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EUREOS
European Society of Eosinophilic Oesophagitis

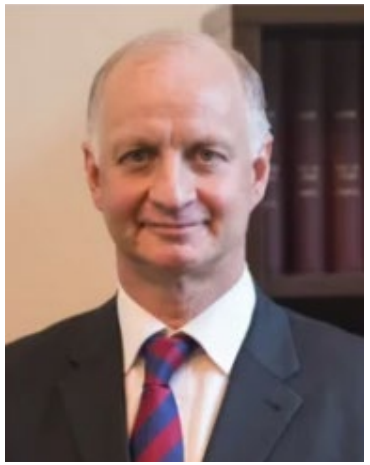


Behandeling Eosinofiele Oesofagitis Dieet en Medicatie

Tim Vanuytsel MD PhD

Gastroenterology and Hepatology University Hospitals Leuven
Leuven Intestinal Failure and Transplantation (LIFT)
Translational Research Center for Gastrointestinal Disorders (TARGID)

The ‘early’ days



Esophageal Eosinophilia with Dysphagia

A Distinct Clinicopathologic Syndrome

STEPHEN E.A. ATTWOOD, MB, FRCS, THOMAS C. SMYRK, MD, TOM R. DEMEESTER, MD, and JAMES B. JONES, PharmD



Straumann A:
‘Idiopathic **Eosinophilic Esophagitis**: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings.’

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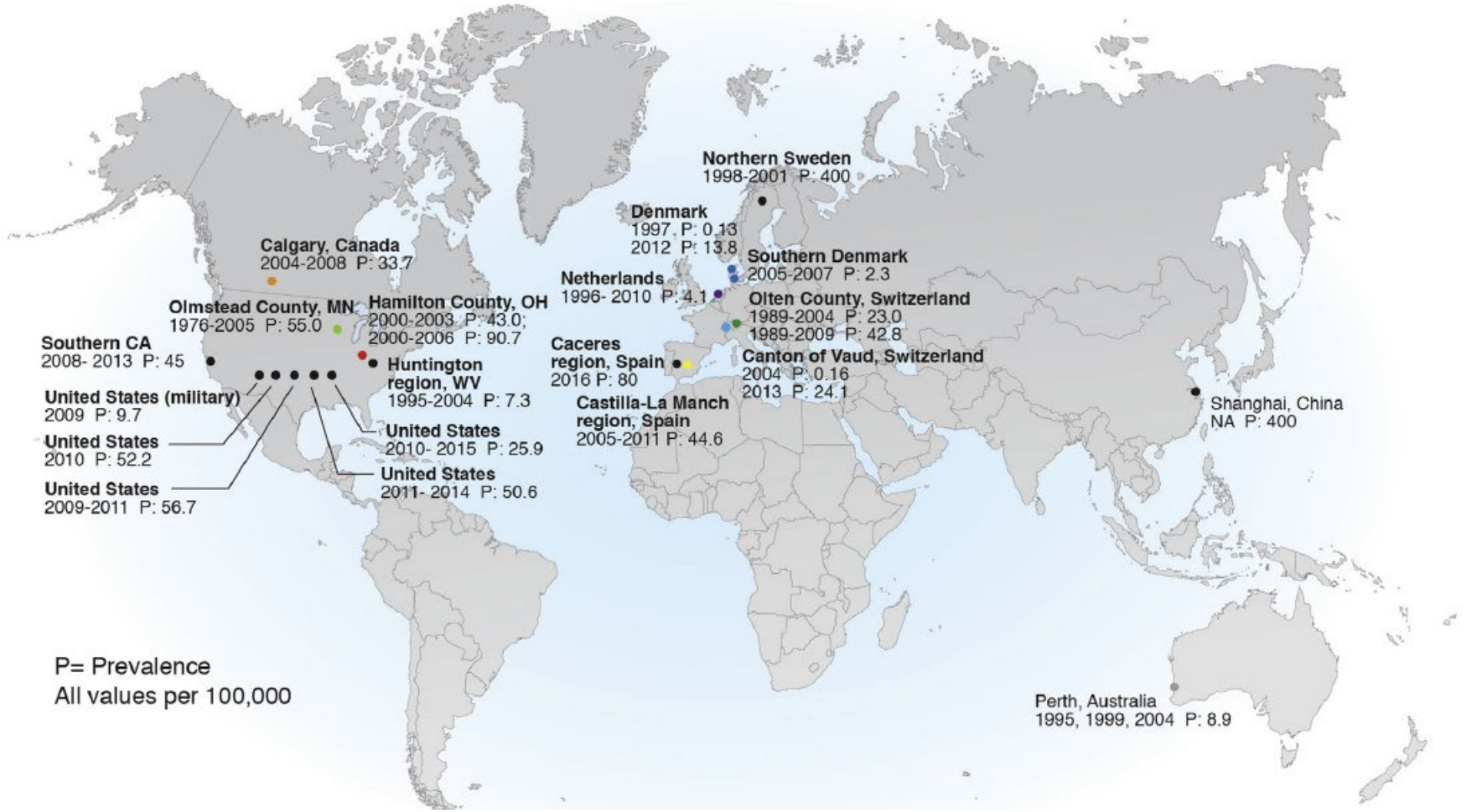
Attwood et al. Dig Dis Sci 1993
Straumann et al. Schweizerische Medizinische Wochenschrift1994

Epidemiology

Prevalence: 1/2000 – 1/1000



Dellon and Hirano. Gastroenterology 2018

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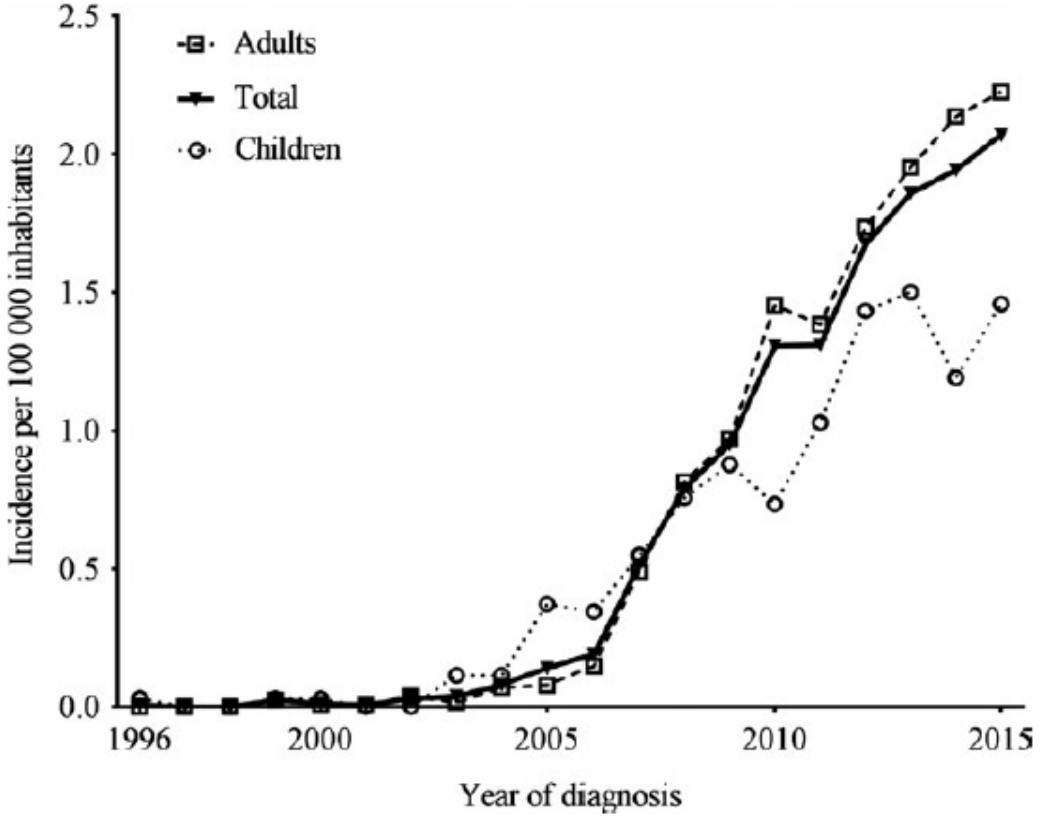
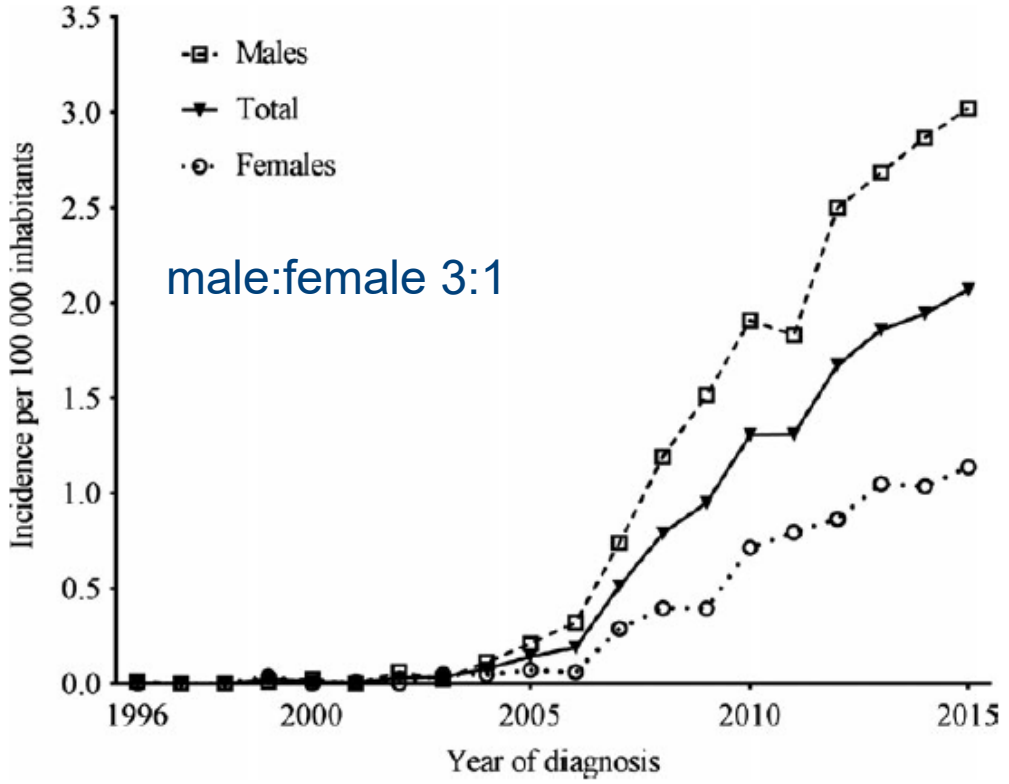
Epidemiology

Nationwide Dutch pathology database (PALGA): esophageal eosinophilia





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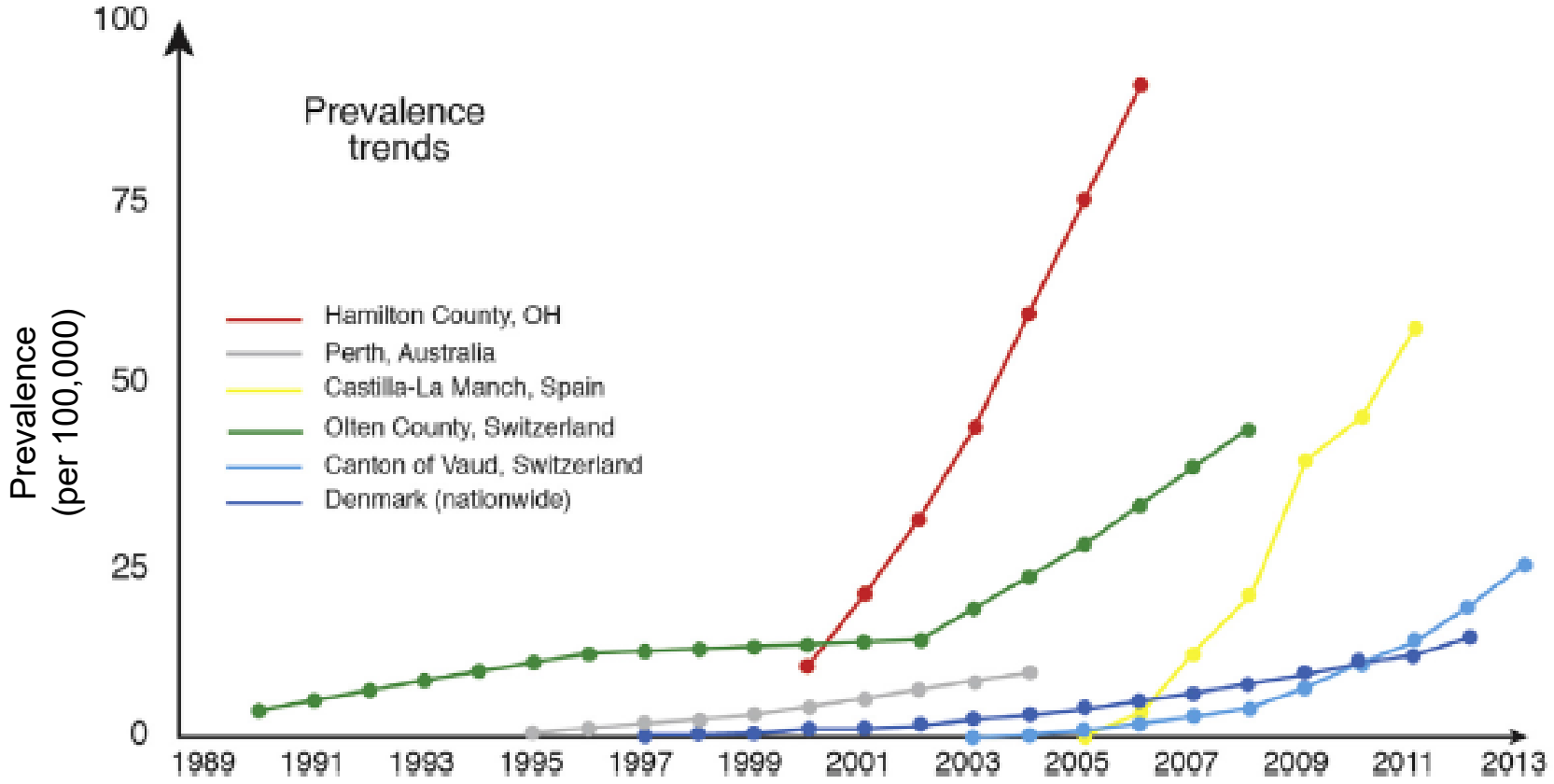
Epidemiology



Dellon and Hirano. Gastroenterology 2018

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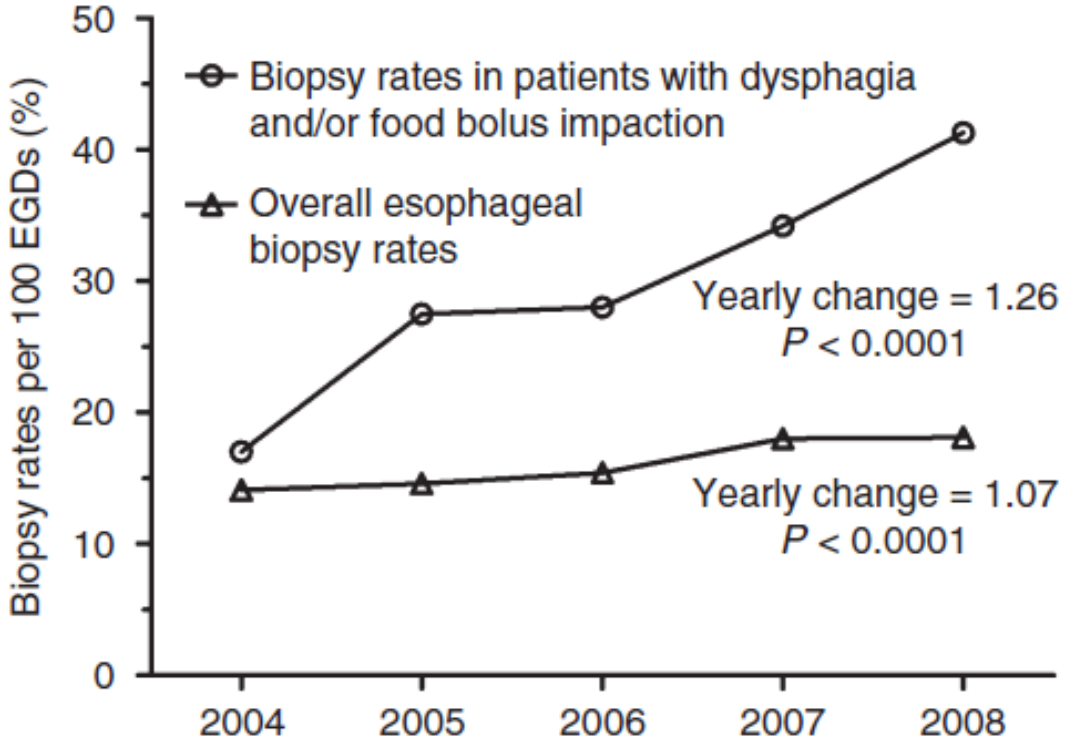
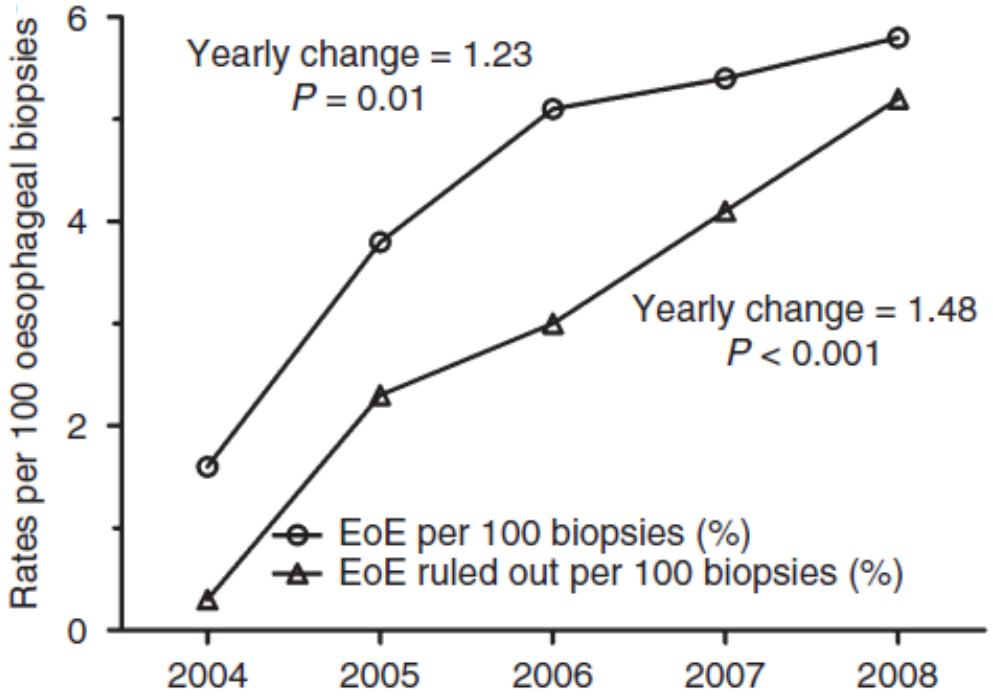
Epidemiology: awareness?

