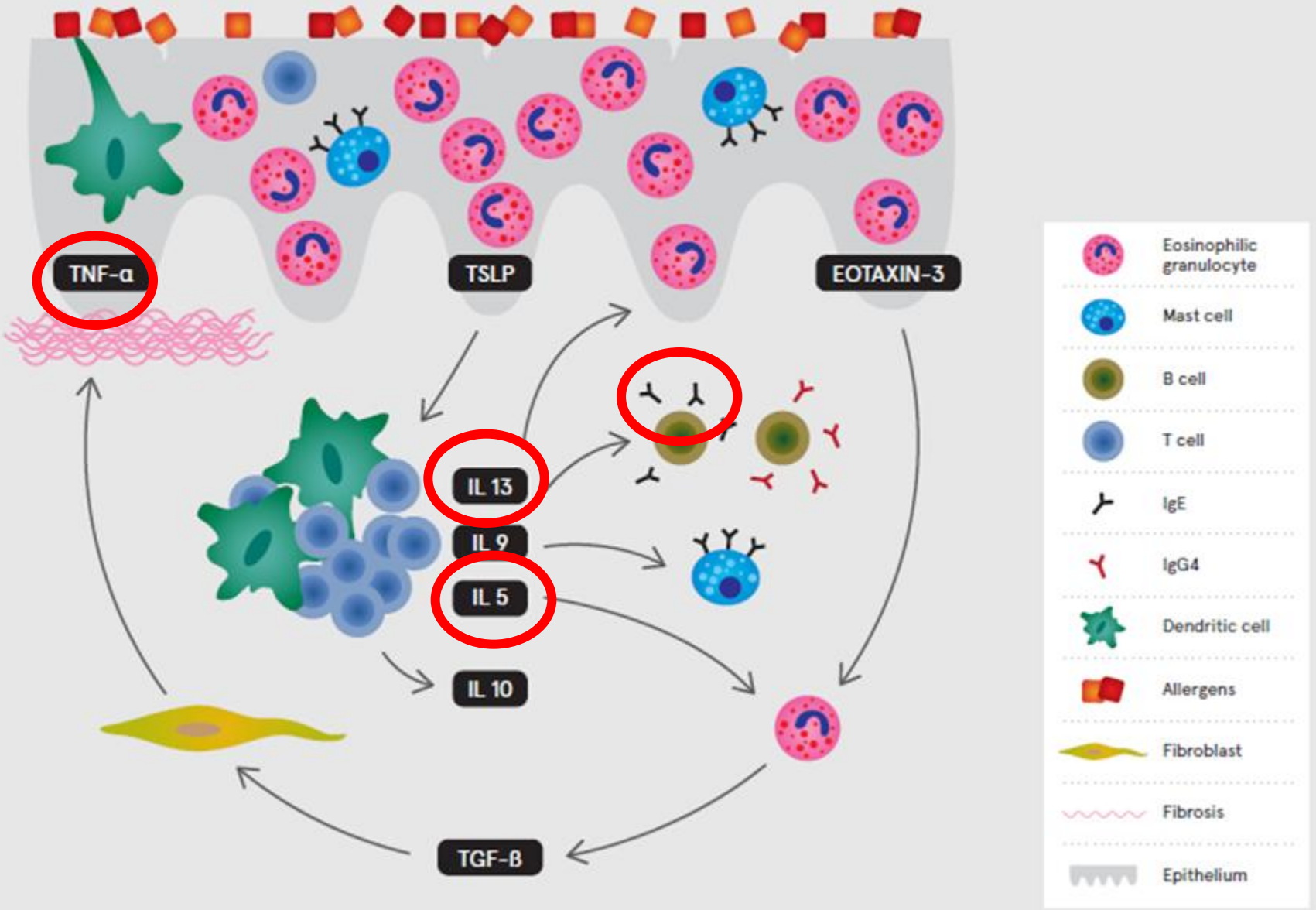


Median follow-up time 5 years

Swallowed budesonide can reduce subepithelial fibrosis



Straumann et al. *Clin Gastro Hepatol 2011*



DIETS



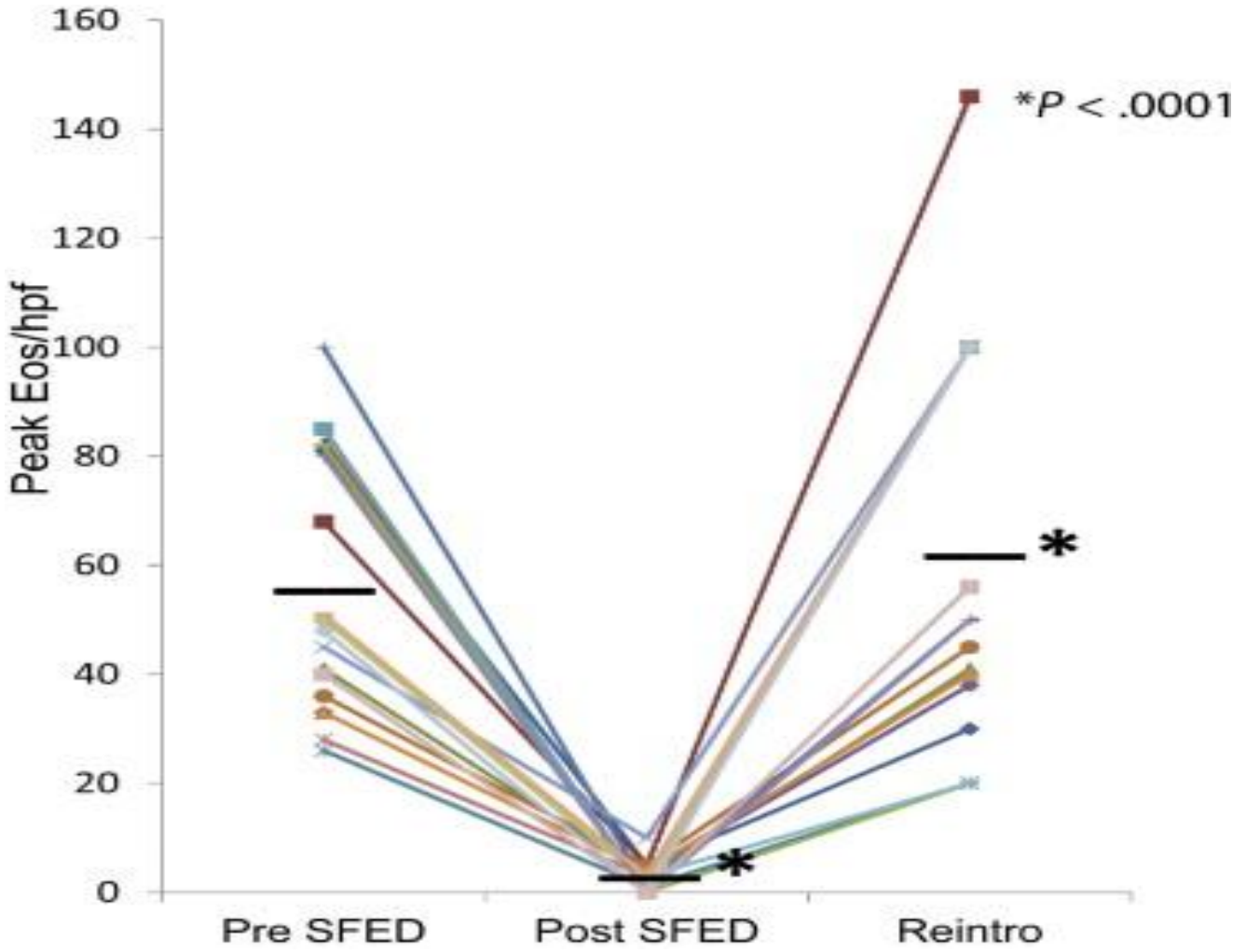
Most common food allergens

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.

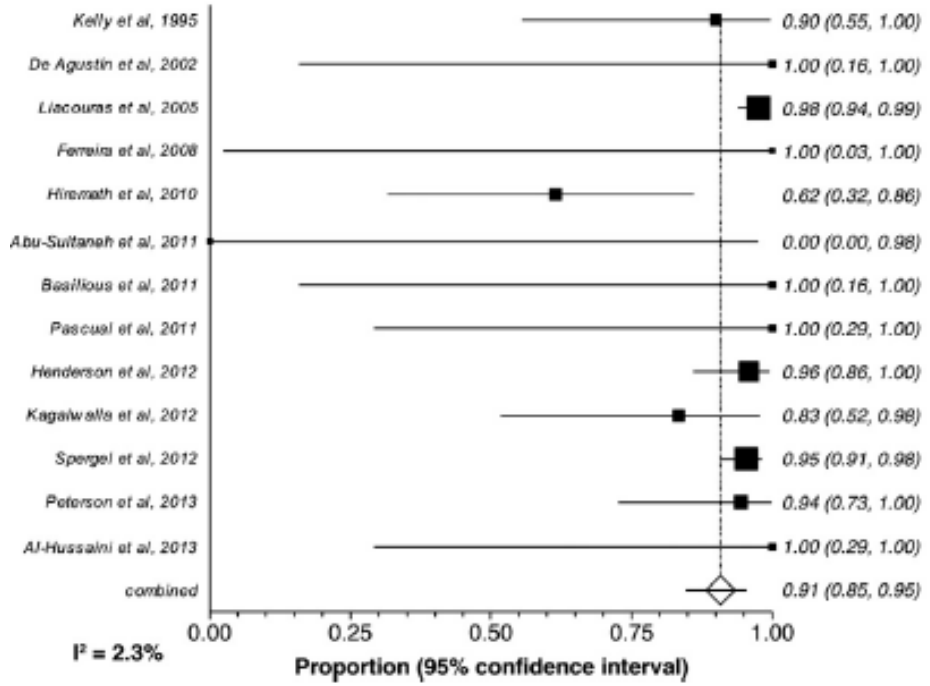
Straumann A, Schoepfer A. Gut 2014

Table 2. Summary of Histologic Remission Rates and 95% CIs for the Different Dietary Treatment Options Published for Children and Adults With Eosinophilic Esophagitis[a]

