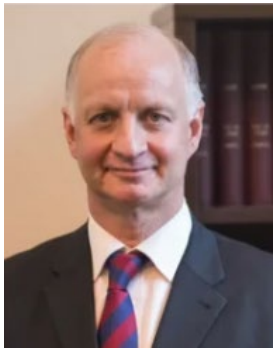
De gastro-enteroloog: Epidemiologie, Pathogenese Diagnostiek en Therapie

Tim Vanuytsel – Maag-, Darm-, Leverziekten
UZ Leuven

De ‘ontdekking’ van een nieuwe ziekte (1993-1994)





Esophageal Eosinophilia with Dysphagia

A Distinct Clinicopathologic Syndrome

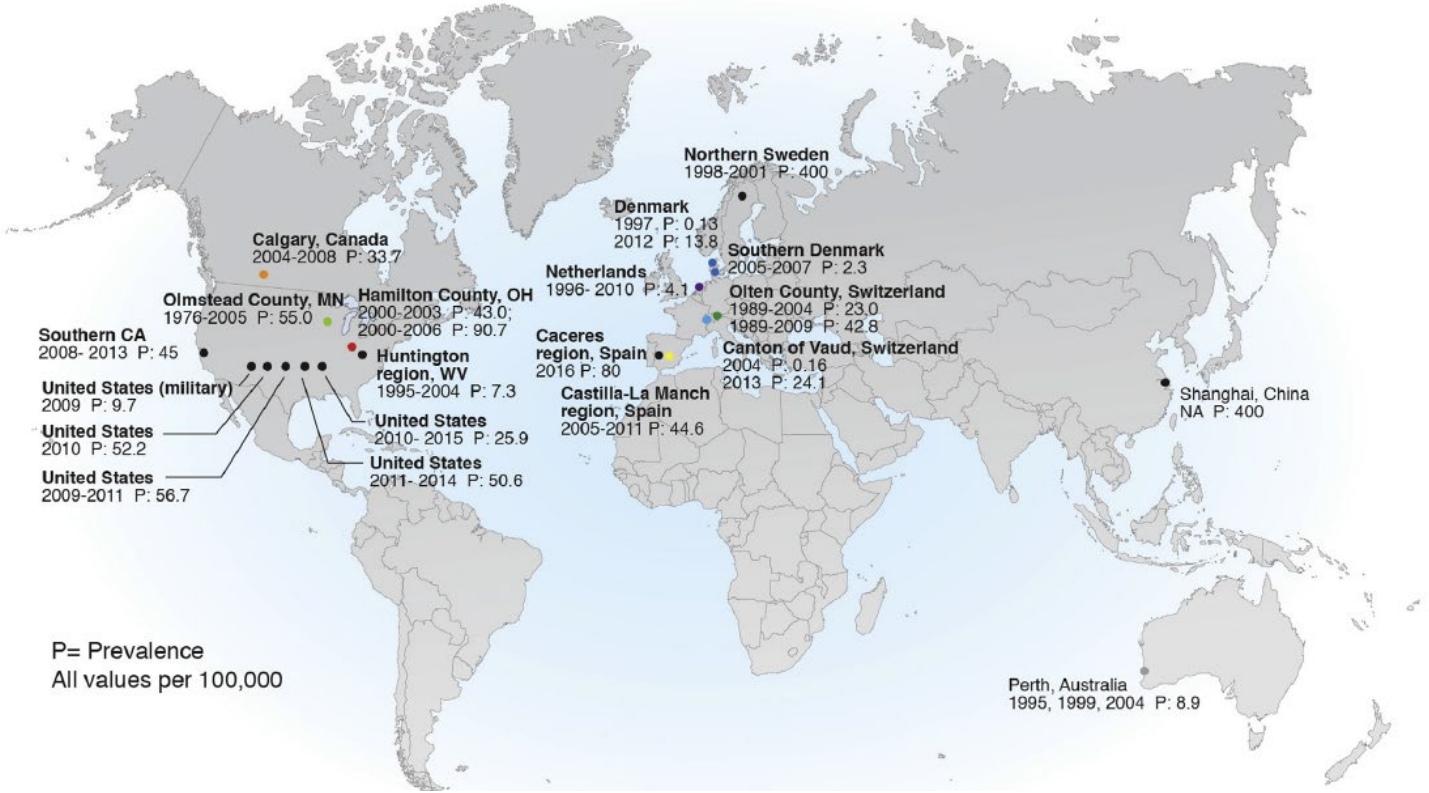
STEPHEN E.A. ATTWOOD, MB, FRCS, THOMAS C. SMYRK, MD, TOM R. DEMEESTER, MD, and JAMES B. JONES, PharmD