Increased esophageal biopsy rates



Increased awareness of the pathologist



Syed et al. Aliment Pharmacol Ther 2012

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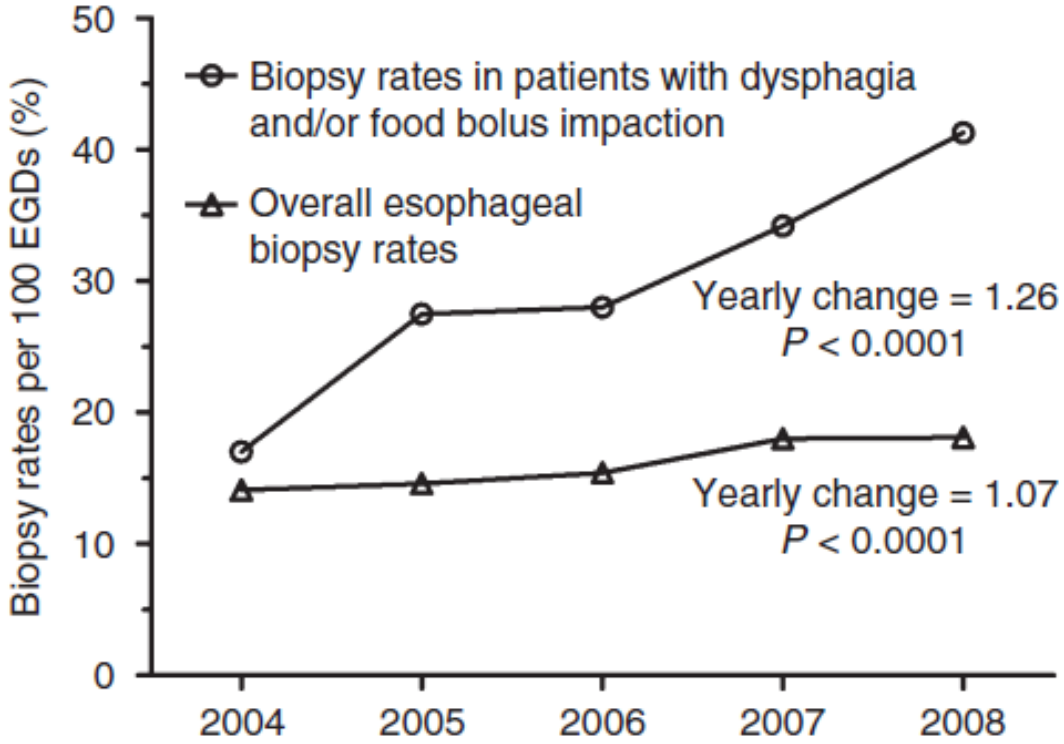
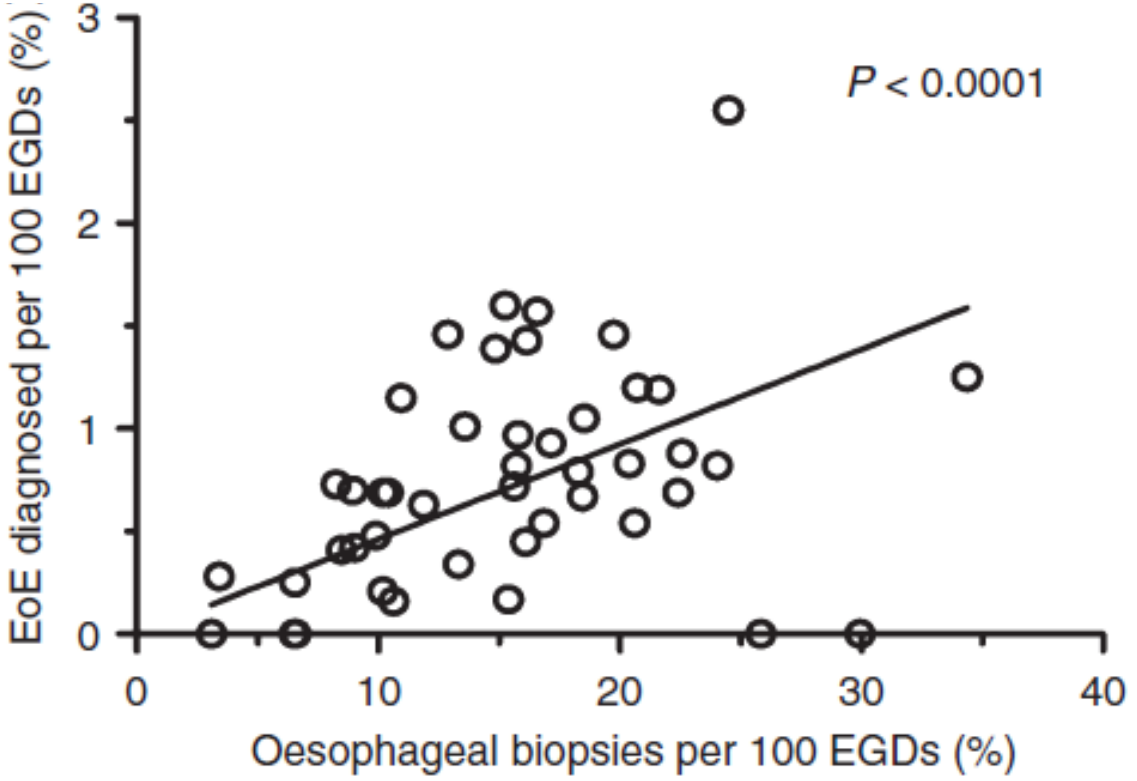
Epidemiology: awareness?

Increased esophageal biopsy rates





Syed et al. Aliment Pharmacol Ther 2012

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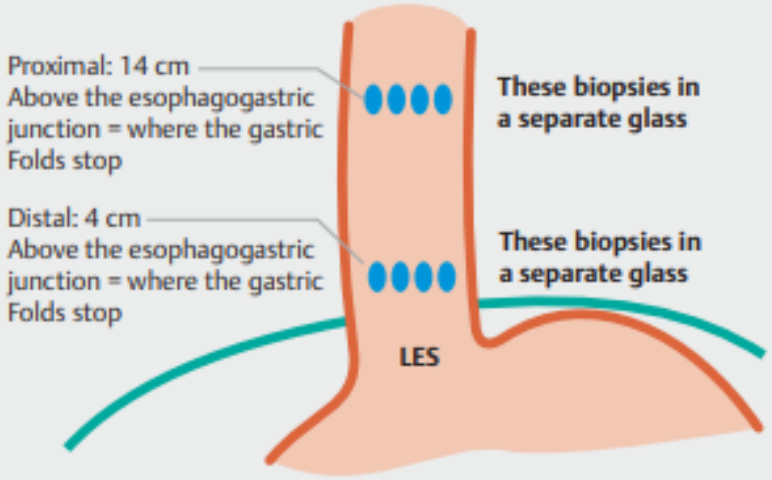
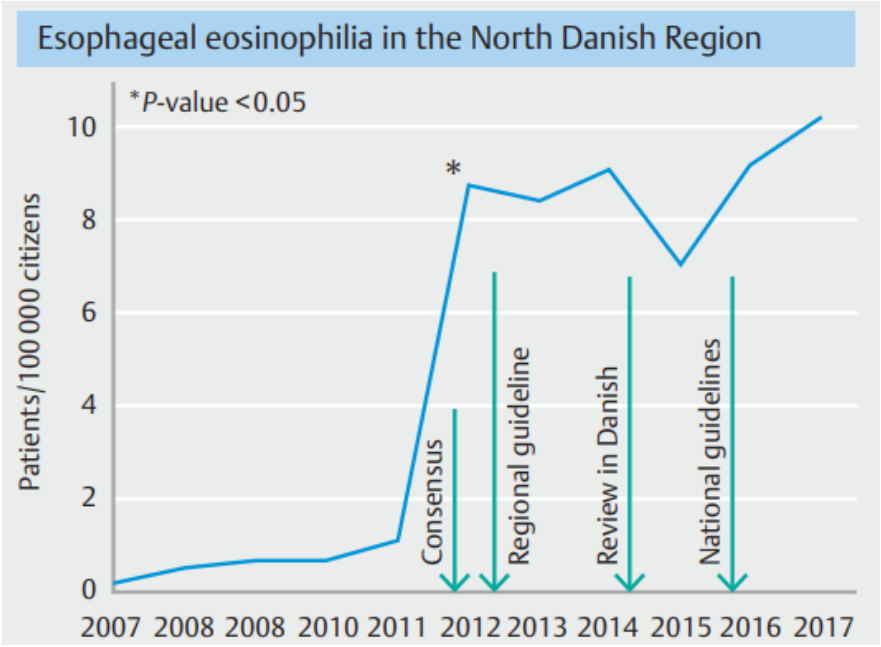
Epidemiology: awareness?

Biopsy protocol for **all** patients with DYSPHAGIA **regardless** of a macroscopic normal mucosa.
REMEMBER 4 – 14 – 4
Take 4 biopsies 14 cm and 4 cm above the esophago-gastric junction.
15 % will have eosinophilic esophagitis regardless of other comorbidity.



This strategy is the result of the consensus meeting for the endoscopy leaders in the North Danish Region September 2011. For details see the regional guideline on eosinophilic esophagitis. Questions: _____ email: _____



Krarup et al. Endoscopy 2021

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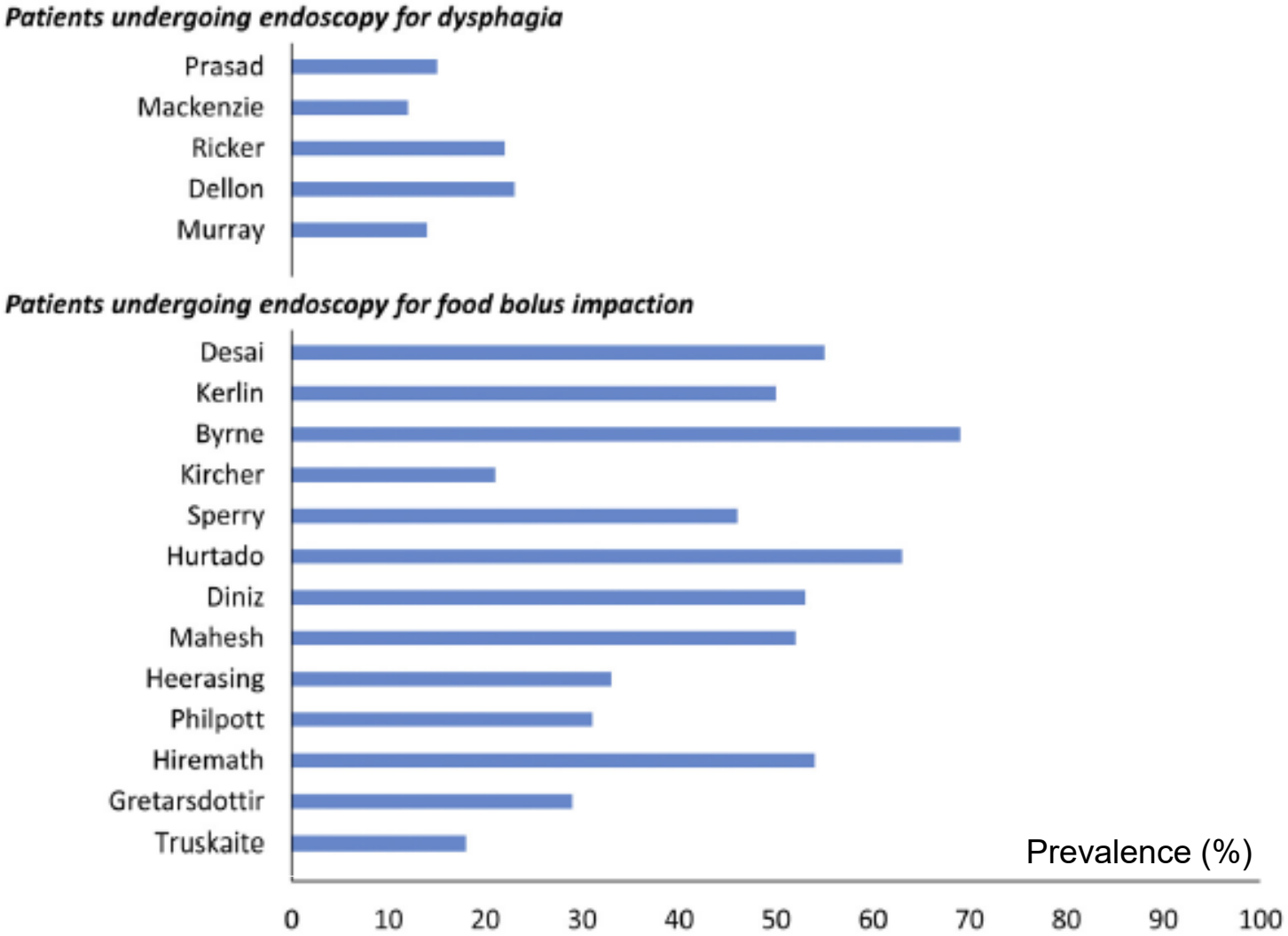
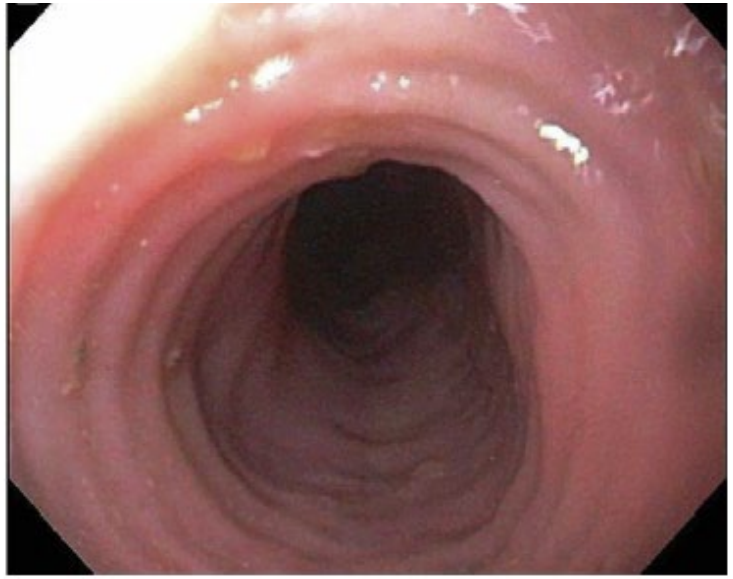
Symptom patterns







Dellon and Hirano. Gastroenterology 2018

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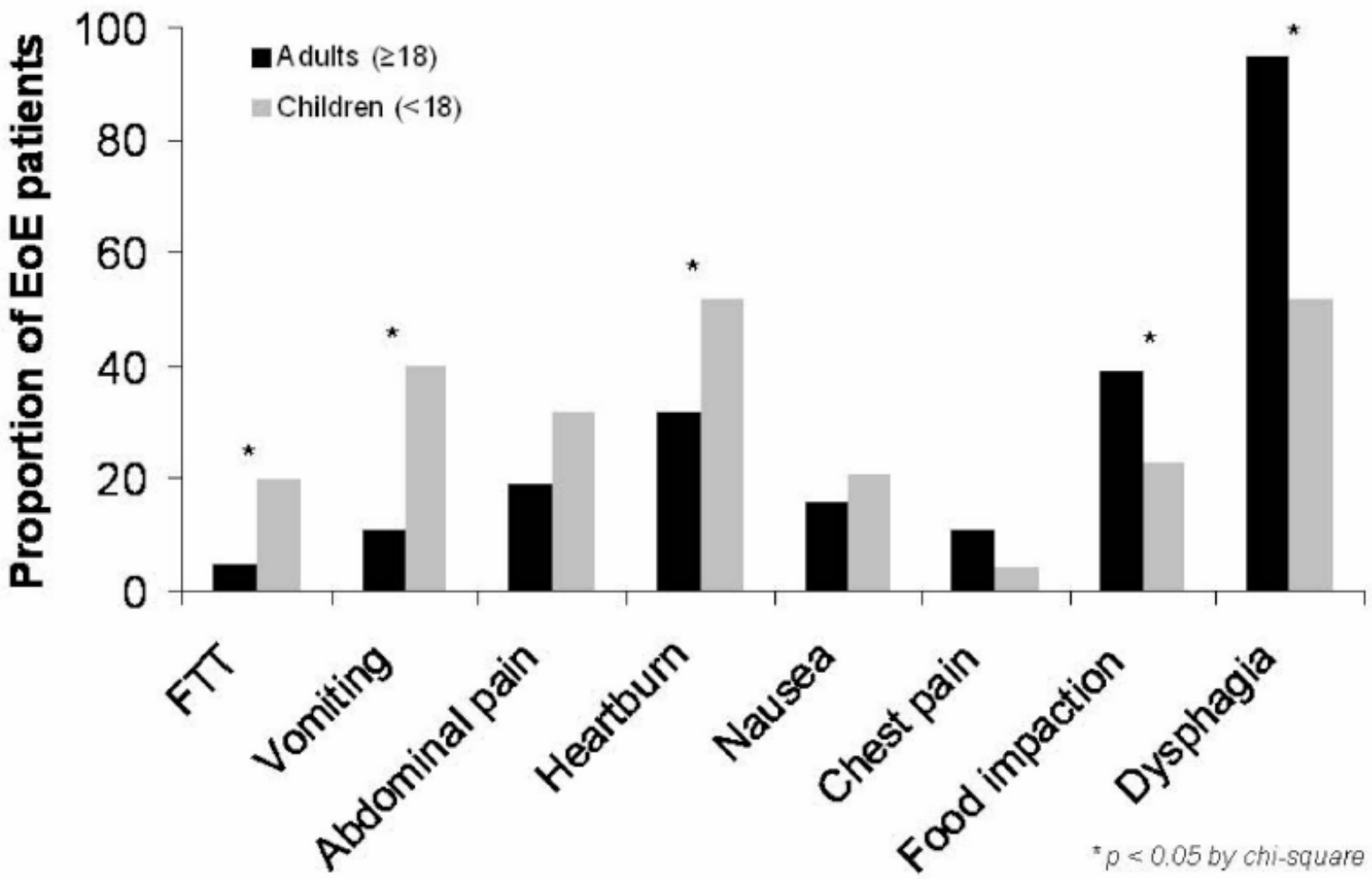
Symptom patterns



Other symptoms in kids:

- Eating slowly
- Holding food in mouth
- Food refusal
- Irritability
- Excessive drinking during meal