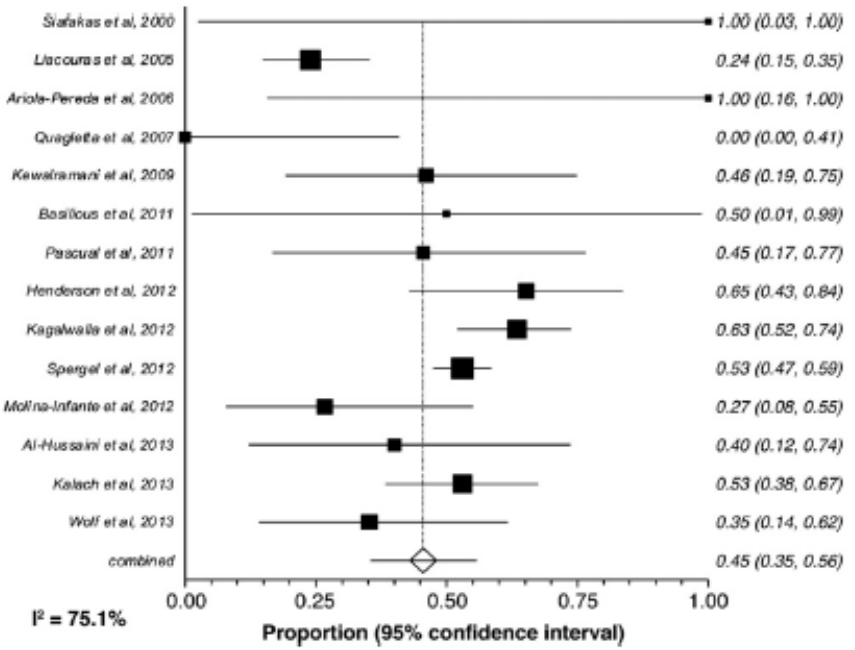
Dietary treatment	Overall effect, %	n	Children, %	n	Adult, %	n
All	66.3 (56.9–75)	47	67.2 (55.9–77.5)	36	63.6 (47.8–77.9)	10
Elemental diets	90.8 (84.7–95.5)	13	90.4 (83.5–95.5)	12	94.4 (17/18)	1
Allergy testing–direct elimination diets	45.5 (35.4–55.7)	14	47.9 (36.8–59.1)	12	32.2 (17.8–48.7)	2
SFED	72.1 (65.8–78.1)	7	72.8 (62.5–82)	4	71.3 (61.7–80)	3
FFED	53.4 (35.7–70.6)	2	60 (9/15)	1	46.2 (6/13)	1
Gluten-free diet	58.7 (23.1–89.7)	7	45.5 (2.6–93.8)	4	88.8 (50.5–99.1)	2
Milk elimination diet	68.2 (47.8–85.6)	3	66.3 (44.7–84.8)	2	100 (1/1)	1
Others (soy-free diet)	100 (1/1)	1	100 (1/1)	1	—	—
Subgroups according to quality						
Medium/high to high	68.7 (57.8–78.7)	34	69.8 (56.4–81.6)	27	66.8 (48.7–82.7)	6
Low to medium/low	59 (37.5–78.7)	13	58.5 (32.2–82.3)	9	55.6 (27.5–81.8)	4
Subgroups according to type of publication						
Article	68.8 (57.7–79)	35	69.2 (56.4–80.8)	30	69.4 (48.4–86.8)	4
Abstract/poster	53.1 (45.2–60.9)	12	54.8 (45.5–64)	6	48.8 (34.4–63.2)	6
Subgroups according to design						
Prospective	62.4 (49.3–74.7)	16	61.2 (42.7–78.2)	11	65.5 (46.4–82.4)	5
Retrospective	61.3 (49.9–72.1)	31	69.4 (55.9–81.5)	25	59.4 (32.8–83.2)	5