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

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

Epidemiologie

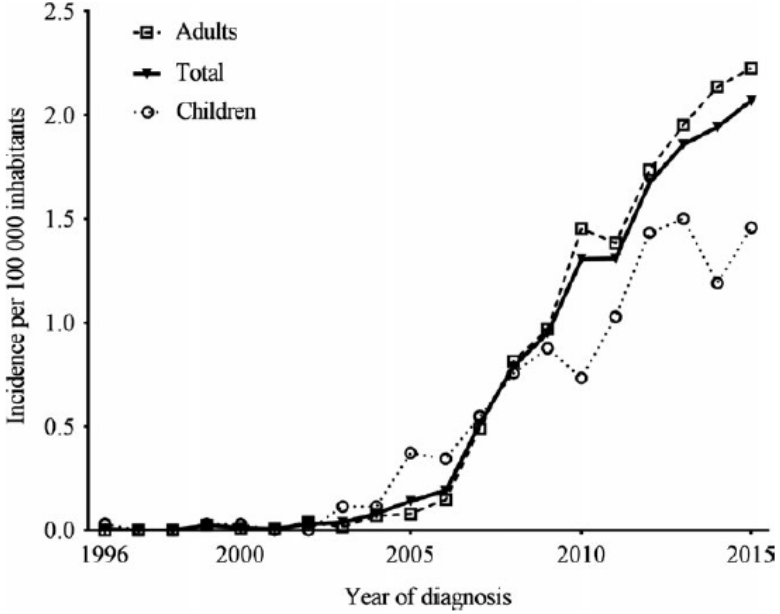
Prevalentie: 1/2000 – 1/1000

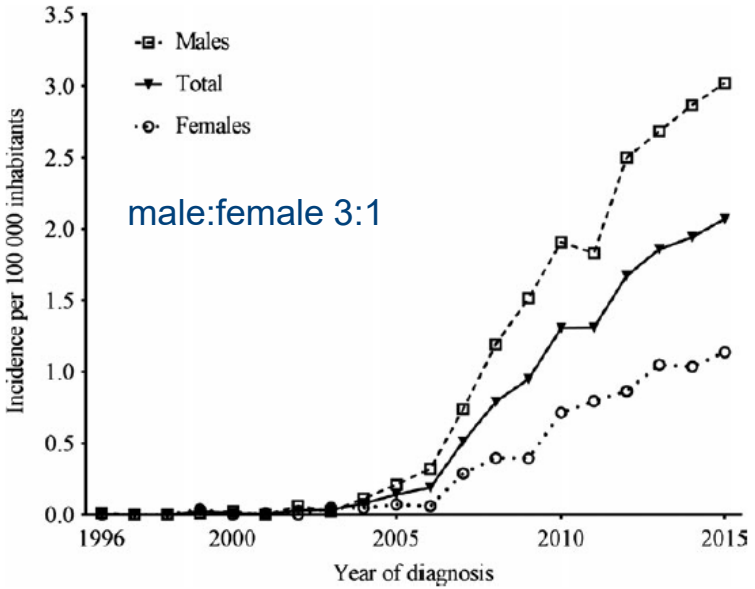


Dellon and Hirano. Gastroenterology 2018

Epidemiologie

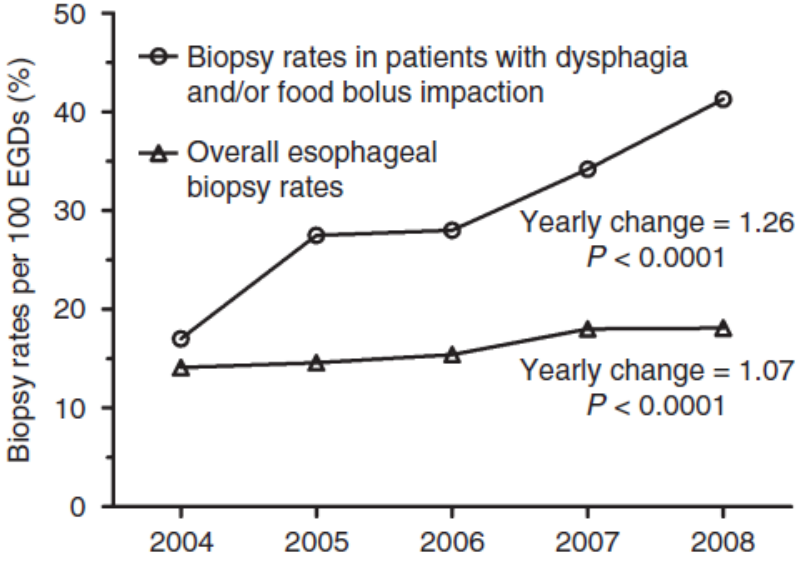
Toename van incidentie van eosinofilie in de slokdarmbiopten