Dellon et al. Clin Gastroenterol Hepatol 2009

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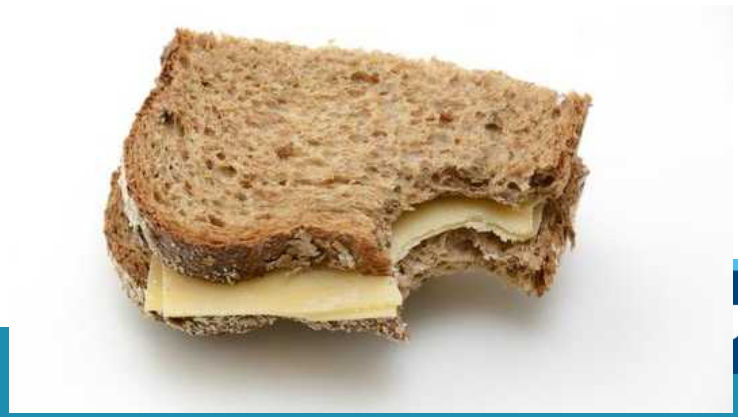
Symptom patterns

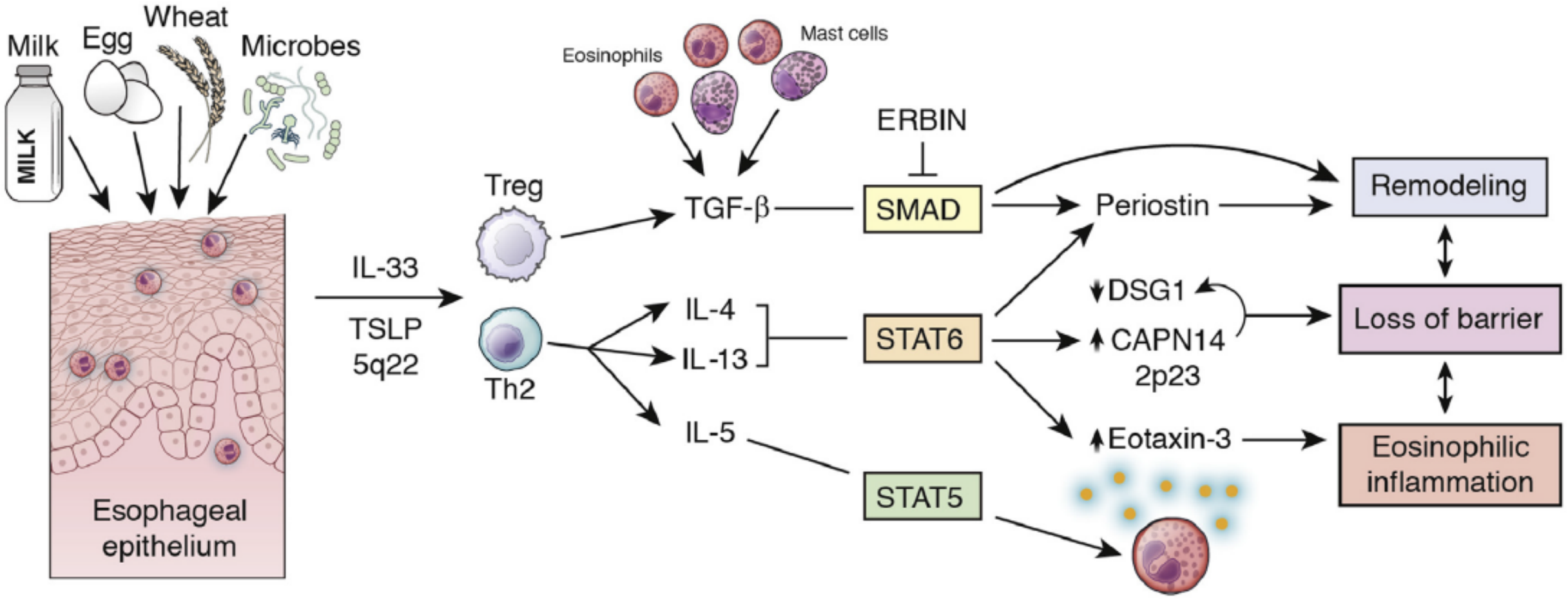








Pathophysiology



O'Shea et al. Gastroenterology 2018

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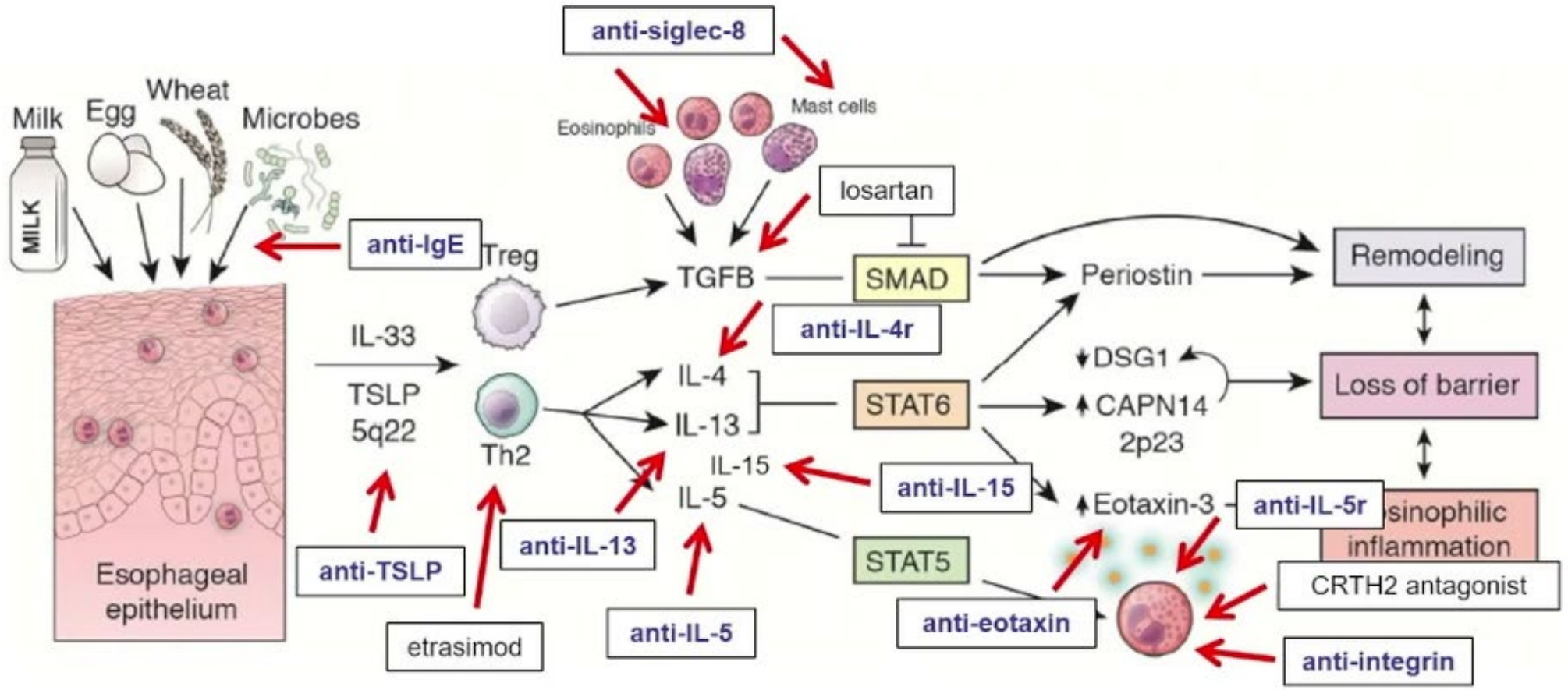
Pathophysiology



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Pathophysiology: (Food) Allergy

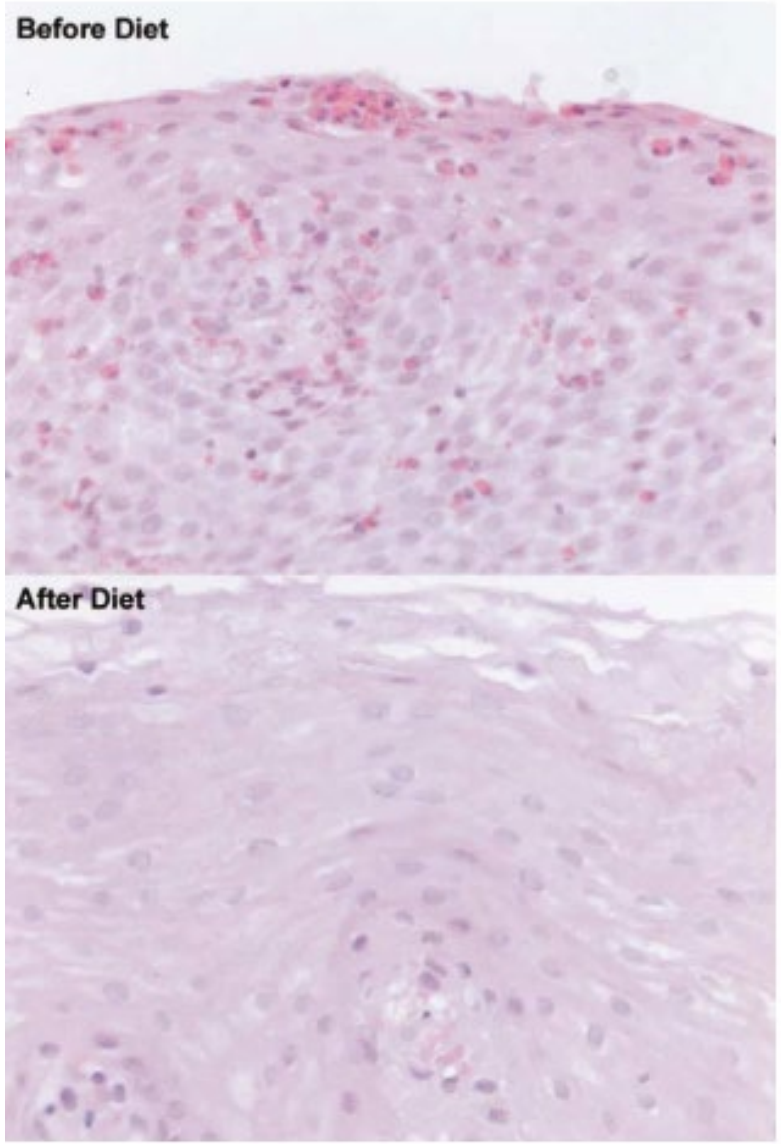
- Higher incidence of atopic disease
- Improvement on elemental diet

51 children (3-16y)

Table 2. Number of Patients With Symptoms Before (Prediet) and After 1 Month of Treatment With Elemental Diet (Postdiet)

	Prediet	Postdiet	*p*
Eosinophils/HPF	33.7 ± 10.3	1.0 ± 0.6	<0.01
Abdominal pain	40	2	<0.01
Vomiting	36	1	<0.01
Heartburn	27	2	<0.01
Water brash	11	1	<0.01
Globus	9	1	<0.01
Dysphagia	7	0	<0.01
Chest pain	4	0	0.04
Night cough	5	1	0.1
Irritability	3	0	0.08

HPF = microscopic high-powered field, equivalent to 40×.



Markowitz et al. Am J Gastroenterol 2003

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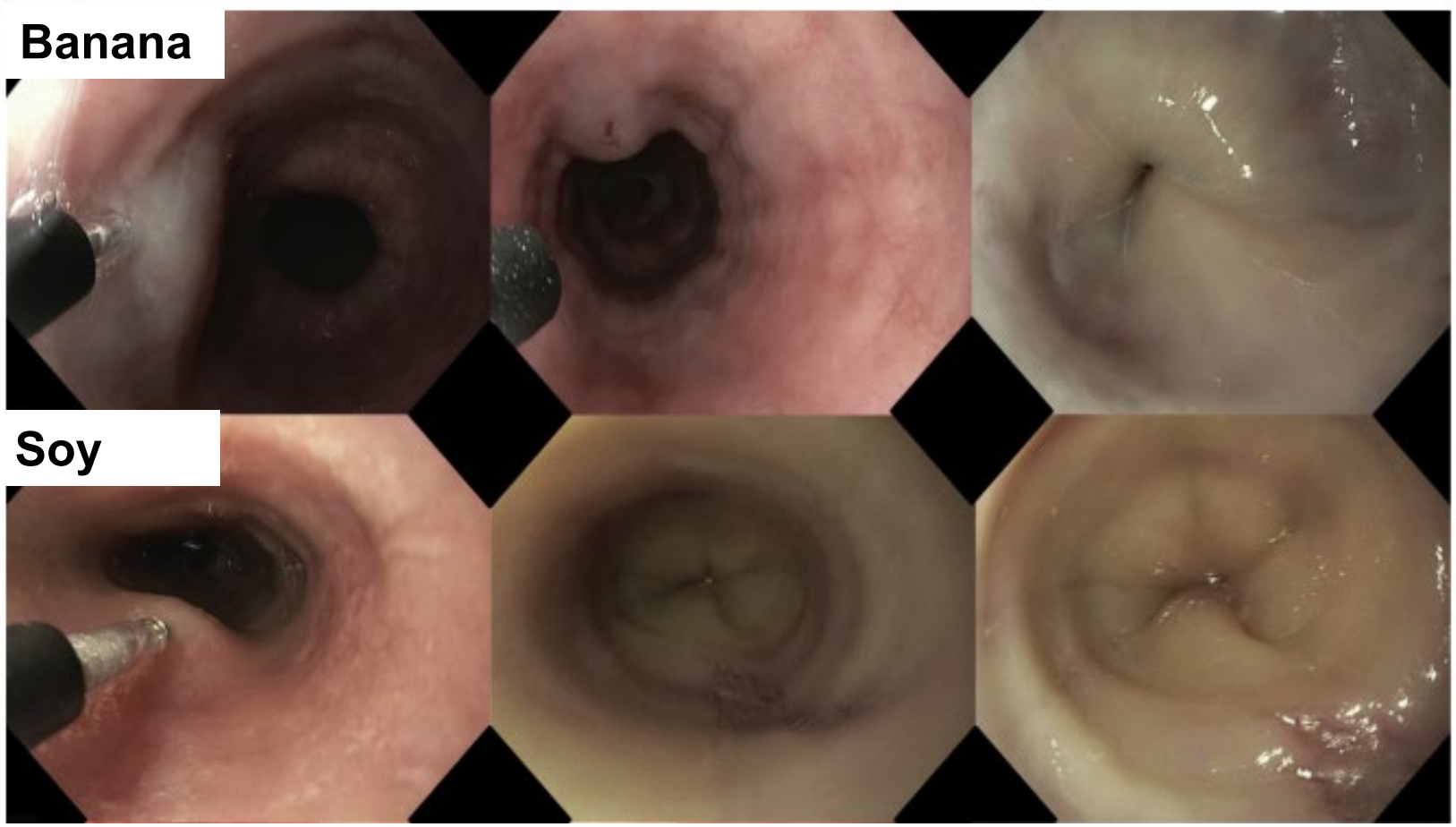
Pathophysiology: (Food) Allergy

- Higher incidence of atopic disease
- Improvement on elemental diet
- Acute reactions on intra-esophageal allergen injection: esophageal prick test

Pathophysiology: (Food) Allergy – Esophageal Prick Test







No reactions to wheat, milk or egg???

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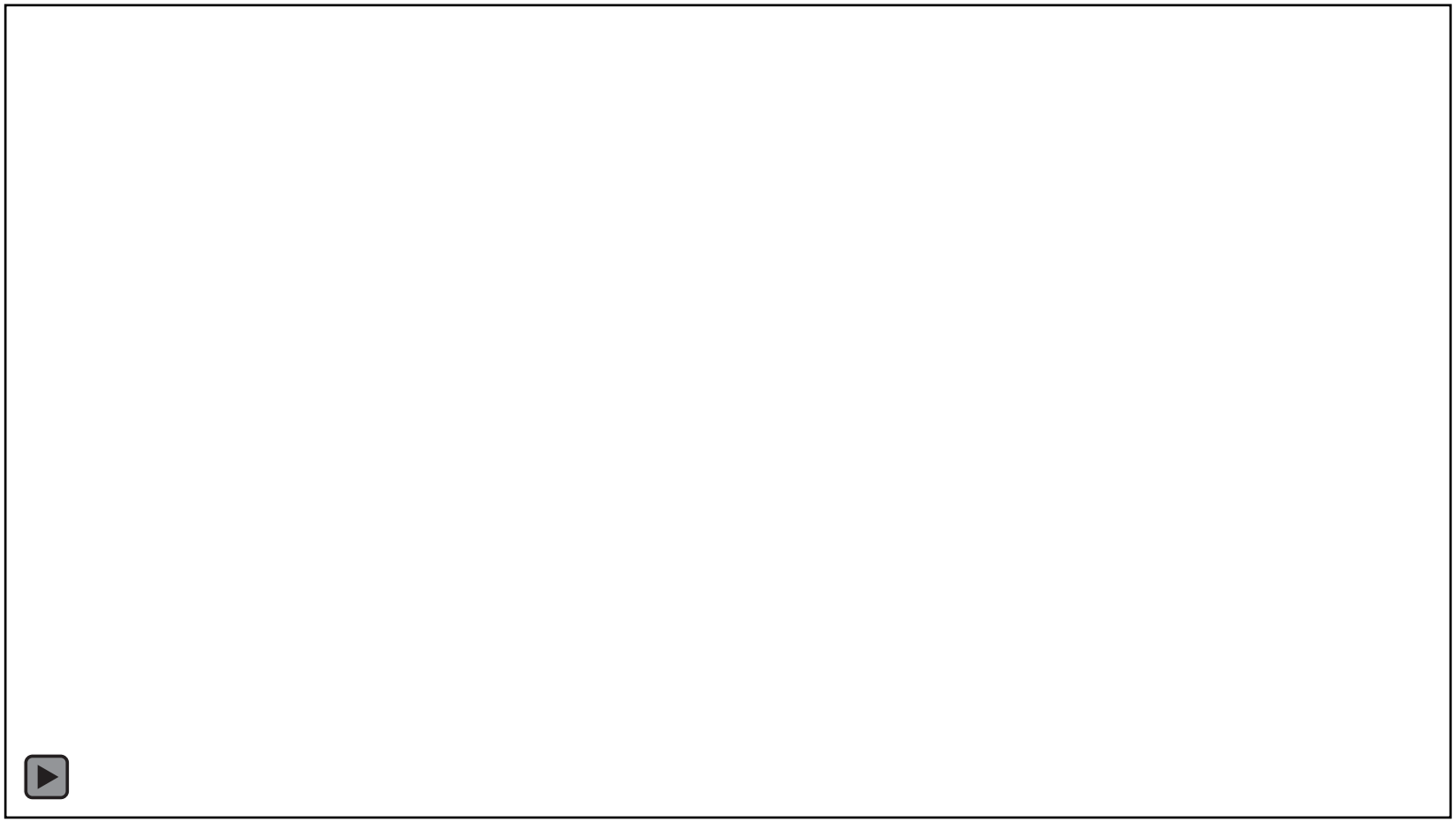
Pathophysiology: (Food) Allergy – Esophageal Prick Test



Warners et al. Gastroenterology 2018

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Pathophysiology: (Food) Allergy

- Higher incidence of atopic disease
- Improvement on elemental diet
- Acute reactions on intra-esophageal allergen injection: esophageal prick test