Arias et al, Gastroenterology 2014

Elemental diet



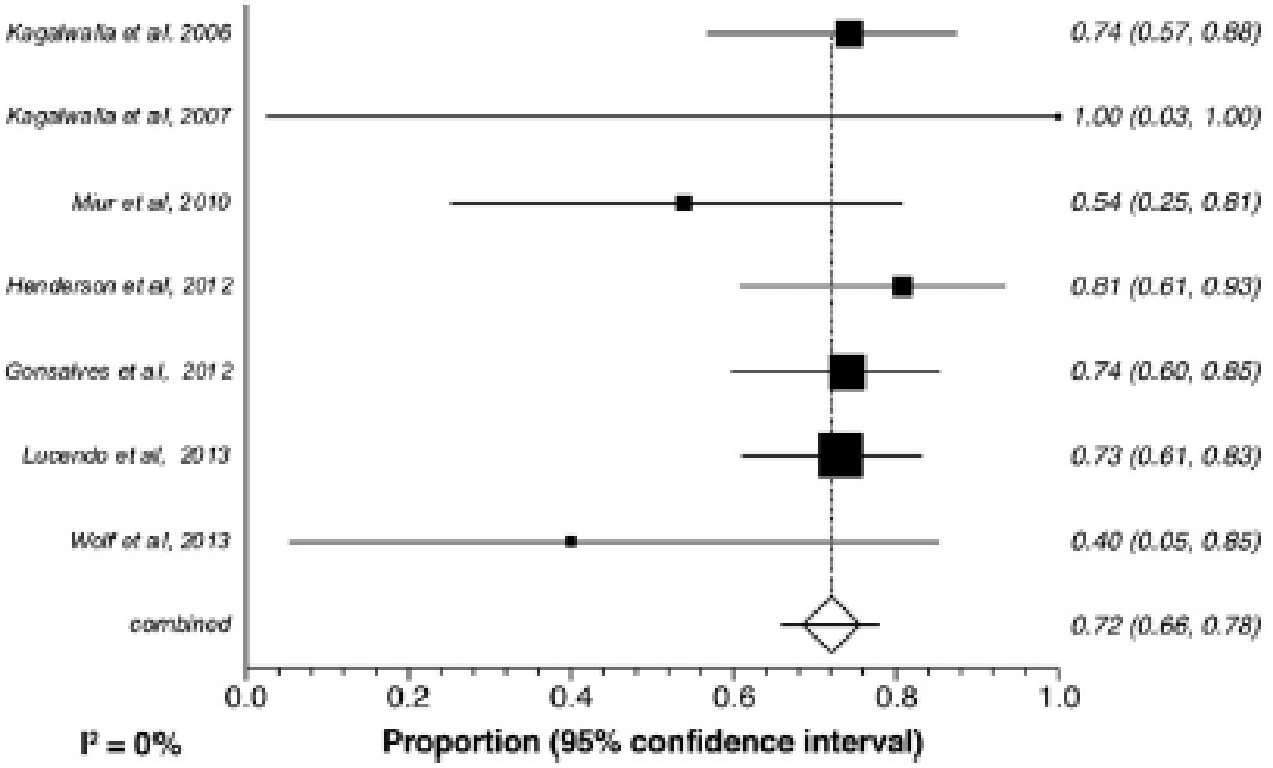
Allergy-testing based elimination diet



Outcome: histologic remission

Arias et al, Gastroenterology 2014

6-food elimination diet



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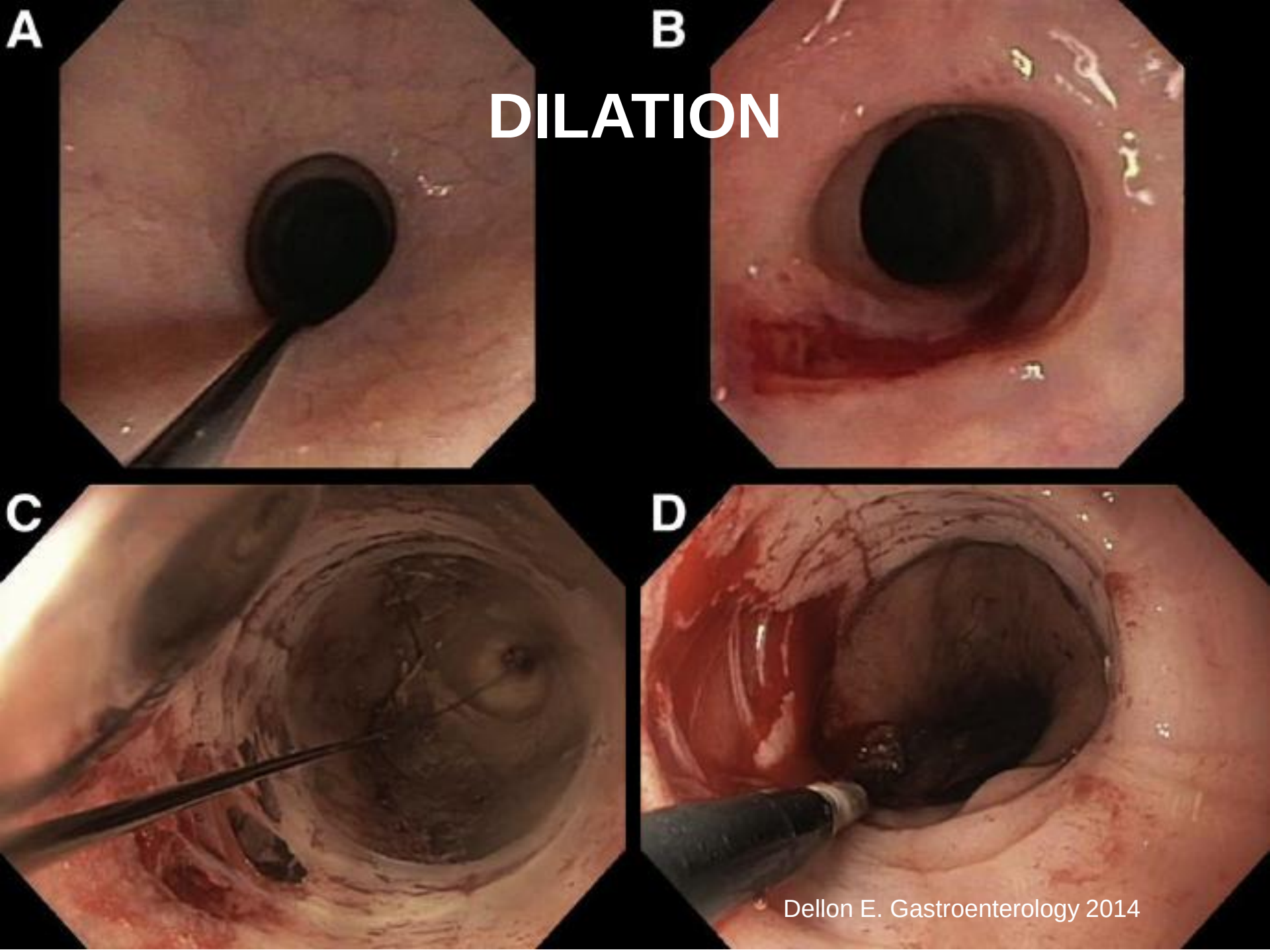
Arias et al, Gastroenterology 2014


A
B
DILATION
C
D
Dellon E. Gastroenterology 2014

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis

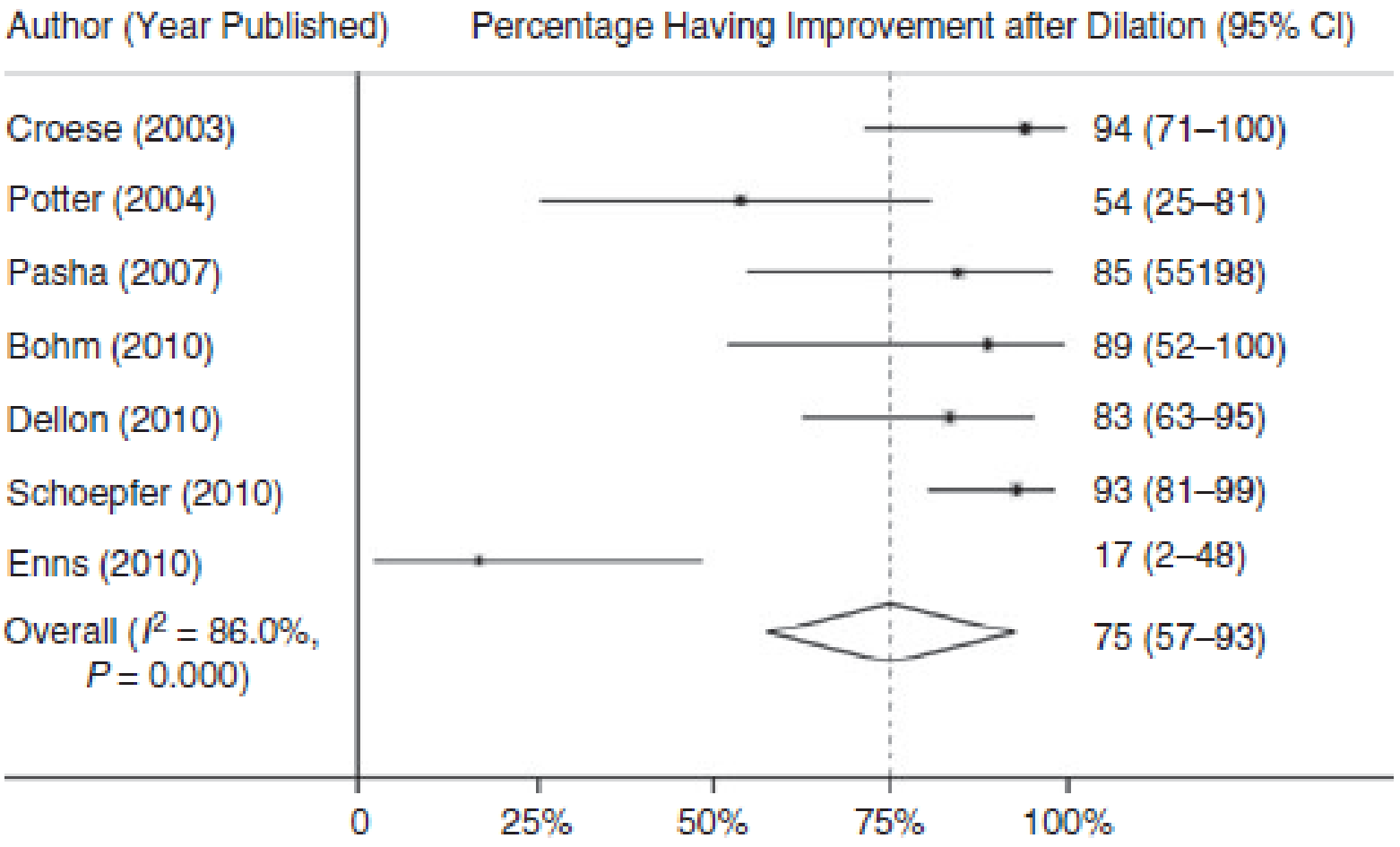
F. J. Moawad*,†, J. G. Cheatham*,† & K. J. DeZee†,‡