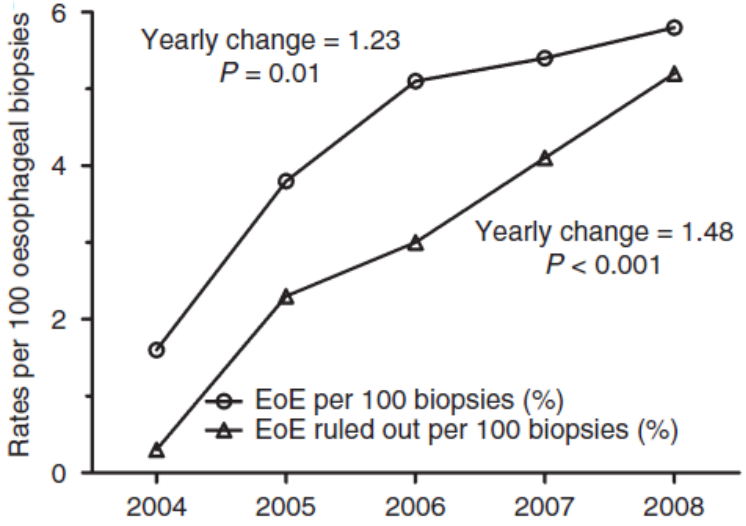


Epidemiologie

We nemen meer slokdarmbiopten



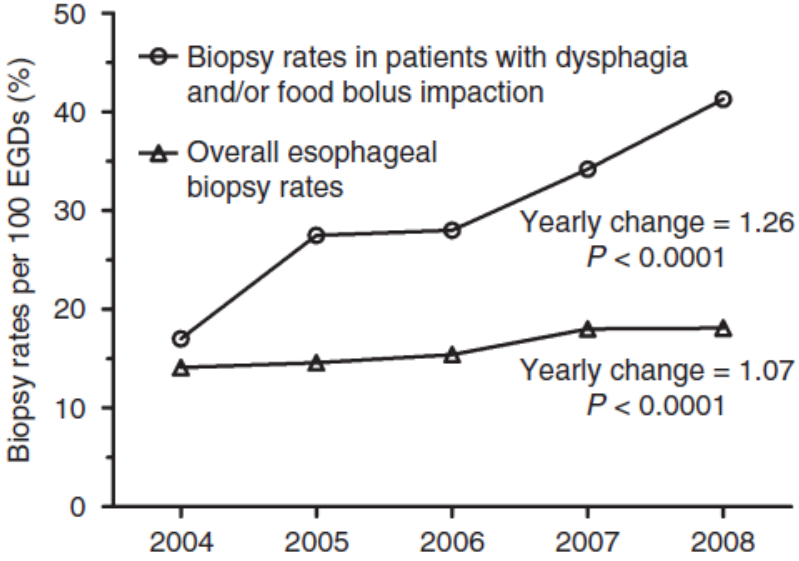
en pathologen denken meer aan EoE



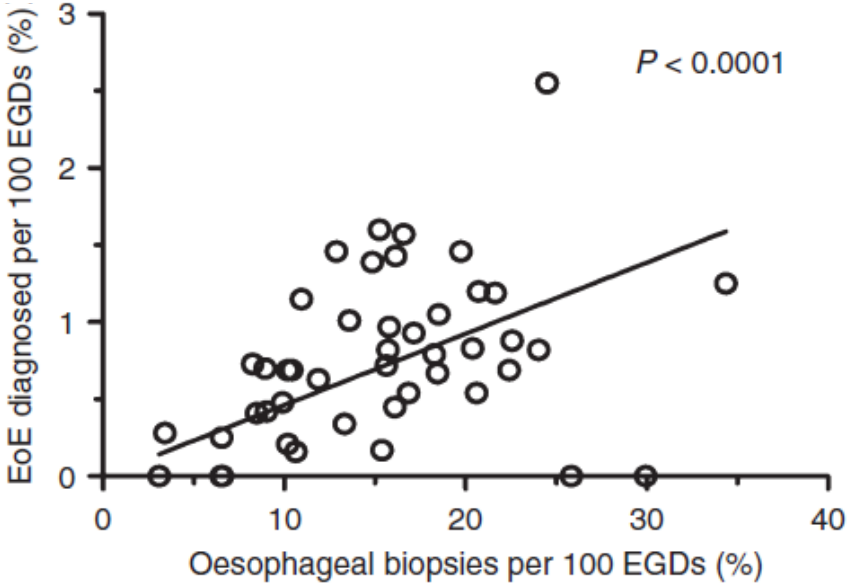