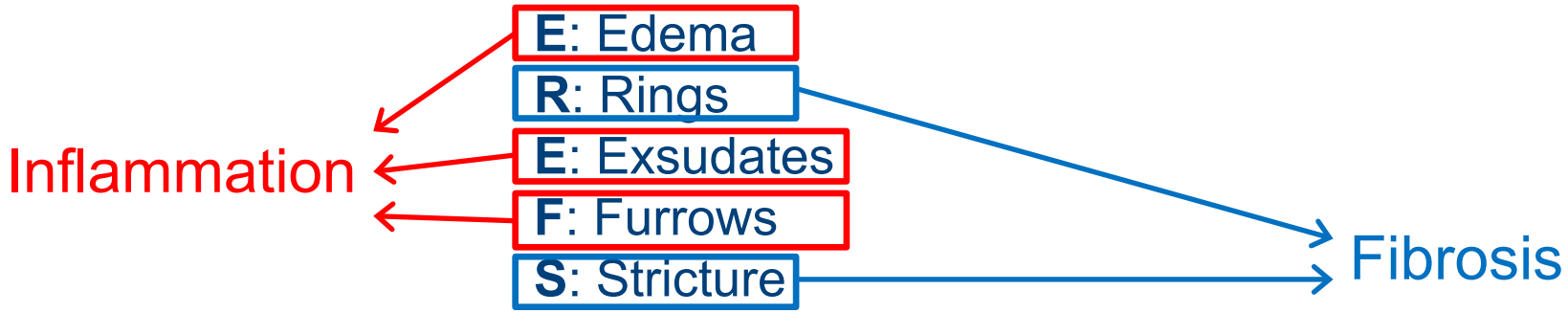
Role in *'Food-induced Immediate Reaction of the Esophagus'*? 'FIRE'

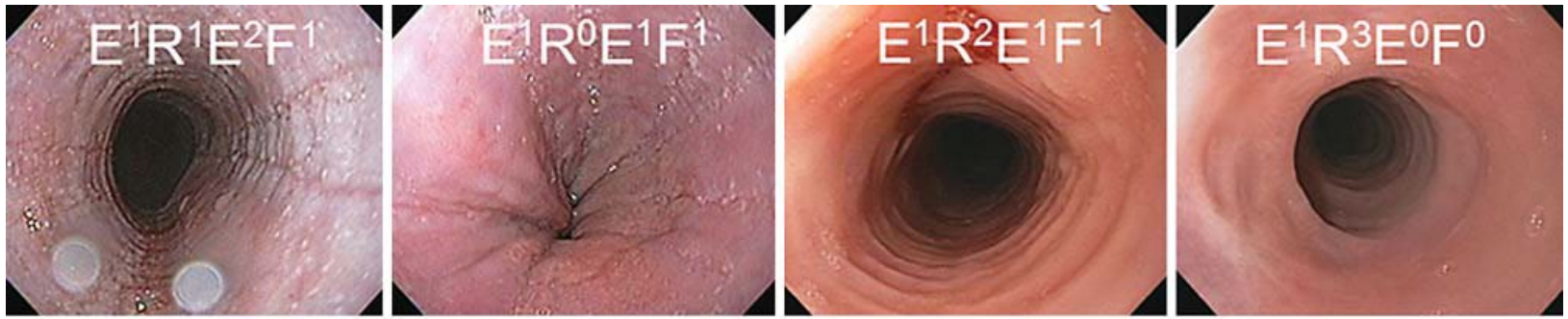


Diagnosis: Endoscopy

EREFS: EoE Endoscopic Reference Score

7% have normal endoscopy!





Hirano et al. Gut 2012

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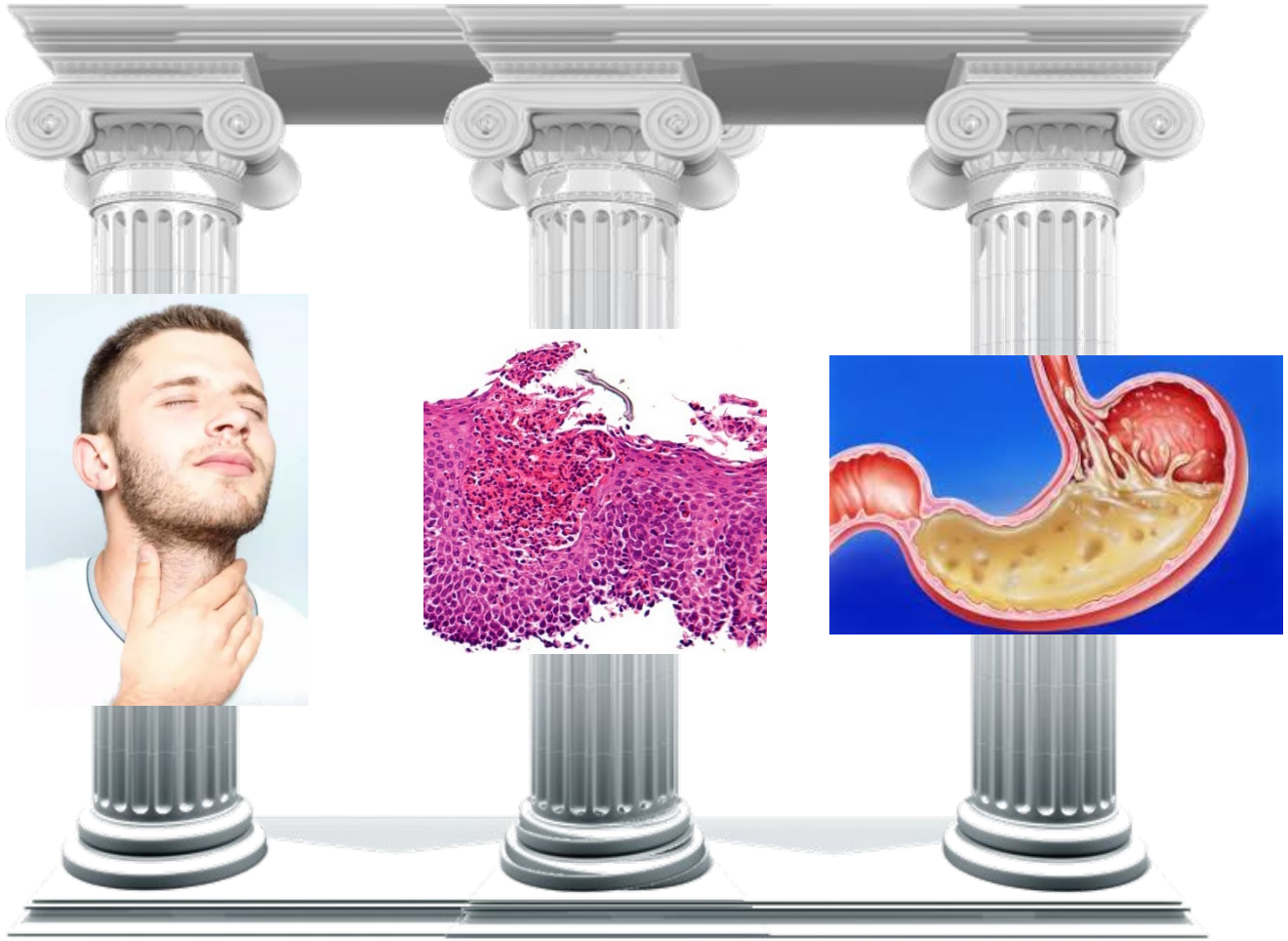
Diagnosis:



Symptoms **Pathology** **Exclusion of other causes**

Hirano et al. Gut 2012

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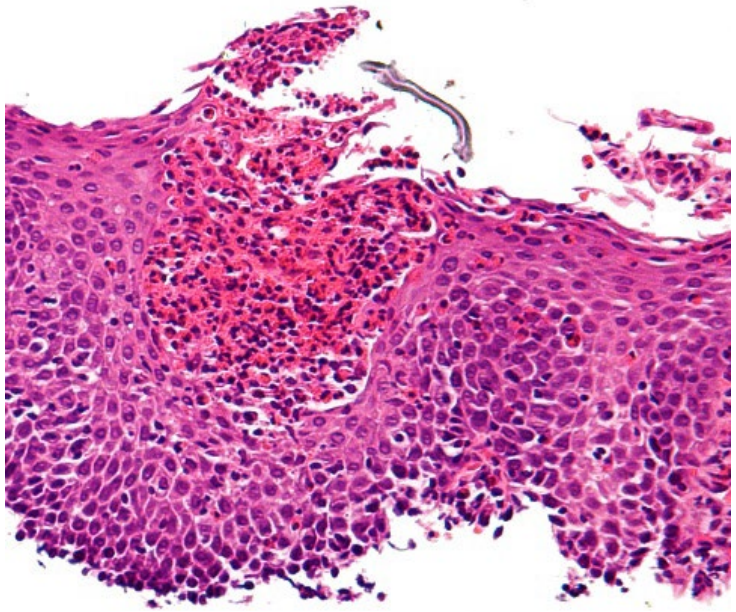
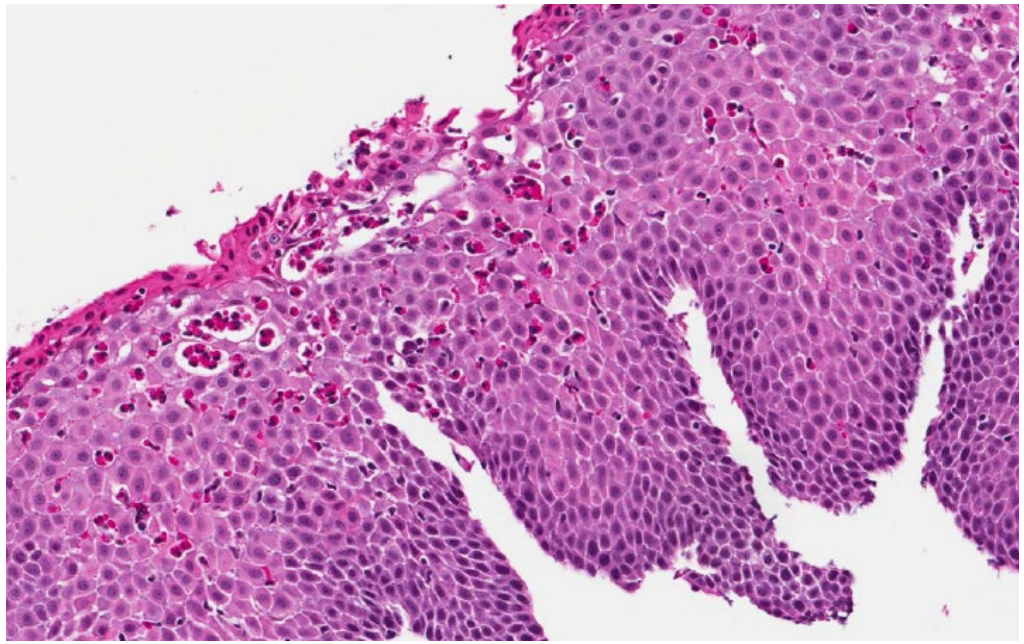
Diagnosis: Pathology

	≥15 eos/hpf	≥10 eos/hpf	≥20 eos/hpf	Degranulation	Microabscesses	Lamina propria fibrosis
Sensitivity	100	100	90	93	56	27
Specificity	96[a]	87	97	81	98	97
Positive predictive value	85	35	86	54	89	69
Negative predictive value	100	100	98	98	91	85

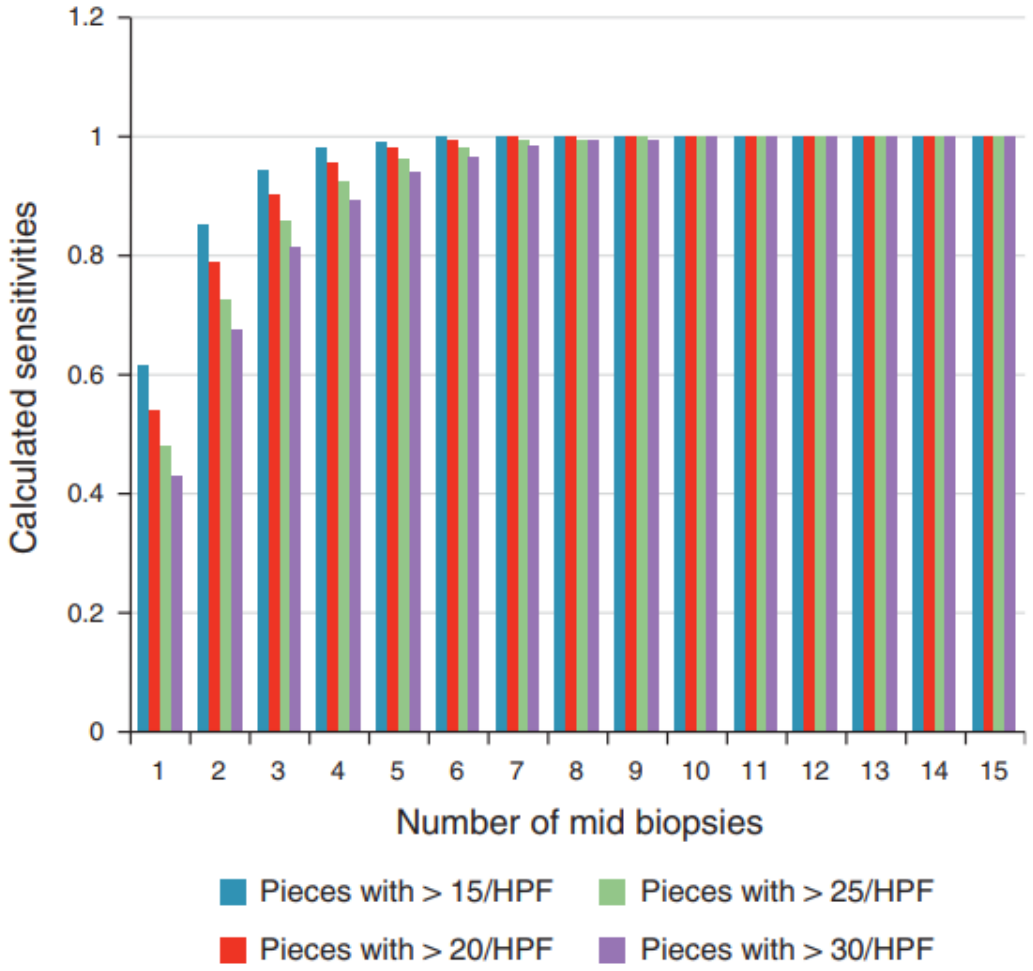




HPF = X400

Dellon et al. Mod Pathology 2015
Dellon et al. Clin Gastroenterol Hepatol 2012

Diagnosis: Pathology



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%).

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Nielsen et al. Am J Gastroenterol 2014
Lucendo et al. UEG Journal 2017

Diagnosis: Exclusion of other causes of eosinophilia

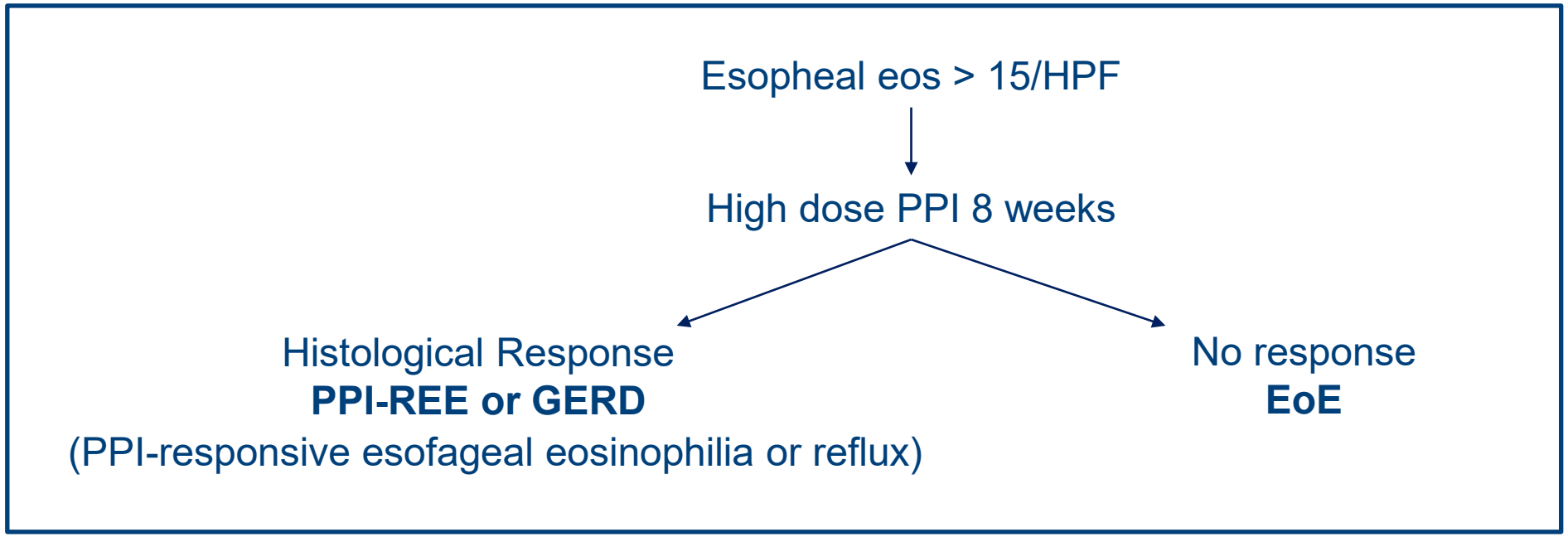
Diseases associated with esophageal eosinophilia
EoE
GERD
PPI-responsive esophageal eosinophilia
Eosinophilic gastrointestinal diseases
Esophageal infections (e.g., fungal, viral, parasitic)
Crohn's disease
Celiac disease
Achalasia
Hypereosinophilic syndrome
Pemphigus
Vasculitis
Drug hypersensitivity
Connective tissue diseases
Graft vs. host disease

Important conditions to exclude:

- GERD
- Achalasia

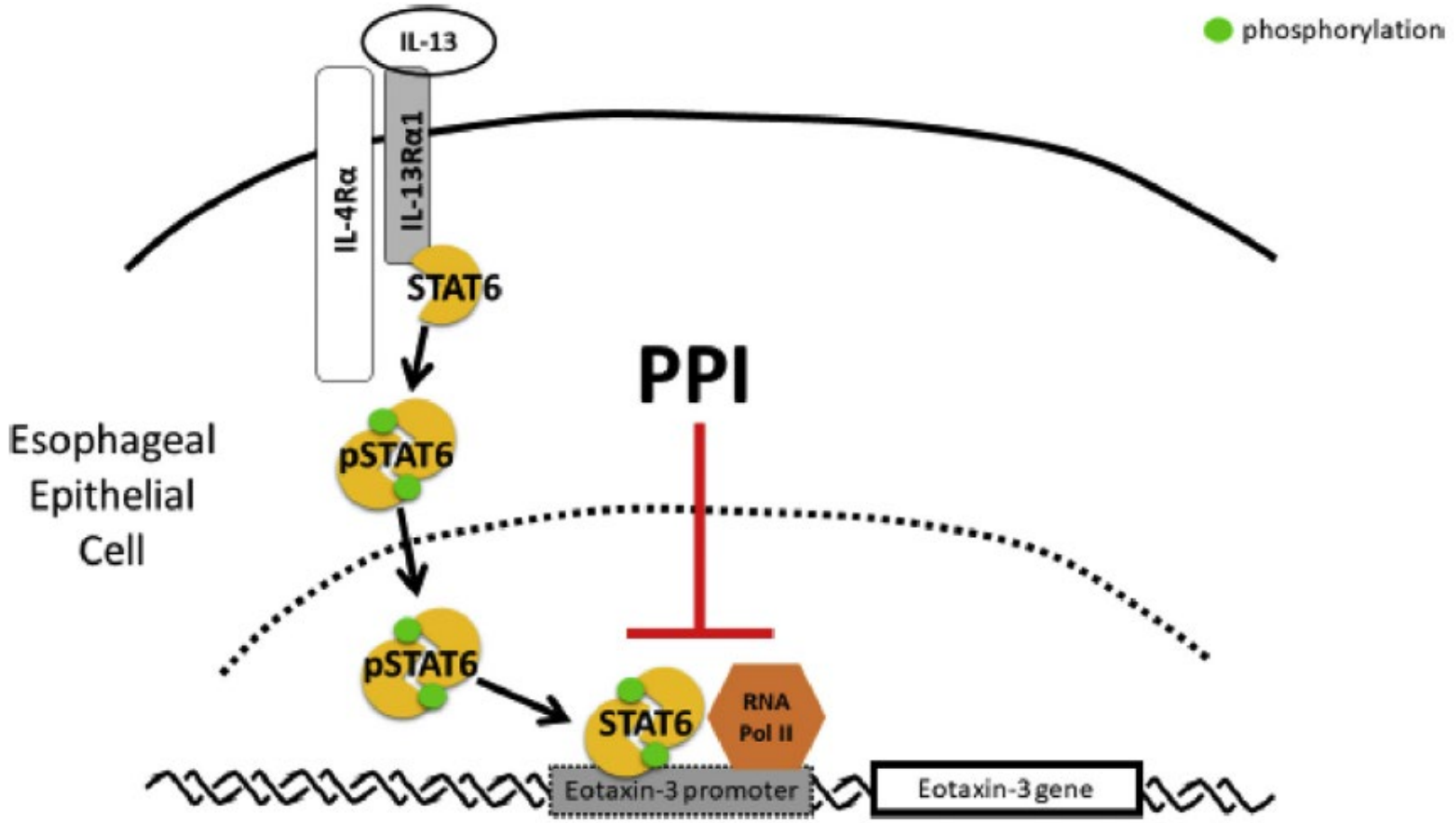
Diagnosis: Exclusion of other causes of eosinophilia

The ‘old’ days (2016):



Mechanism of PPI

Anti-inflammatory effects of PPI



Dellon et al. Gastroenterology 2018, the AGREE conference

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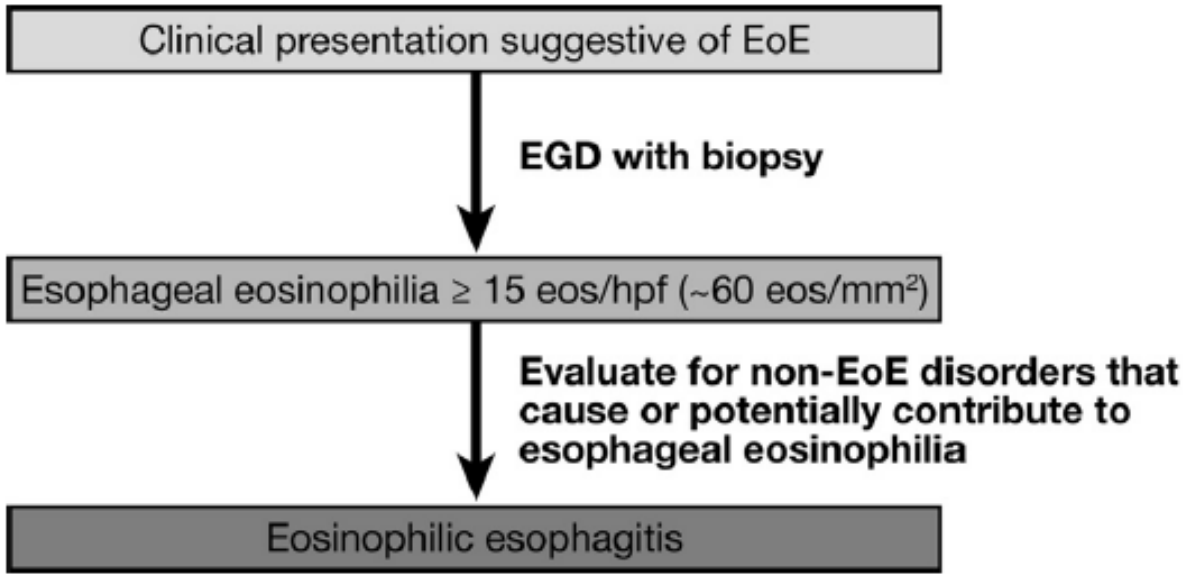
Treatment algorithm EoE



PPI

Topical Corticosteroids

Elimination (or elemental) Diet

Dellon et al. Gastroenterology 2018, the AGREE conference

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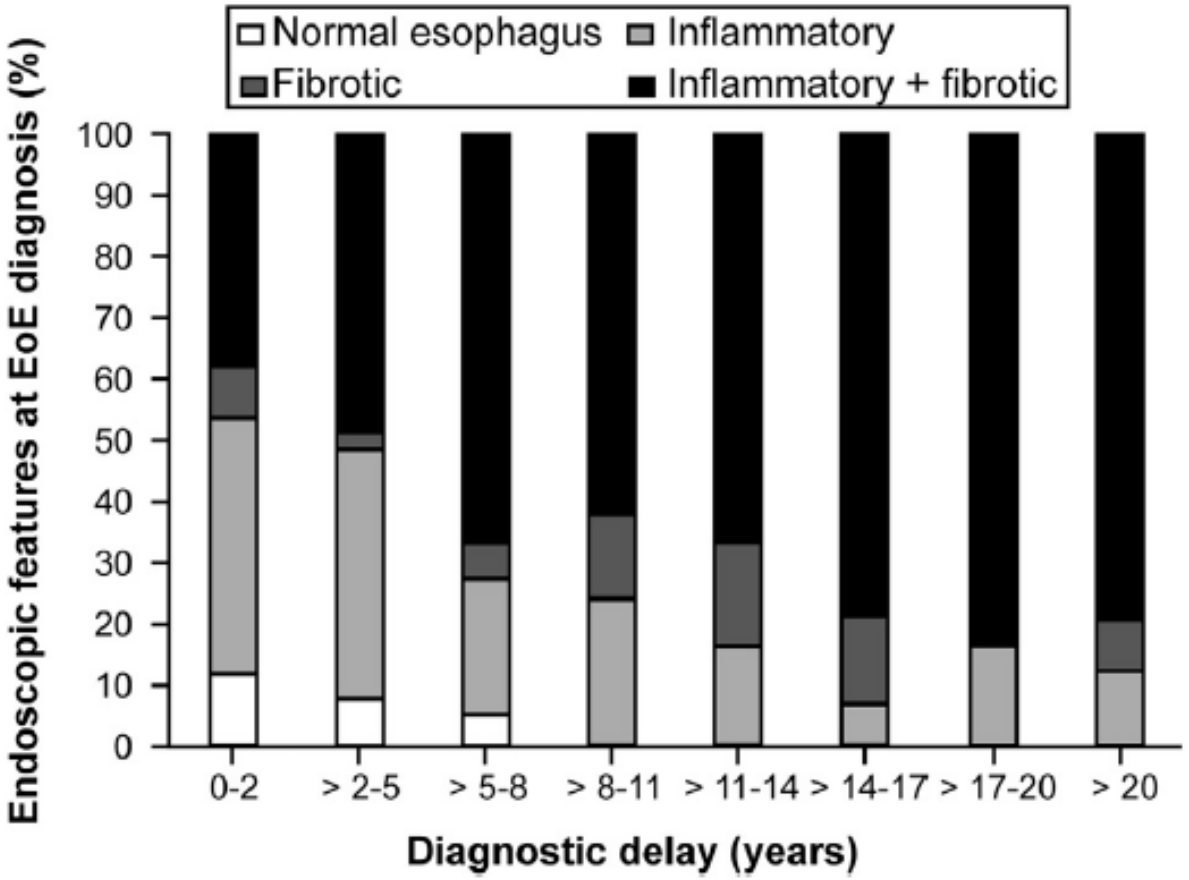
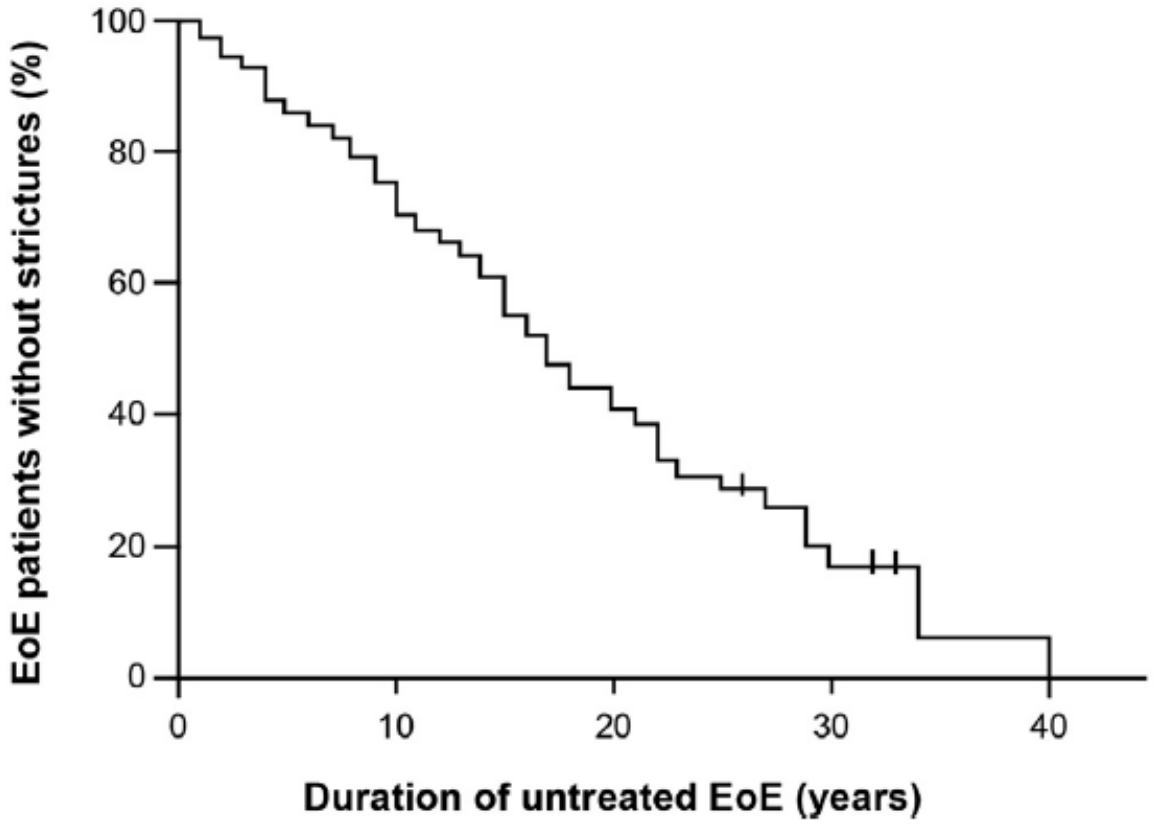
Treatment: Why?

Fibrotic signs increase with longer diagnostic delay.



Risk of strictures in untreated EoE.



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Schoepfer et al. Gastroenterology 2013

Treatment: Topical Corticosteroids

- Fluticasone powder or puff
  Dose: 750µg (3 puffs) 2x/d or 1000 µg (2 comp in disk) 2x/d
- Budesonide oral viscous solution
  Dose: starting 2x1mg/d (1mg budesonide + xanthane gum up to 10mL; 2x/d)
- Endoscopic and histological evaluation after 8-12 weeks



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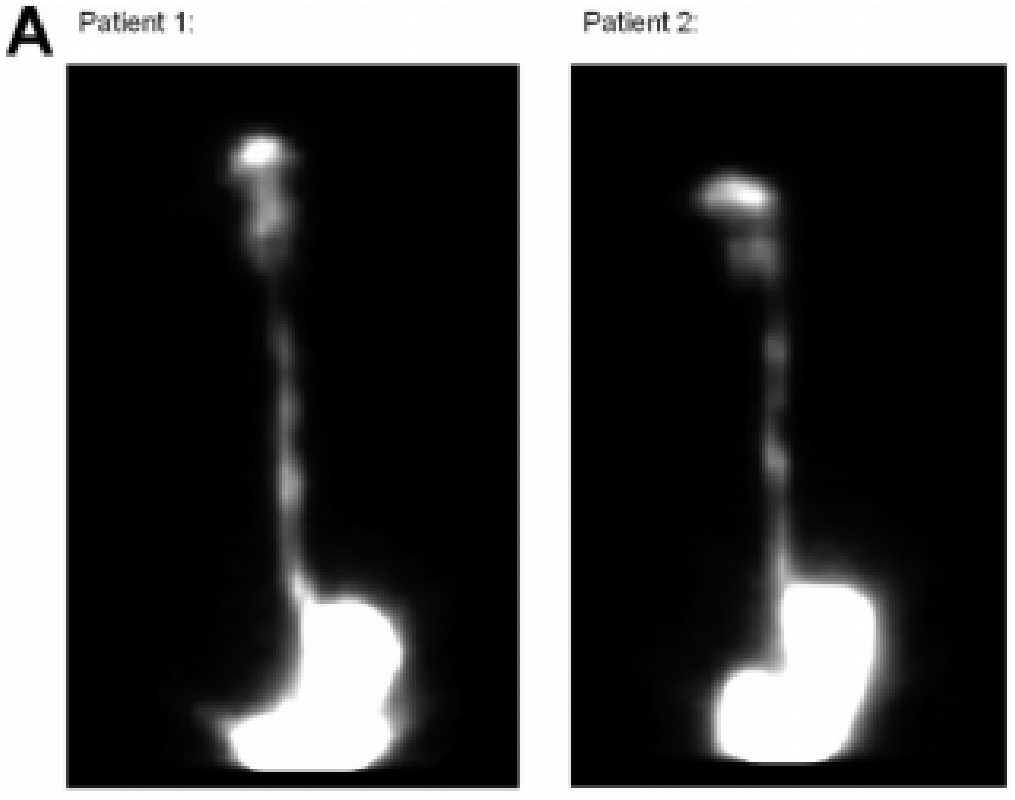
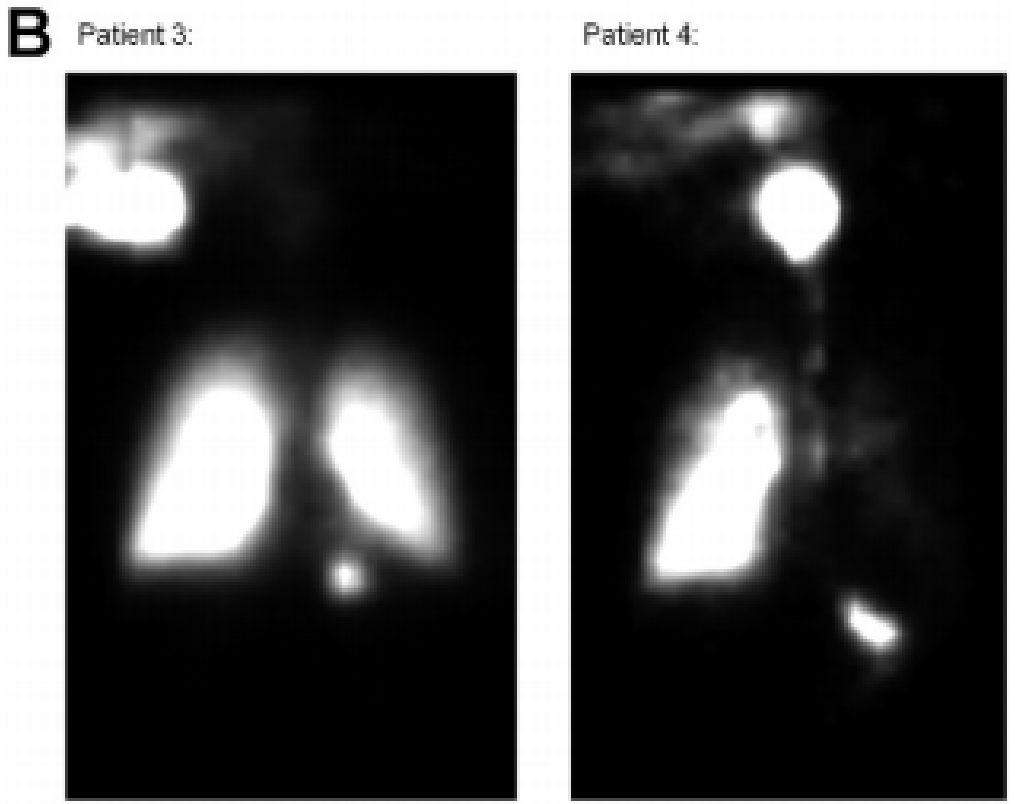
Treatment: Topical Corticosteroids