Table 1 | Demographics, clinical outcomes and complications for each study included in the meta-analysis

Author	Year	EoE pts total	EoE pts dilated	Total # dilations	Mean age	Male (%)	Clinical improvement (%)	Duration of follow-up (mo)	Perforations	Haemorrhage	Chest pain (%)
Croese[13]	2003	31	17	58	34	77	94	NR	0	0	3.4
Potter[35]	2004	29	13	13	35	72	54	2.5	0	NR	NR
Pasha[36]	2007	42	13	13	44	74	85	NR	0	NR	NR
Bohm[34]	2010	16	9	11	41	75	89	22	0	NR	8.3
Dellon[18]	2010	124	36	70	26	76	83	NR	0	NR	4.2
Schoepfer[8]	2010	207	207	453	44	80	93	15	0	0	7.2
Enns[37]	2010	54	15	15	43	76	17	12	0	NR	NR
Jung[38]	2011	161	161	293	44	70	NR	NR	3	1	3
Ally[19]	2012	196	54	66	41	85	NR	NR	0	0	4

NR, not reported; mo, month.

APT 2013



Conclusions

Dilation in patients with eosinophilic oesophagitis is a safe procedure with a low rate of serious complications (<1%), and seems to result in at least a short-term improvement of symptoms in the majority of patients.

APT 2013

Pro / Cons of different therapies

Modality	Advantages	Shortcomings
Drugs - STC	• Effective • No dietary restriction	• No FDA-approved drugs yet on the market • Long-term side effects / safety unknown
- Biologic therapies	• Favorable safety profile	• Costs, availability, limited clinical efficacy
Diets	• Non-pharmacologic, effective treatment option • Antifibrotic	• Repetitive EGDs may be necessary (up to 10x) • Needs motivated patient
Dilation	• Long-lasting symptom improvement	• No influence on underlying inflammation • Post-dilational pain • (safety)

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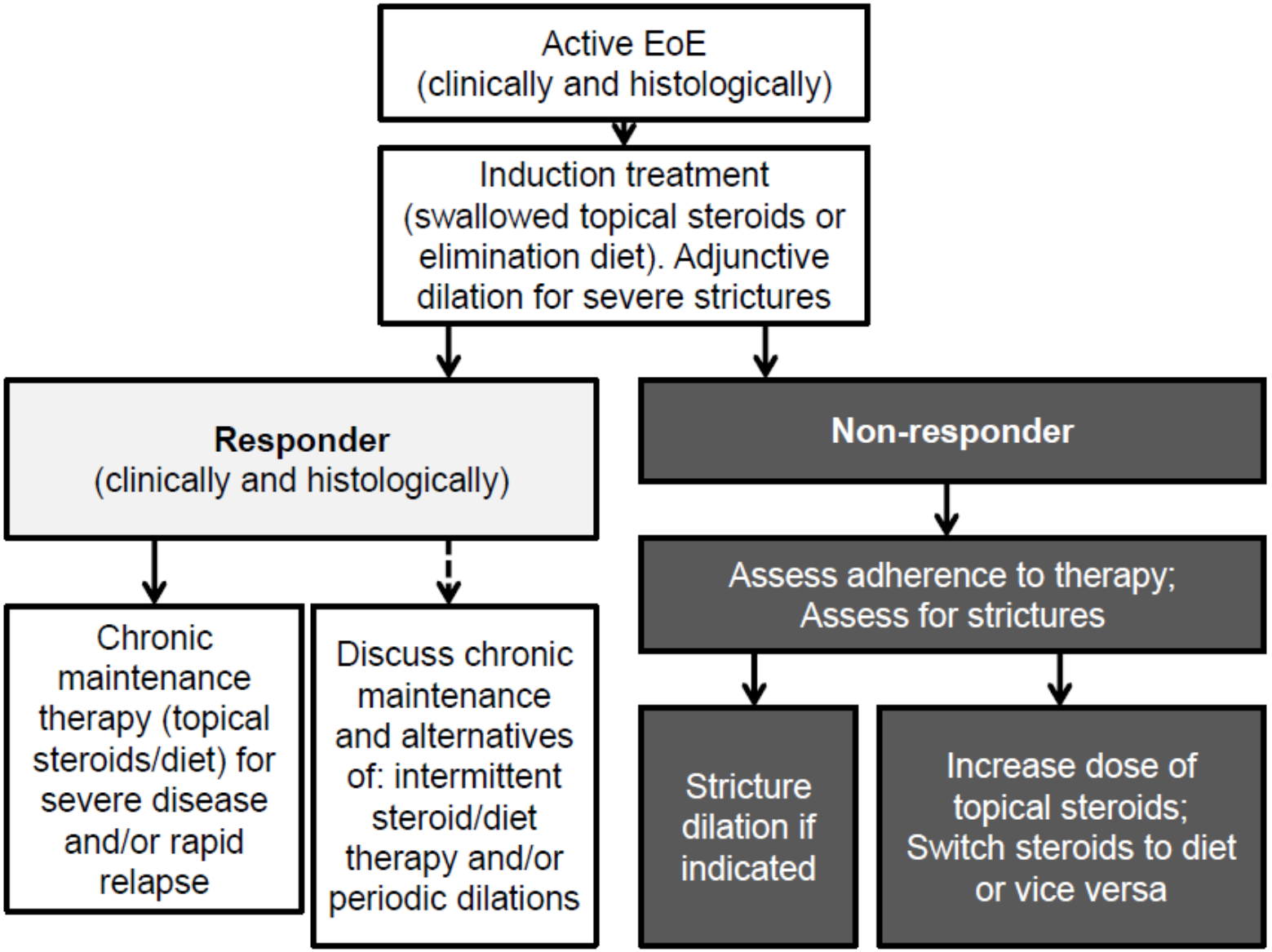
Take home messages