Syed et al. Aliment Pharmacol Ther 2012

Epidemiologie

We nemen meer slokdarmbiopten

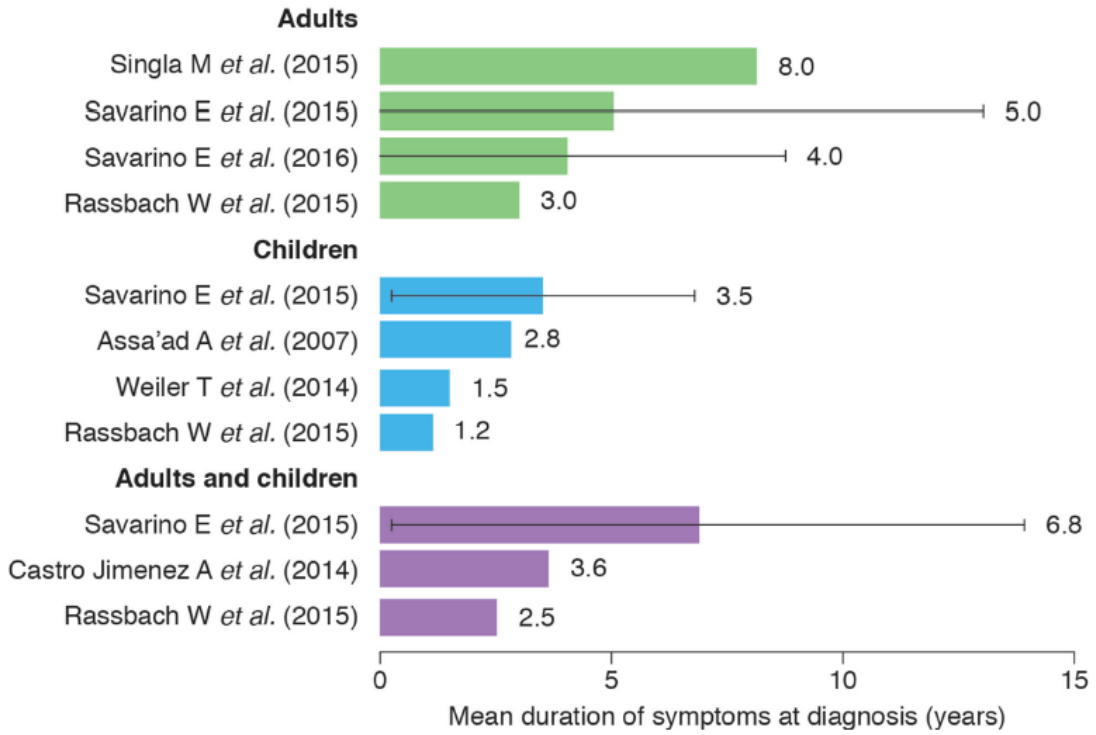


Hoe meer biopten er worden genomen, des te meer EoE wordt gediagnosticeerd.