Oral viscous solution



Nebulized and swallowed



Dellon et al. Gastroenterology 2012

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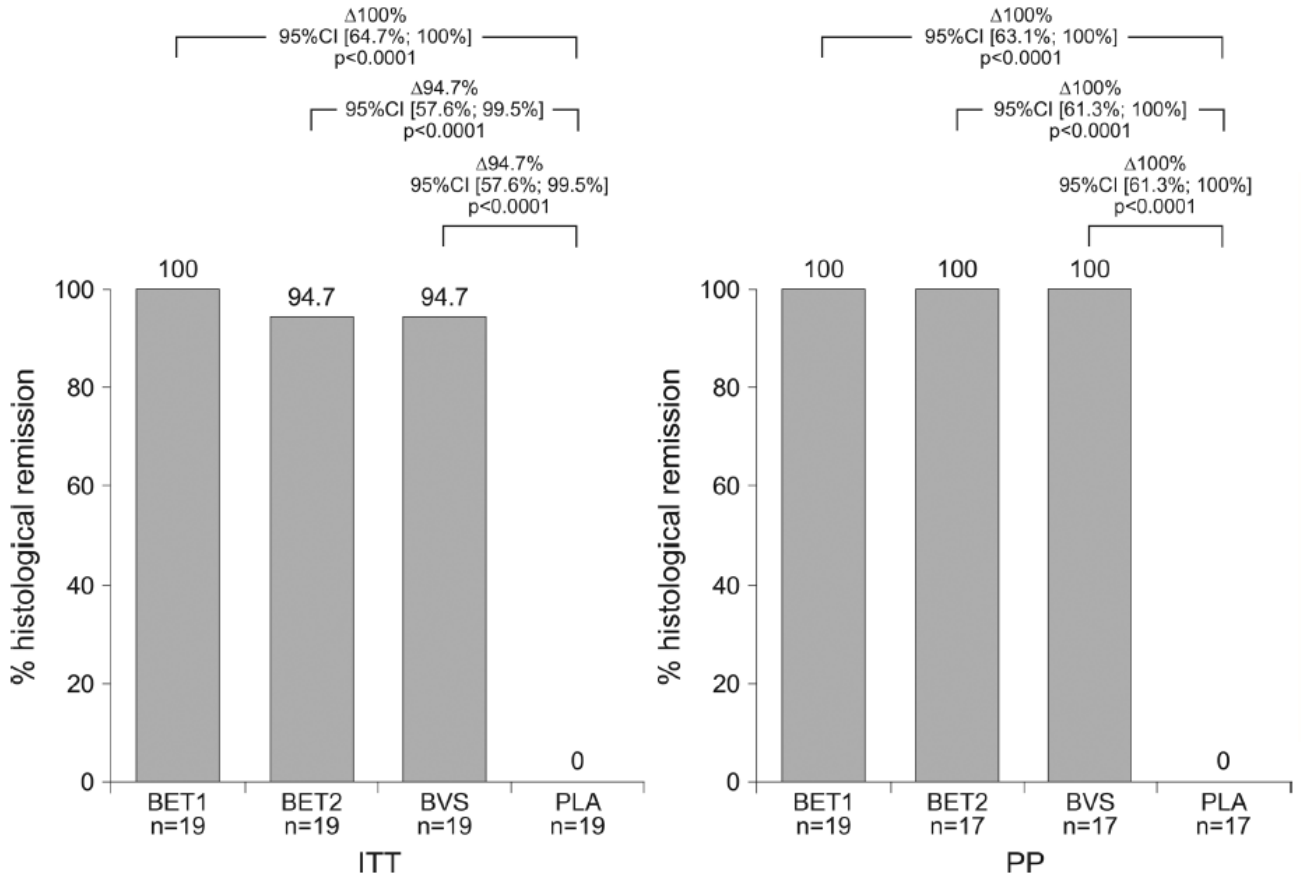
Treatment: Topical Corticosteroids

New Drug Formulations: Budesonide Effervescent Tablets (BET) 1mg – 2mg bid
Budesonide Viscous Gel (BVG) 2mg bid





Miehlke et al. Gut 2016

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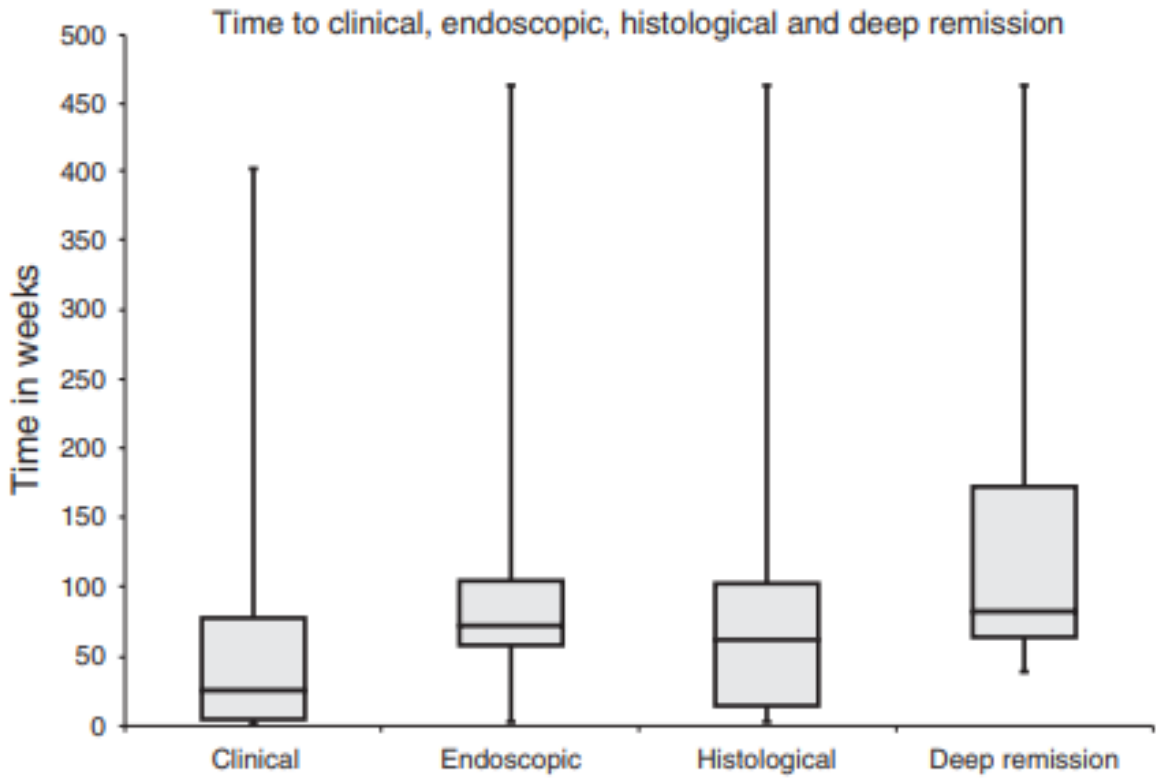
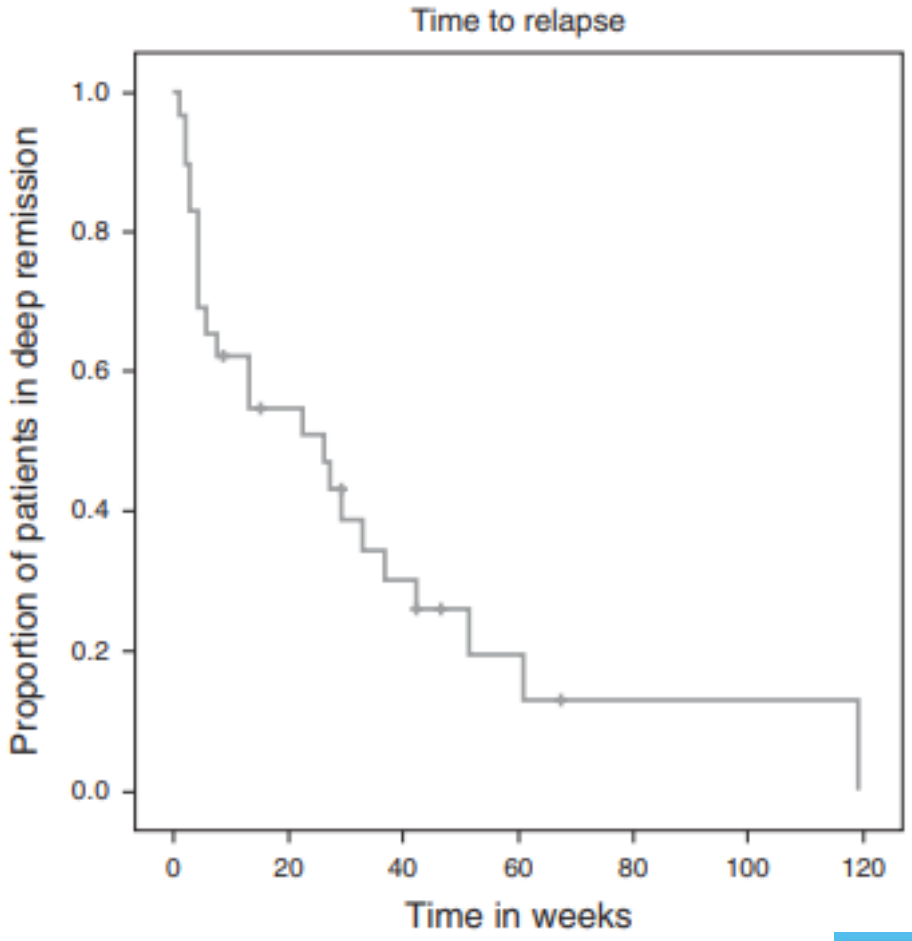
Treatment: Topical Corticosteroids (maintenance)

Deep remission only in 10% of pts on 2x0.25mg budesonide maintenance



Evolution after treatment cessation



Greuter et al. Am J Gastroenterol 2017

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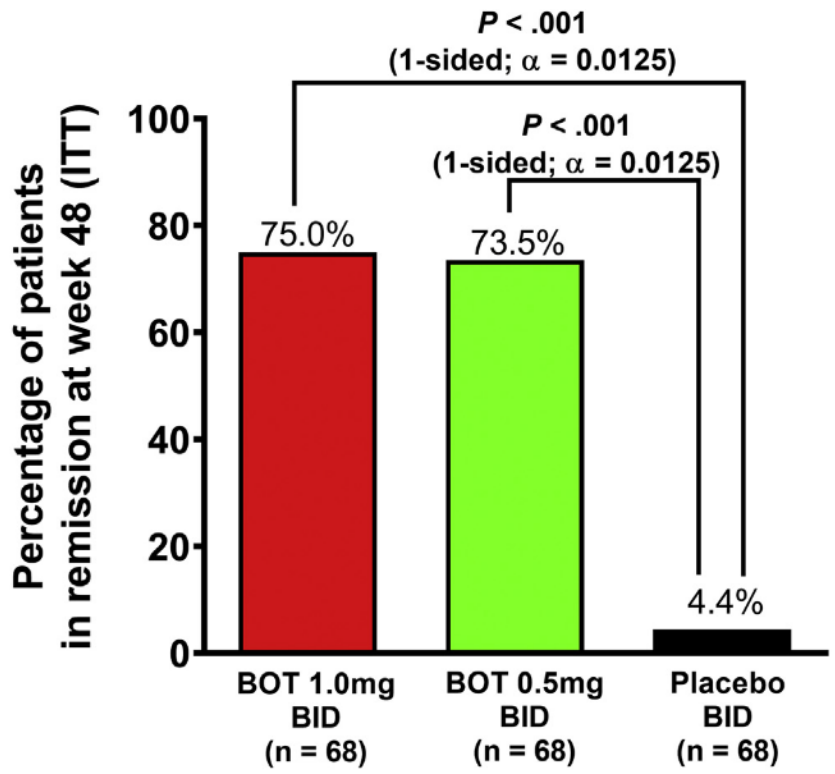
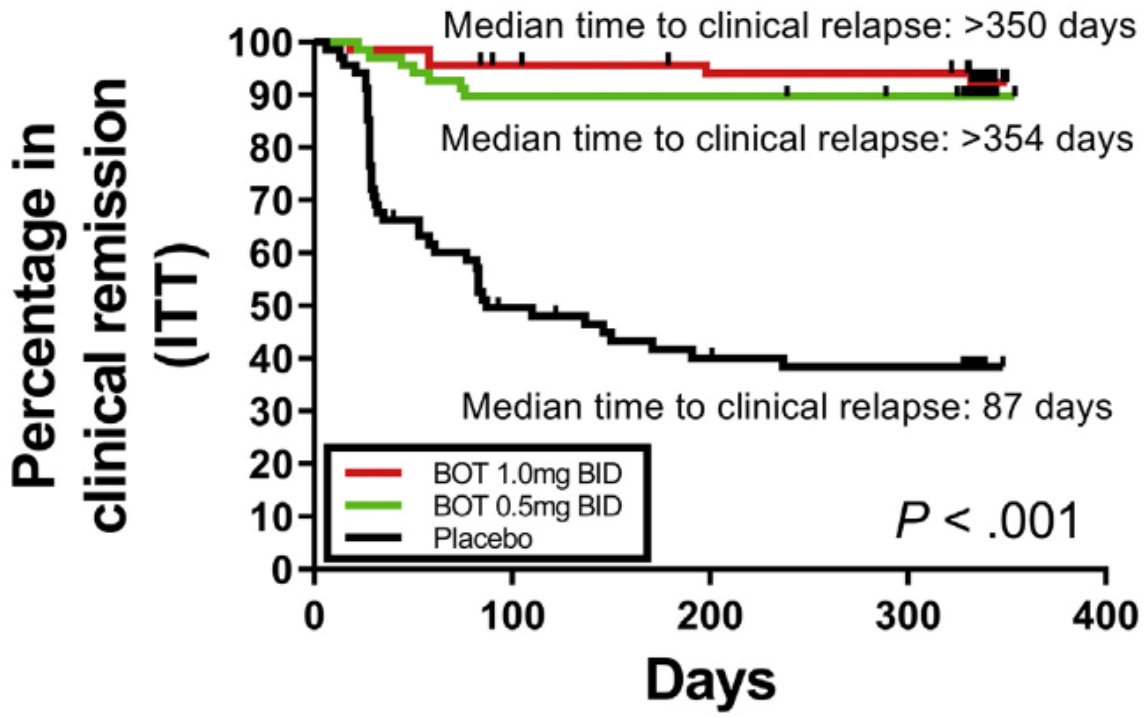
Treatment: Topical Corticosteroids (maintenance)





Maintenance dose budesonide: 2x0.5mg/d

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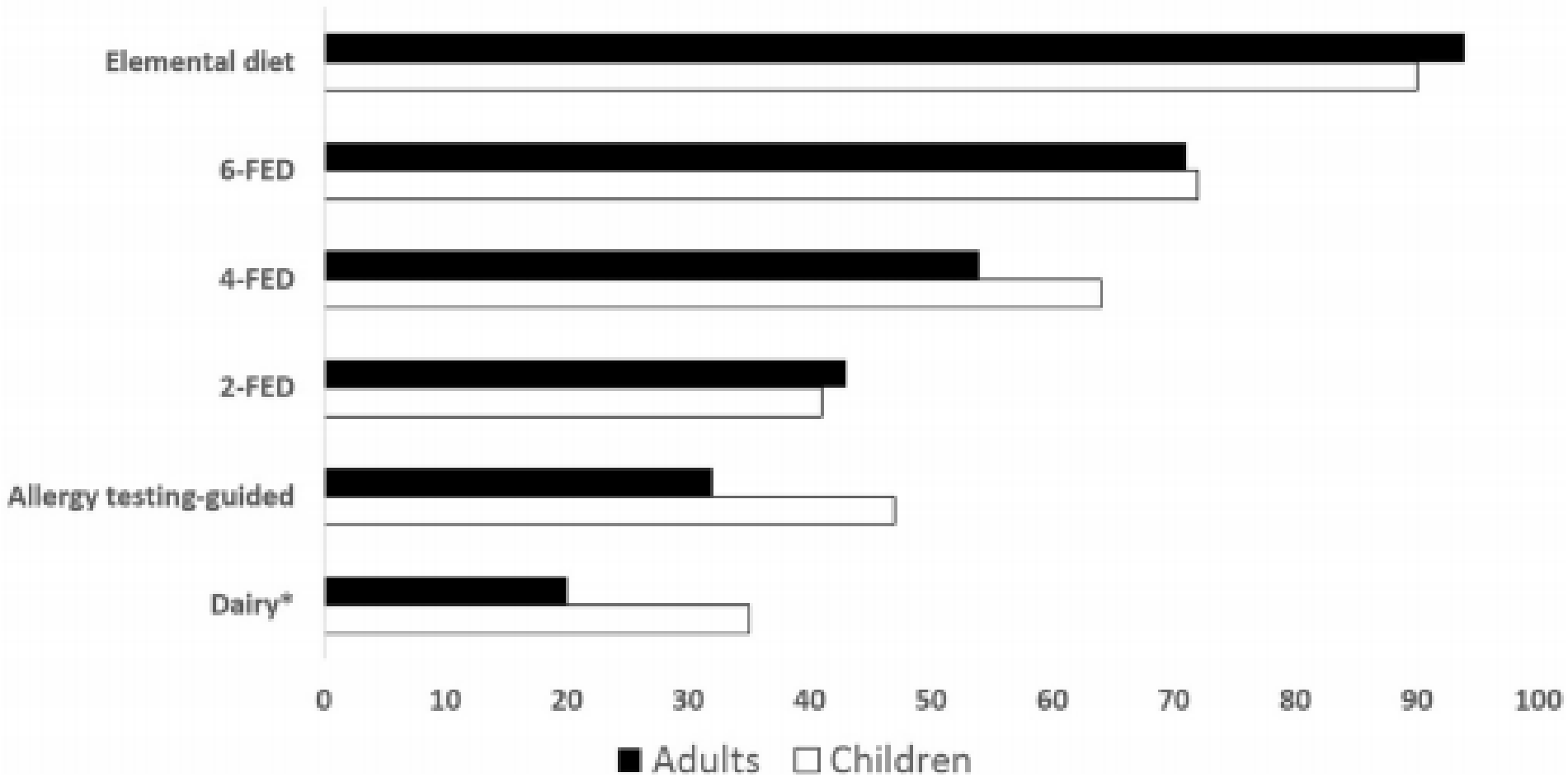
Treatment: Diets



Molina Infante and Lucendo. J All Clin Immunol 2018

Treatment: Diets

- Compliance!
- Severely symptomatic patiënts should be treated with steroids first
- CAVE restrictive diets for combined food allergy – EoE
- Trained dietitian and written information
- Minimum of 6 weeks before re-evaluation (shorter with reintroduction?), always with biopsies!