- there is no «one fits all» therapy
- before you initiate a therapy you should
  - assess the EoE phenotype
  - ask patient about preferences
  - decide how you assess treatment success
- Therapy options: drugs, diets, and dilation
- Unmet needs: many (longterm efficacy and safety data, biologics, etc)

Thank you!

Therapeutic principles in EoE in 2016



Reslizumab in children and adolescents with eosinophilic esophagitis: Results of a double-blind, randomized, placebo-controlled trial

Jonathan M. Spergel, MD, PhD,[a] Marc E. Rothenberg, MD, PhD,[c] Margaret H. Collins, MD,[d] Glenn T. Furuta, MD,[e] Jonathan E. Markowitz, MD,[f] George Fuchs III, MD,[g] Molly A. O'Gorman, MD,[h] Juan Pablo Abonia, MD,[c] James Young, MS,[i] Timothy Henkel, MD, PhD,[j] H. Jeffrey Wilkins, MD,[j] and Chris A. Liacouras, MD[b] *Philadelphia and Frazer, Pa, Cincinnati, Ohio, Aurora, Colo, Greenville, SC, Little Rock, Ark, Salt Lake City, Utah, and Ann Arbor, Mich*

- reslizumab = anti-IL5 antibody
- included: patients with moderate to severe symptoms and ≥24 eos/hpf
- randomized to perfusions with reslizumab 1, 2, or 3mg/kg at weeks 0, 4, 8, and 12
- primary endpoints: changes in peak eos counts and physician global assessment at week 15 (end of therapy)