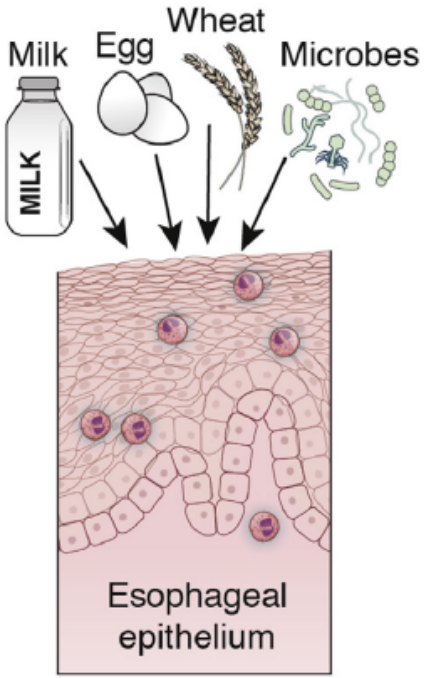
Syed et al. Aliment Pharmacol Ther 2012

Tijd tot diagnose

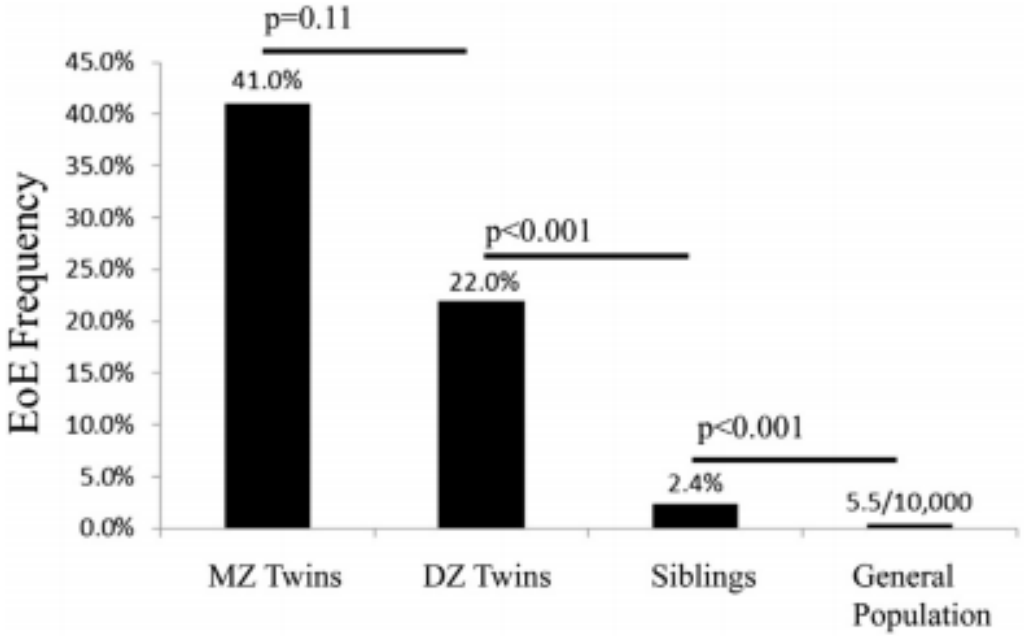


Shaheen et al. Dis Esophagus 2018

Pathofysiologie



Pathofysiologie: Genetica



Pathofysiologie: Genetica

Genetic risk loci	Genes encoded	Odds ratio for most associated SNP at each locus	Genetic mechanism	Pathogenic mechanism
2p23	*CAPN14*	1.98	Promoter variant leads to genotype-dependent expression of CAPN14, likely involving epigenetic mechanism	CAPN14 is a proteolytic enzyme specific to the esophagus that is induced by IL-13 and involved in epithelial homeostasis and repair
5q22	*TSLP* *WDR36*	0.74	Multiple risk alleles associated with genotype-dependent expression of TSLP	TSLP induces Th2 cell development and activates eosinophils and basophils