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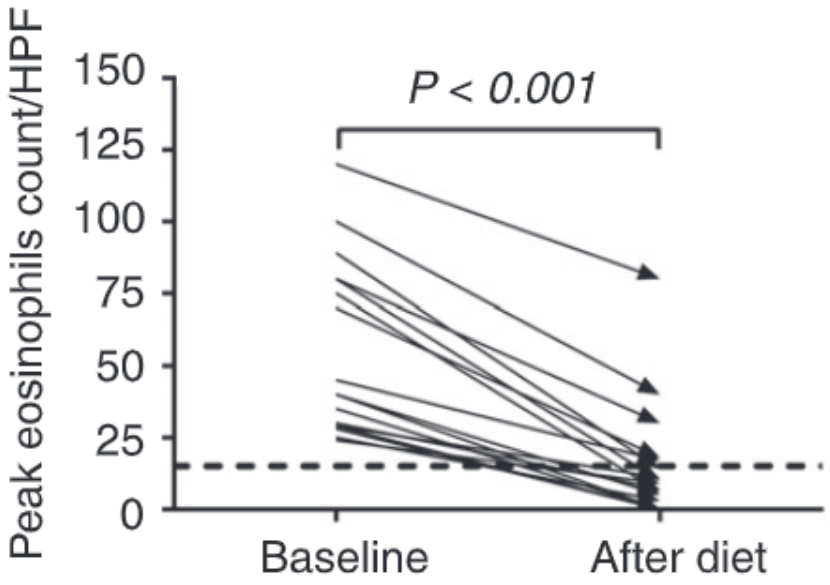
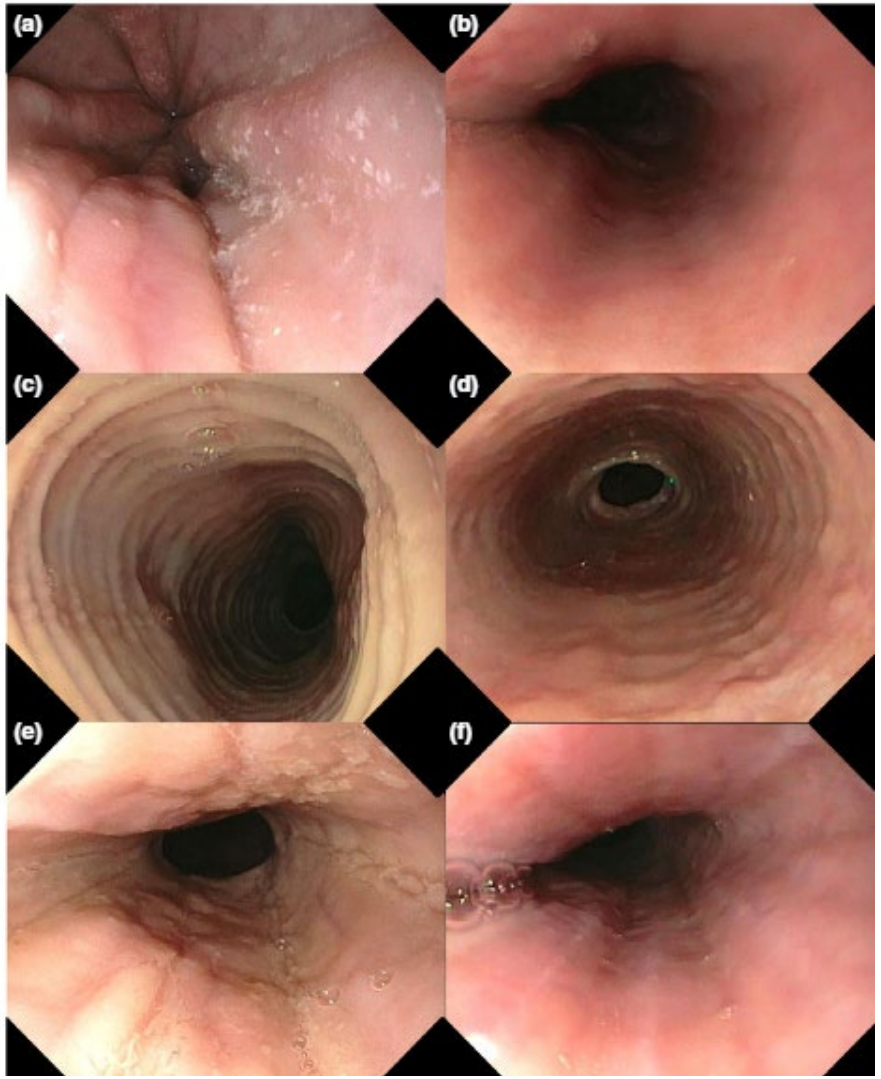
Treatment: Elemental Diets in adults

Neocate Nutricia as exclusive nutrition during 4 weeks
Water, green/black tea allowed
Sugar-free chewing gum





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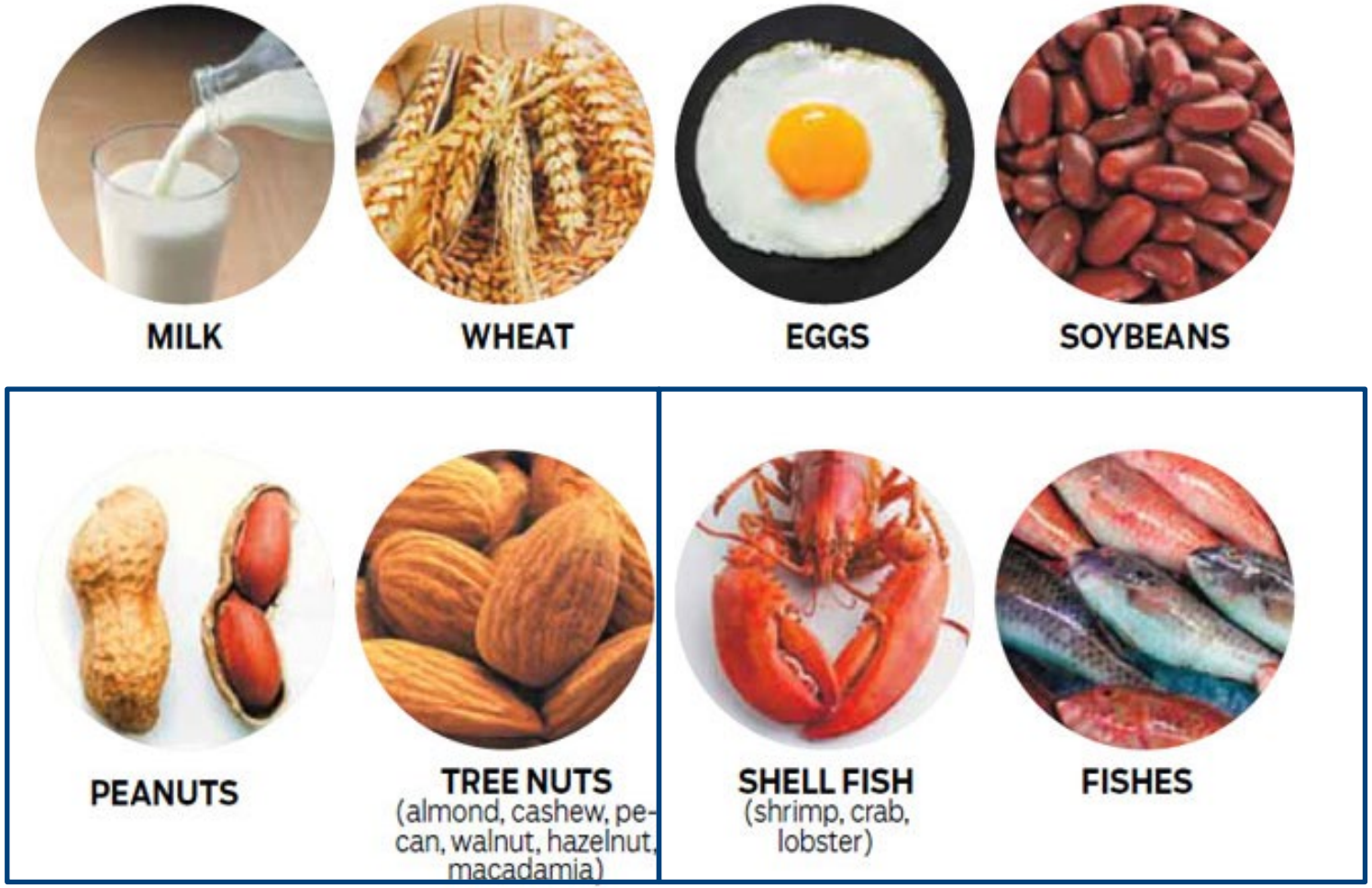
Treatment: Diets – 6 Food Elimination Diet (6FED)



Treatment: Diets – 6 Food Elimination Diet (6FED)

First author, year of publication, country	Diet/population/design	Histologic remission	No. of culprit foods identified through individual reintroduction of either 6, 4, or 2 food groups			Most common food triggers identified through individual food reintroduction
			1	2	>2	
Kagalwallaet al, 2011, United States[23]	6-FED/children/unicenter	74%	72%	8%*	8%*	Milk = 74% Wheat = 26% Eggs = 17%
Gonsalves et al, 2012, United States[24]	6-FED/adults/unicenter	70%	85%	15%*		Wheat = 60% Milk = 50%
Lucendo et al, 2013, Spain[25]	6-FED/adults/unicenter	72%	36%	31%	33%	Milk = 62% Wheat = 29% Egg = 26% Legumes = 24%
Rodriguez-Sanchez et al, 2014, Spain[26]	6-FED/adults/unicenter	53%	—	—	—	Milk = 64% Wheat = 28% Egg = 21% Legumes = 7%
Philpott et al, 2016, Australia[27]	6-FED/adults/unicenter	52%	56%	17%	13%	Milk = 43% Wheat = 43% Egg = 34%

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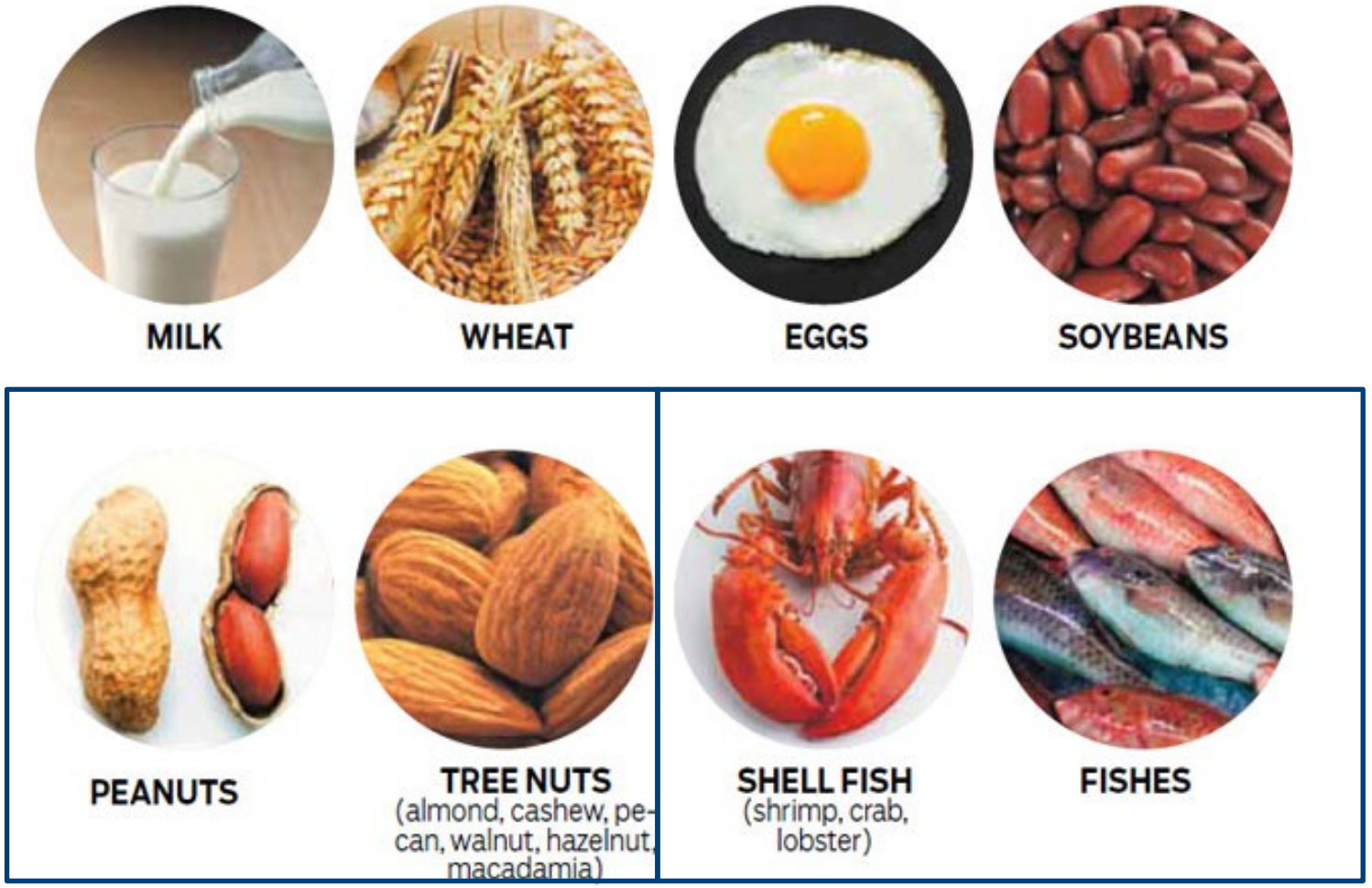
Treatment: Diets – 6 Food Elimination Diet (6FED)



- Up to 42 weeks
- At least 7 endoscopies
- Restrictive diet

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Treatment: Diets – 2 Food Elimination Diet (2FED)

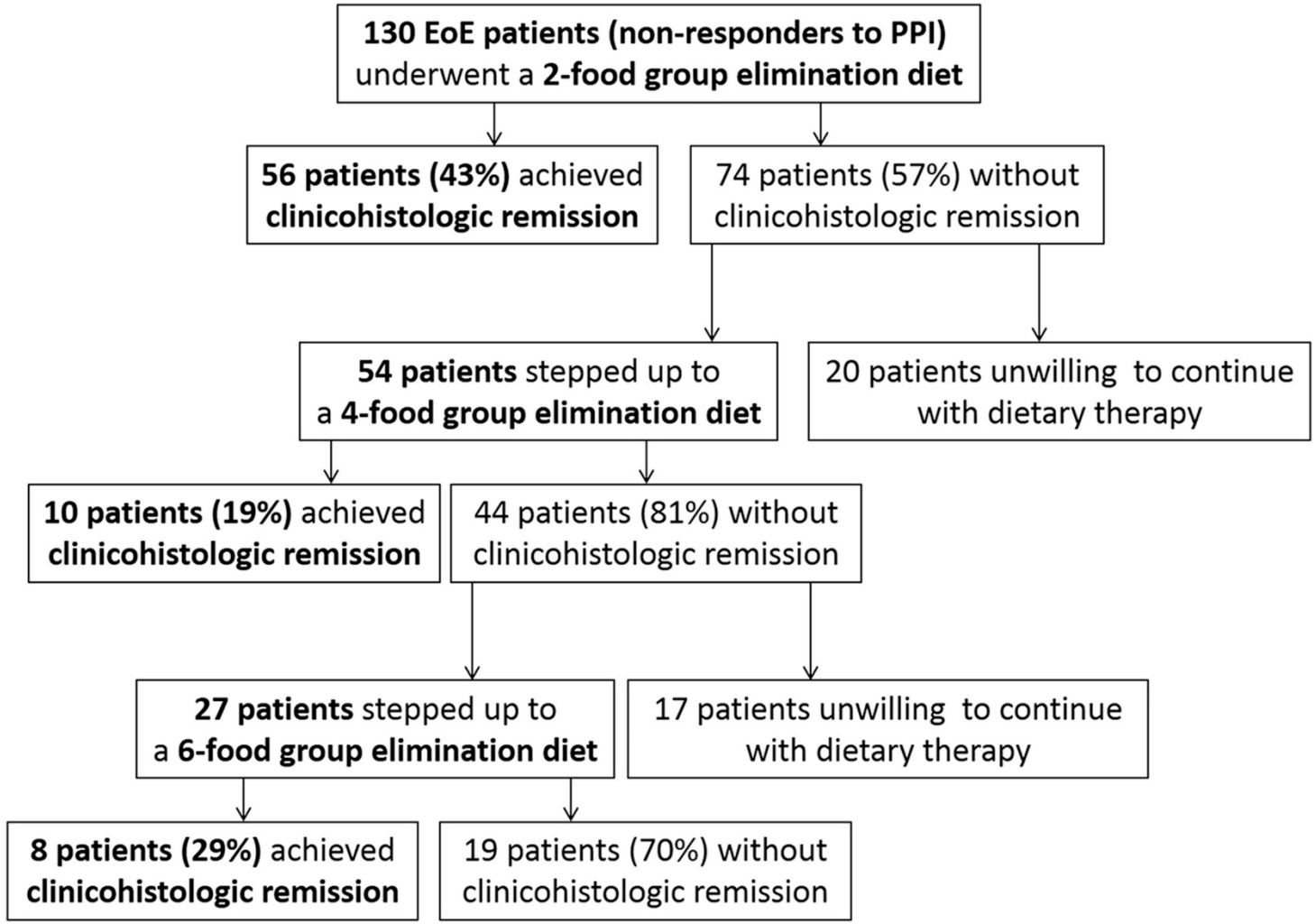
2 FED (milk + gluten)

↓ non-response

4 FED (+egg + legumes)

↓ non-response

6 FED (+nuts, fish, shellfish)



Molina Infante et al. J All Clin Immunol 2018

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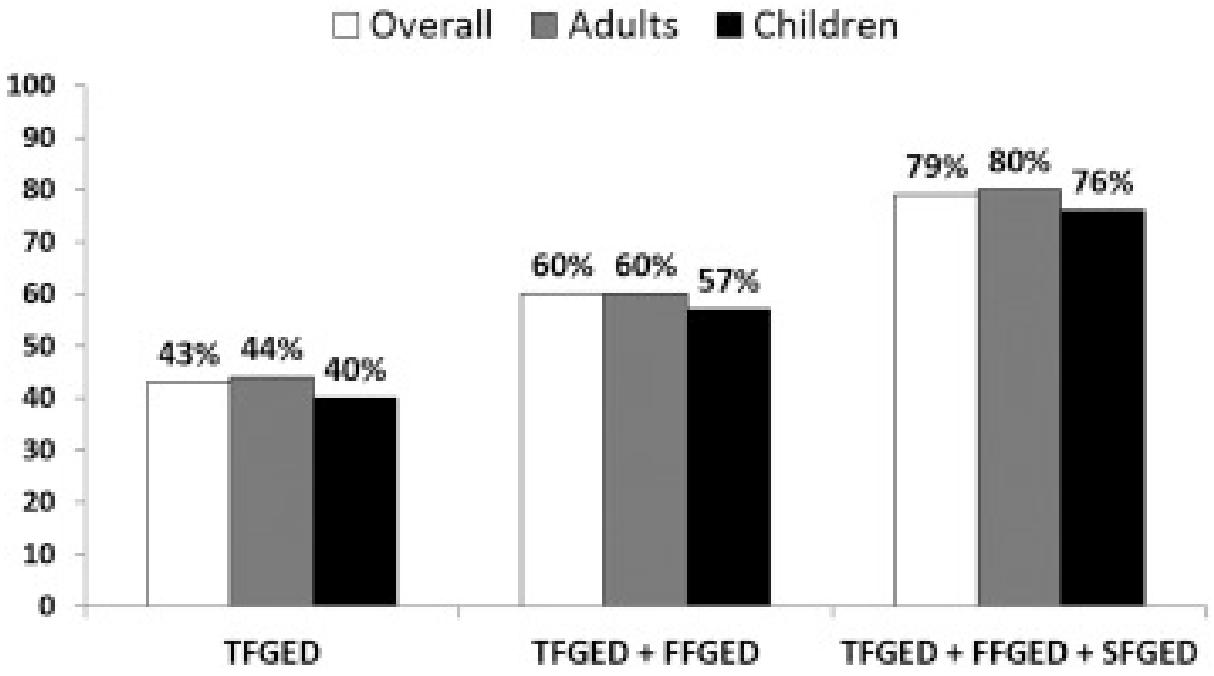
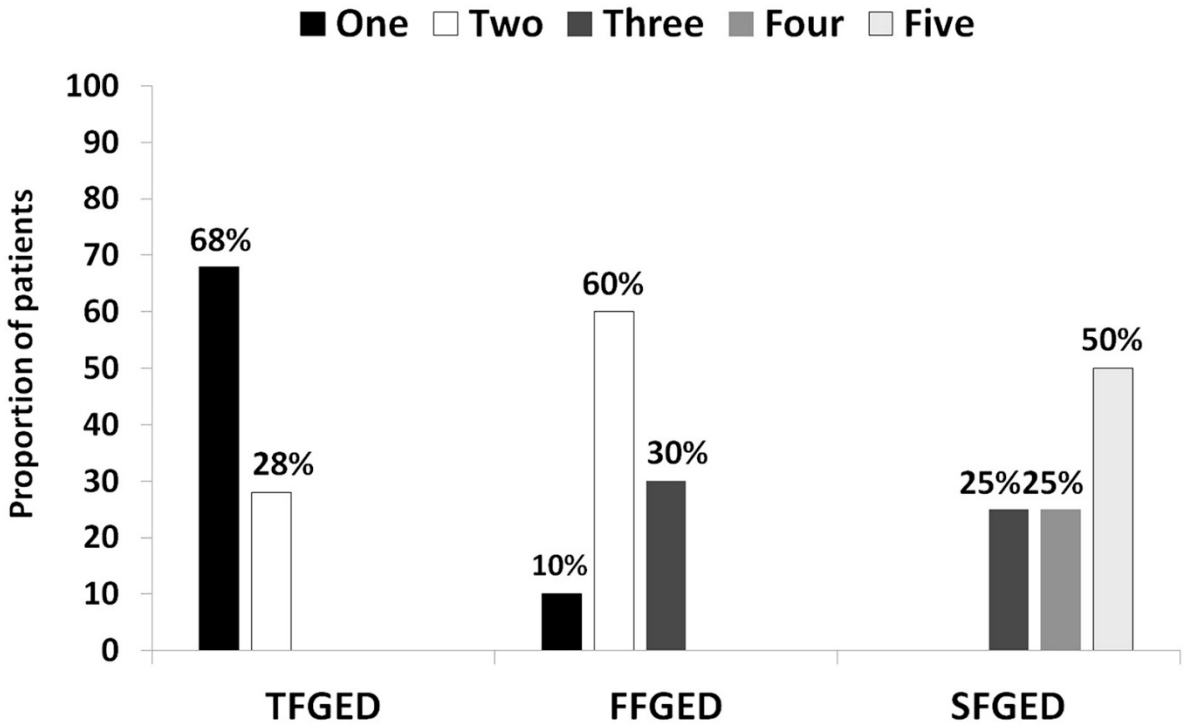
Treatment: Diets – 2 Food Elimination Diet (2FED)