JACI 2012;129:456-63

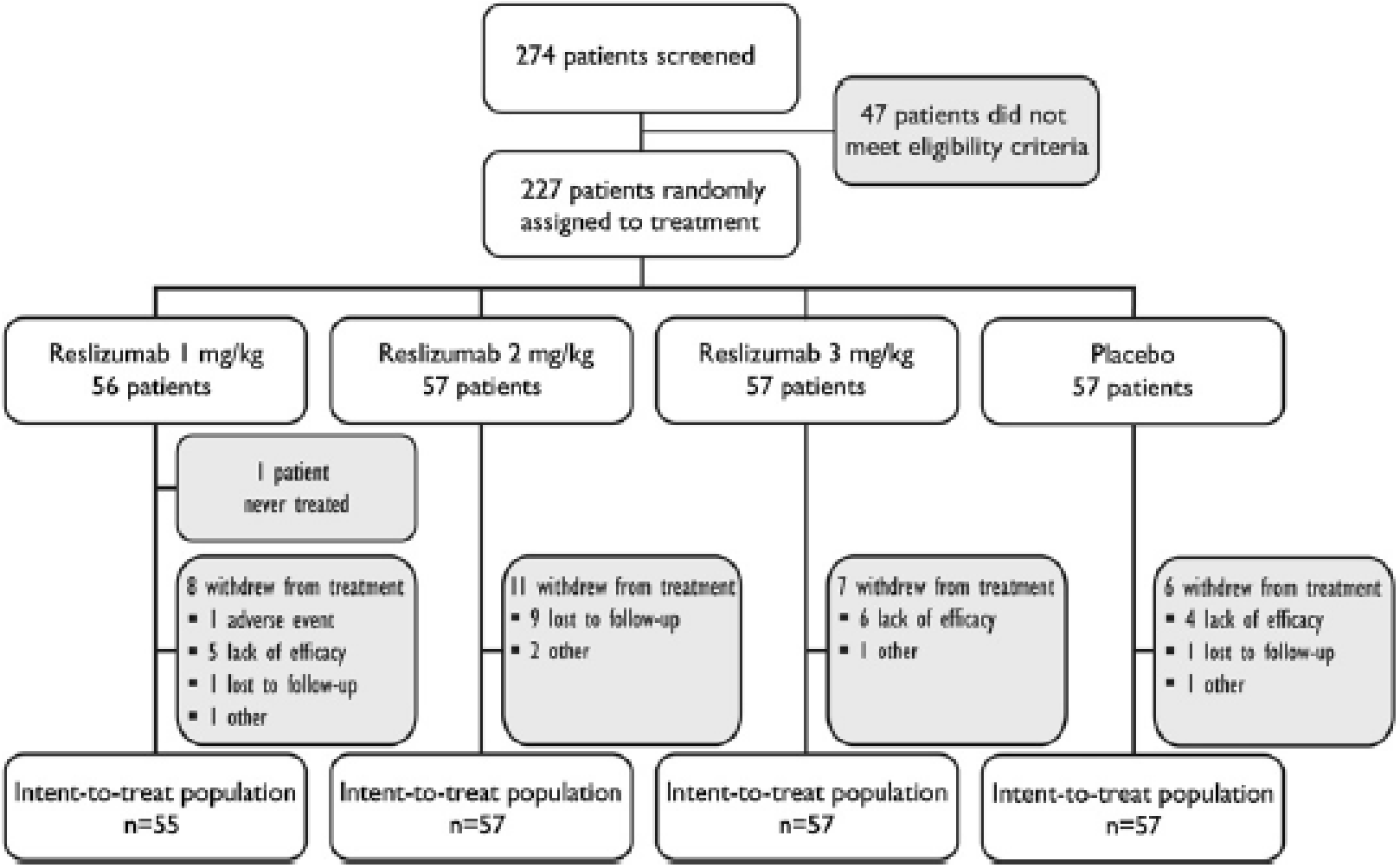
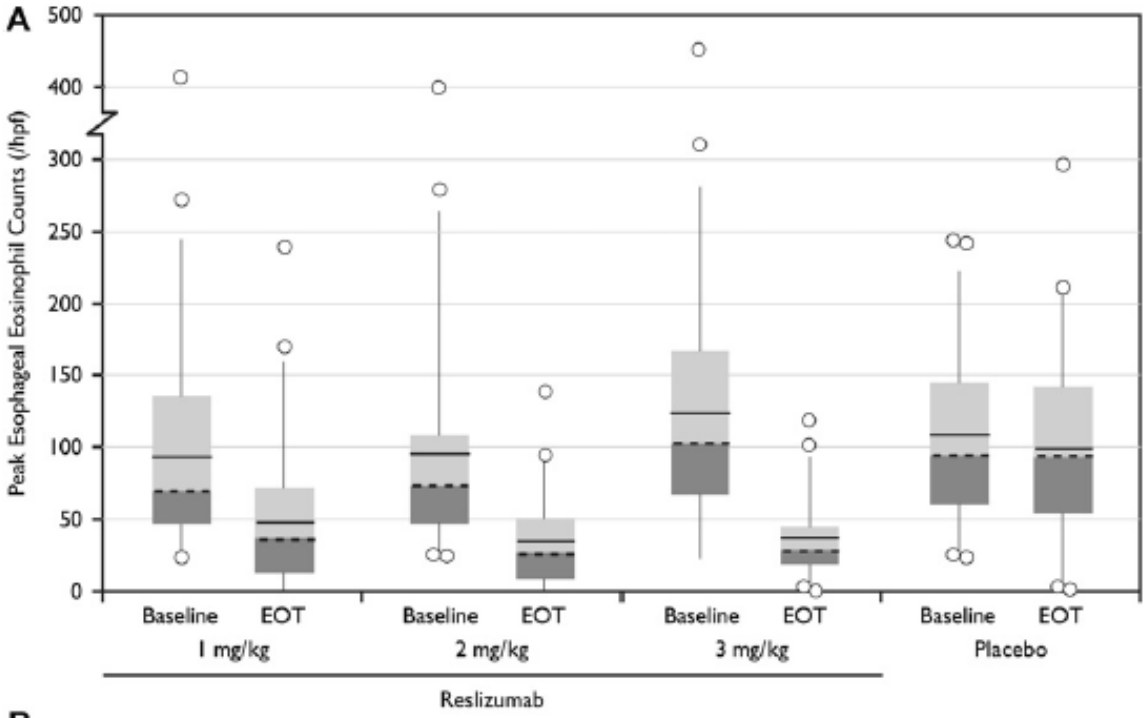