11q13	*LRRC32* *EMSY*	2.49	Not yet described	LRRC32 is a TGF-beta binding protein EMSY is involved in transcriptional regulation
12q13	*STAT6*	1.5	Not yet described	STAT6 is a downstream signaling mediator of IL-4Rα and important for Th2 development
19q13	*ANKRD27* *PDCD5* *RGS9BP*	1.6	Not yet described	ANKRD27 inhibits the SNARE complex PDCD5 is involved in apoptotic pathways RGS9BP is not expressed in the esophagus or by immune cells

NOTE. Risk shown is positive and hence adjusted for being a common or rare allele.
EoE, eosinophilic esophagitis; SNP, single-nucleotide polymorphism; TSLP, thymic stromal lymphopoietin.



Pathofysiologie: Allergie

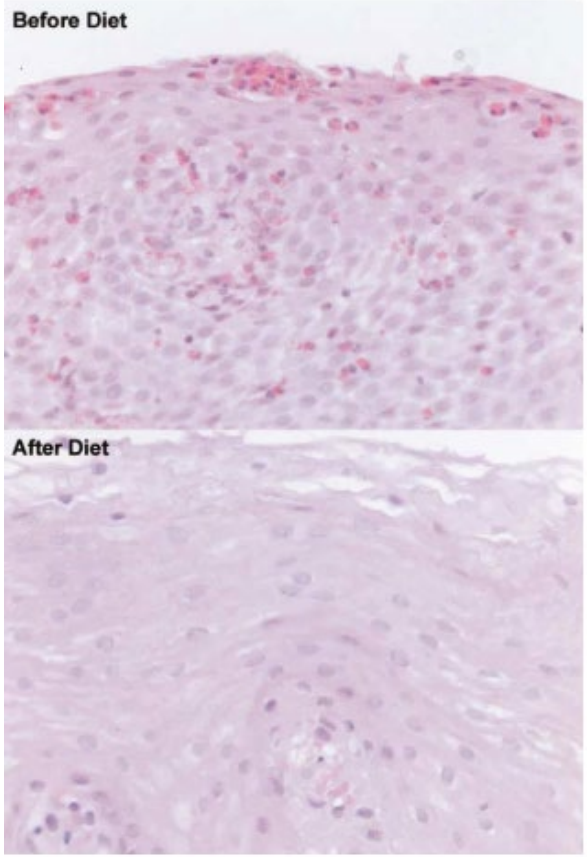
- Frequent voorkomen van atopische constitutie
- Verbetering onder elementair dieet

51 kinderen (3-16 jaar)