Remission rates



Identified culprit food items



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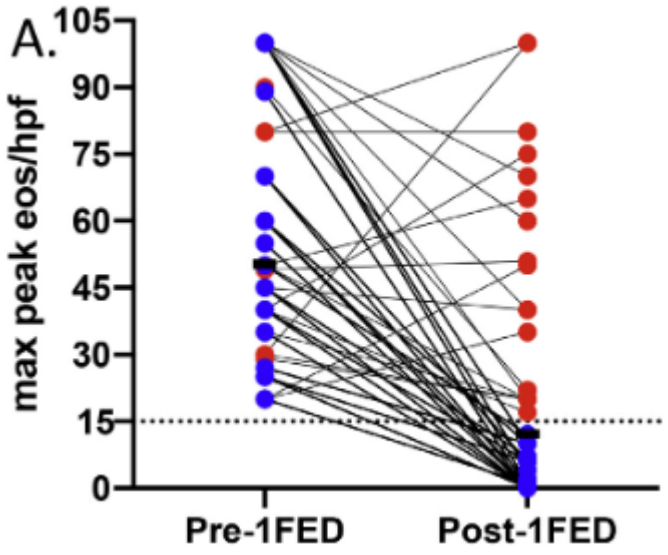
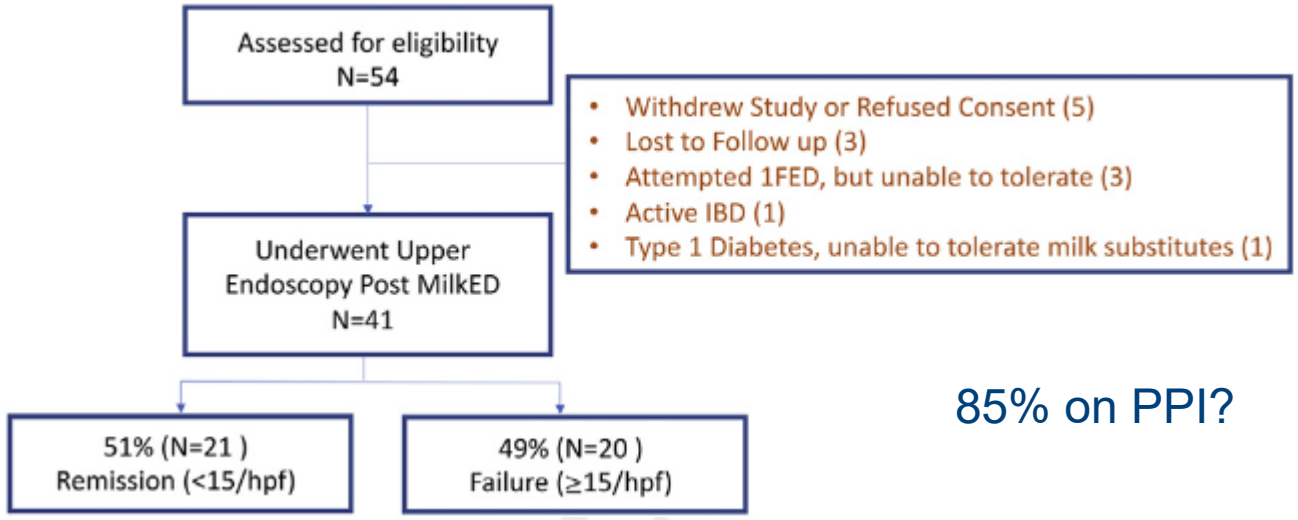
Treatment: Diets – 1 Food Elimination Diet?

A Single Food Milk Elimination Diet Is Effective for Treatment of Eosinophilic Esophagitis in Children

Joshua B. Wechsler,[*,‡] Sally Schwartz,[‡] Nicoleta C. Arva,[*,§] Kwang-Youn A. Kim,[*,‖] Liqi Chen,[*,‖] Melanie Makhija,[*,¶] Katie Amsden,[‡] Kaitlin Keeley,[‡] Saeed Mohammed,[*] Evan S. Dellon,[#] and Amir F. Kagalwalla[*,‡,**]





85% on PPI?

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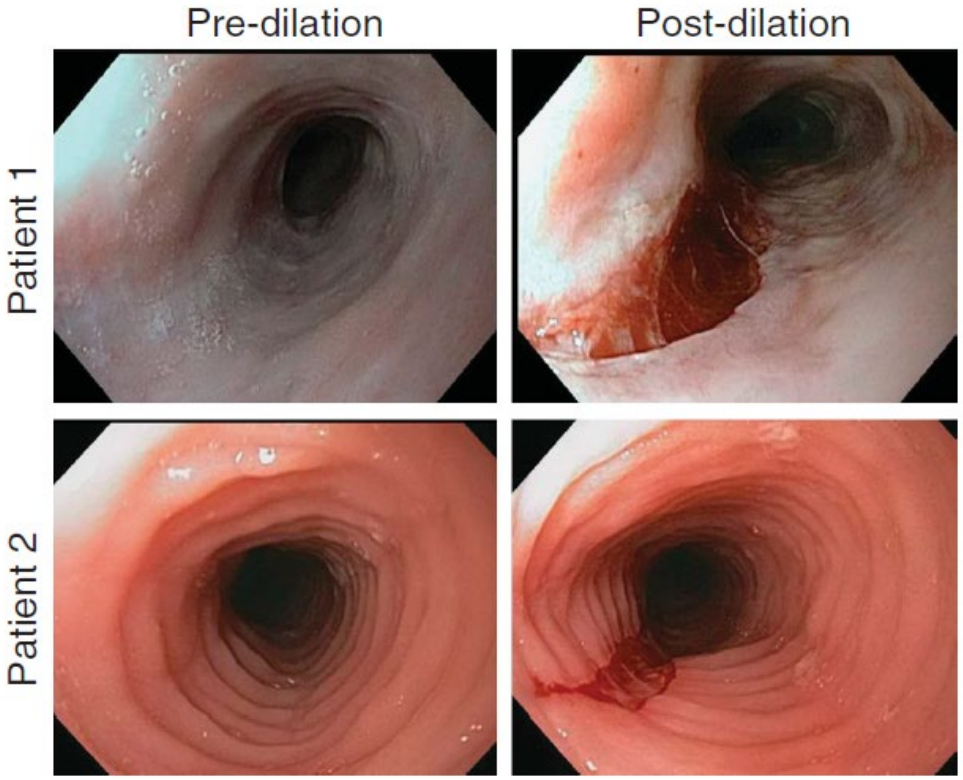
Questions

- Time before endoscopic evaluation after elimination and reintroduction?
- Different gluten-containing grains?
- Importance of trace quantities?
- Ig-E and Ig-G4 based diets, especially in children?

Treatment: Dilation



	Any dilation (*n*=164)
Total number of dilations	486
Number of dilations per patient (mean±s.d.)	3.0±3.7
Dilation method, n *(%)*	
Savary	91 (19)
Balloon	395 (81)
Esophageal diameter (mm) before dilation (mean±s.d.)	12.5±3.0
Esophageal diameter (mm) after final dilation (mean±s.d.)	15.2±2.9
Increase in esophageal diameter (mean mm±s.d.)	2.6±1.4
Symptom response, *n* (%)[a]	108 (87)
Complications, n *(%)*	
Any complication	25 (5.1)
Pain	21 (4.3)
Bleeding	0 (0)
ER visit	5 (1.0)
Hospitalization	2 (0.4)
Perforation	0 (0)
Death	0 (0)

Hirano I. Am J Gastroenterol 2017

Runge et al. Am J Gastroenterol 2016

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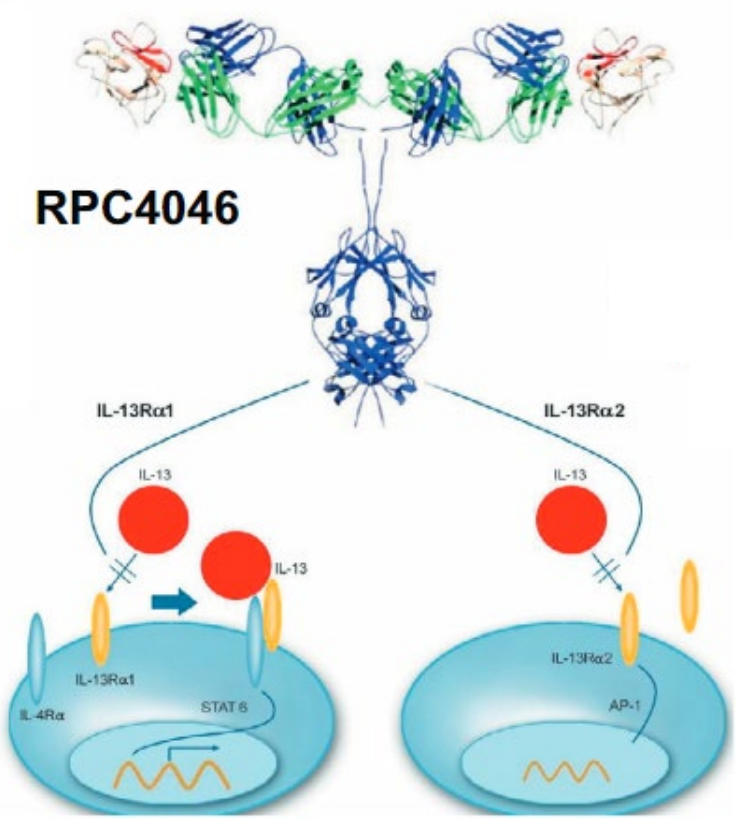
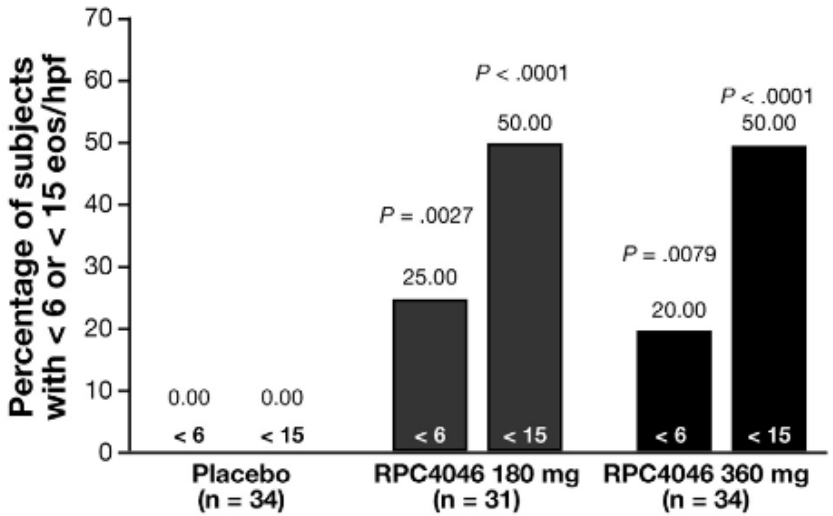
Future Treatments: biologicals

- **Anti-IL5: Mepolizumab and Reslizumab**
  Effect on eosinophilia but not on symptoms
- **Anti IL13: Cendakimab (HEROES; successful in phase 2)**
- **Anti-IL4Rα: Dupilumab** (2 positive phase 3 trials)
- **Anti-IL-5R: Benralizumab**
- **Anti-siglec-8: Lirentelimab**
- **Anti-IL15: CALY-002** (phase 1)

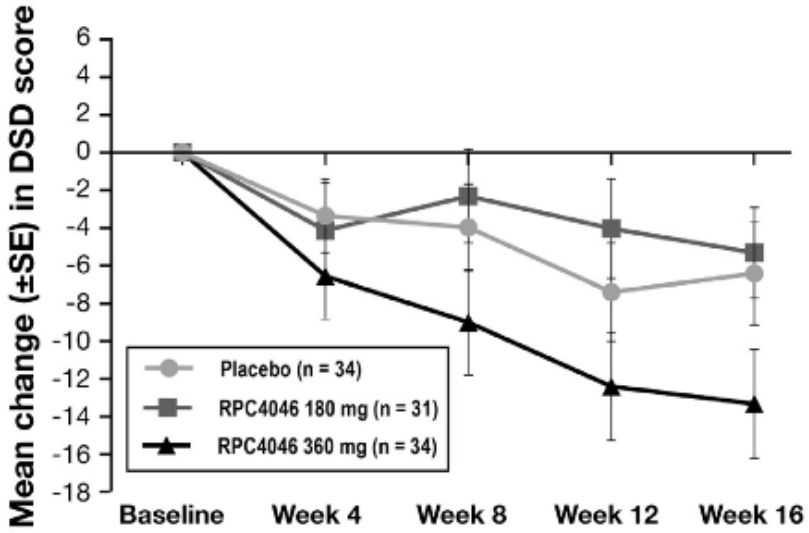
Cendakimab: phase 2



Eosinophilia



Symptoms



Phase 3 ongoing

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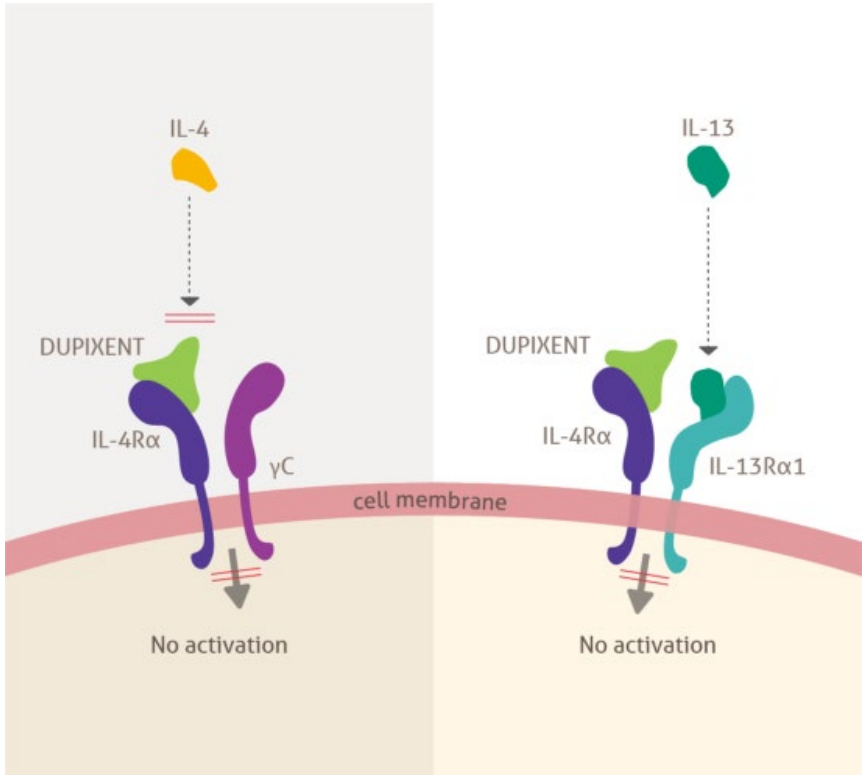
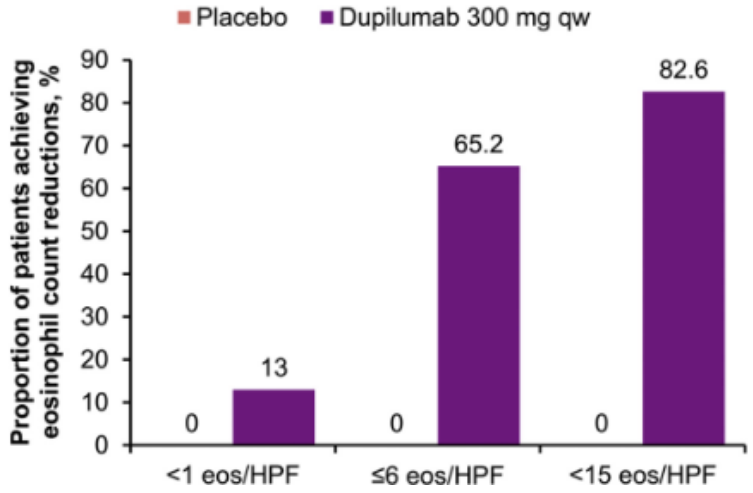
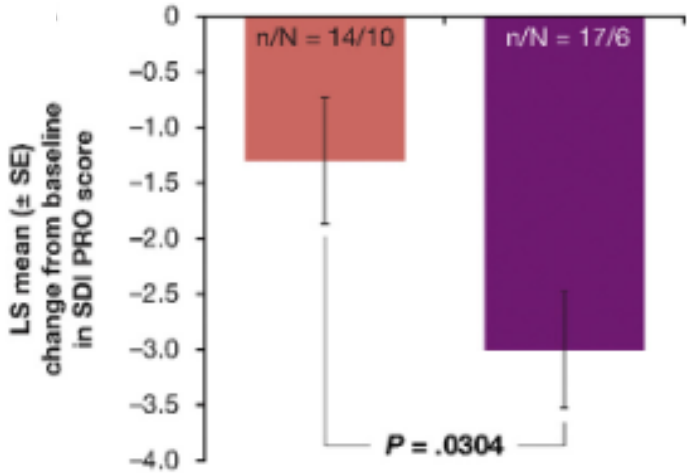
Dupilumab: phase 2



Eosinophilia



Symptoms



Press release 10/2021: 2 positive phase 3 trials

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