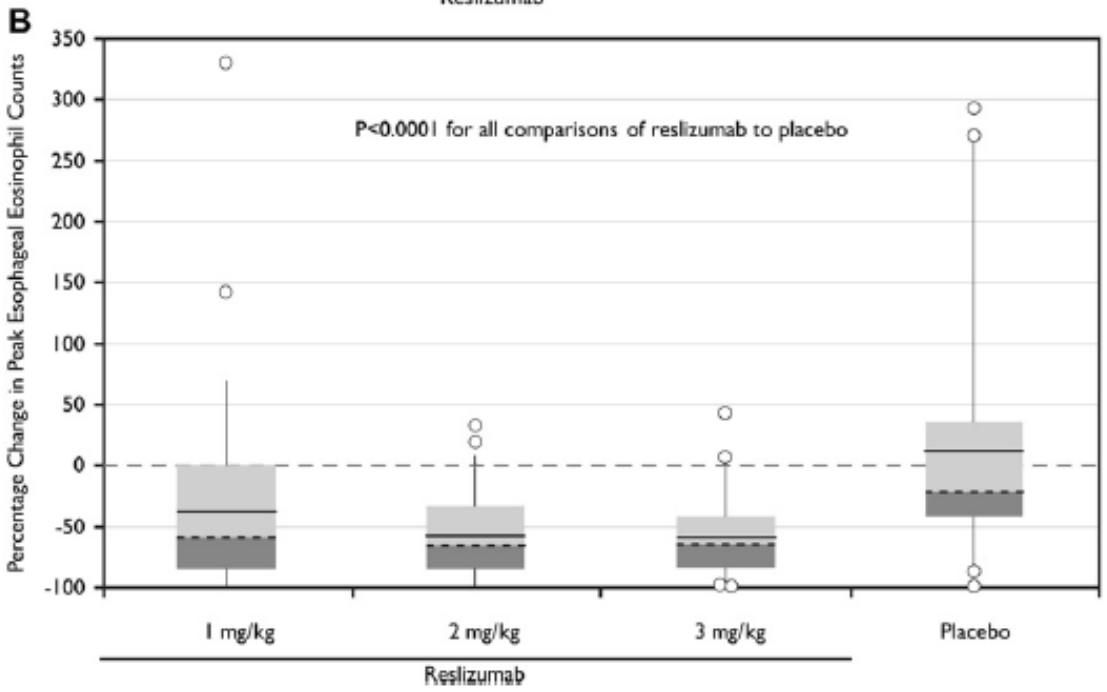
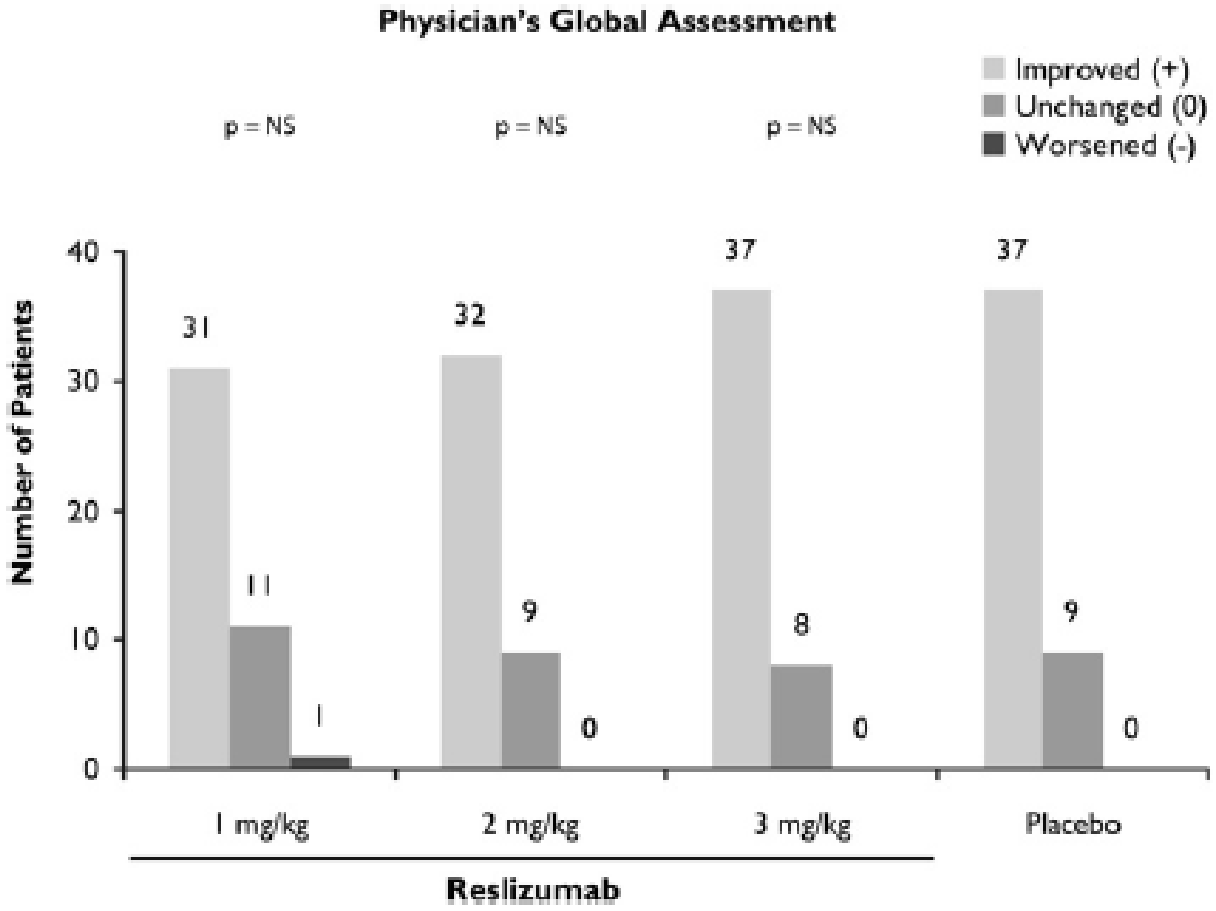


FIG 1. Randomization scheme and disposition of patients.

Spergel J, et al. JACI 2012;129:456-63


A
Peak Esophageal Eosinophil Counts (/hpf)
500
400
300
250
200
150
100
50
0
Baseline
EOT
1 mg/kg
2 mg/kg
3 mg/kg
Placebo
Reslizumab


B
Percentage Change in Peak Esophageal Eosinophil Counts
P<0.0001 for all comparisons of reslizumab to placebo
350
300
250
200
150
100
50
0
-50
-100
1 mg/kg
2 mg/kg
3 mg/kg
Placebo
Reslizumab



Spergel J, et al. JACI 2012;129:456-63

- reslizumab significantly reduced eos counts in patients with active EoE
- all treatment groups showed symptom improvements and these were not associated with changes in esophageal eosinophil counts

Spergel J, et al. JACI 2012;129:456-63

Prevalence of food allergies

Allergen	Prevalence	Remarks	Refer.
All	6-8% at one year 3-4% at age 14-16	Higher prevalence for IgE compared to symptoms	1,2
Cow milk	2-3% until age 2 yrs	Most often outgrown, high IgE correlated to lower chance for outgrow	3
Hen‘s egg	1-2% until age 2 yrs	Mostly outgrown with childhood	4
Peanut / tree nut	0.5-1.4% of children 0.5-1% of general pop.	Mostly lifelong disorder	5
wheat	0.4-1% of children	Mostly outgrown in childhood	6

1 Osborne NJ, et al. JACI 2011;127:668

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

3 Venter C, et al. JACI 2006;117:1118

4 Nickel R, et al. JACI 1997;99:613

5 Sicherer SH, et al. JACI 1999;103:559

6 Keet CA, et al. Ann All Asthm Immunol 2009;102:410