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

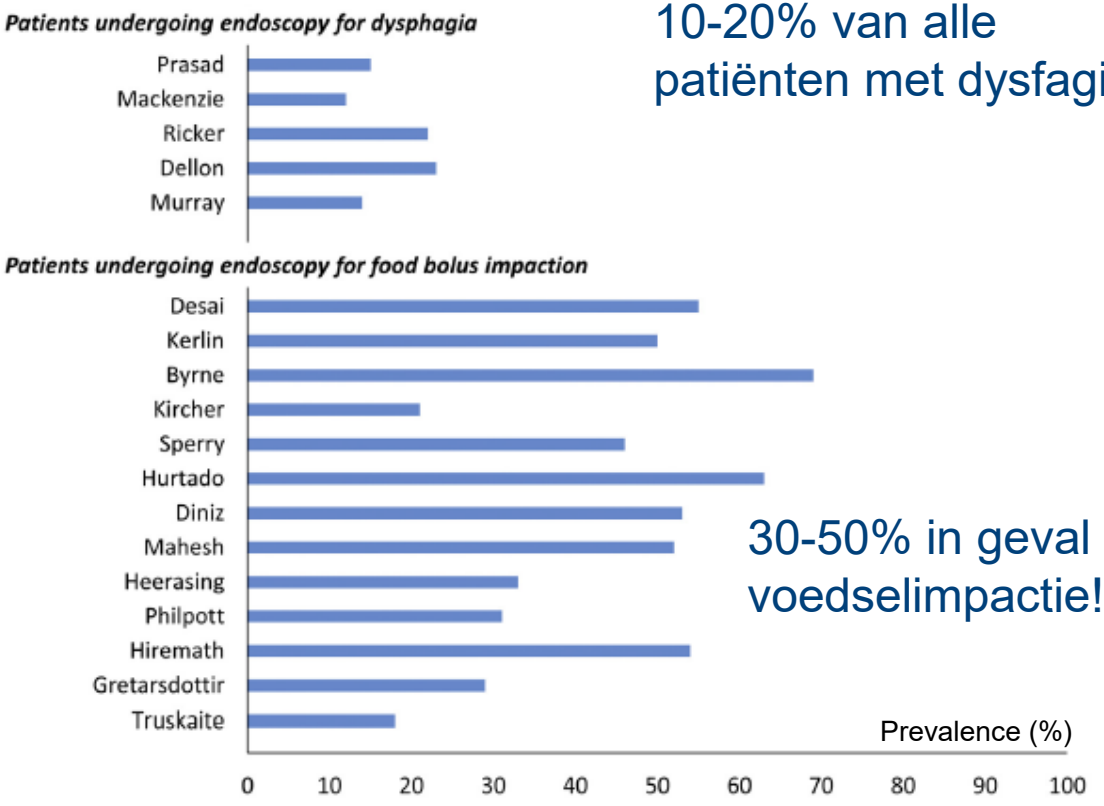
Diagnose: 3 pijlers



Symptomen **Pathologie** **Uitsluiten andere etiologie**

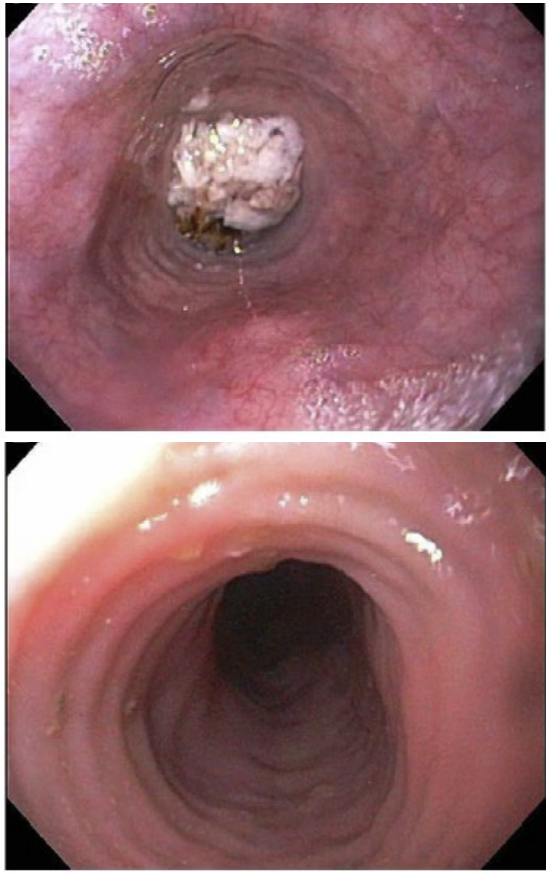
Hirano et al. Gut 2012

Symptomen



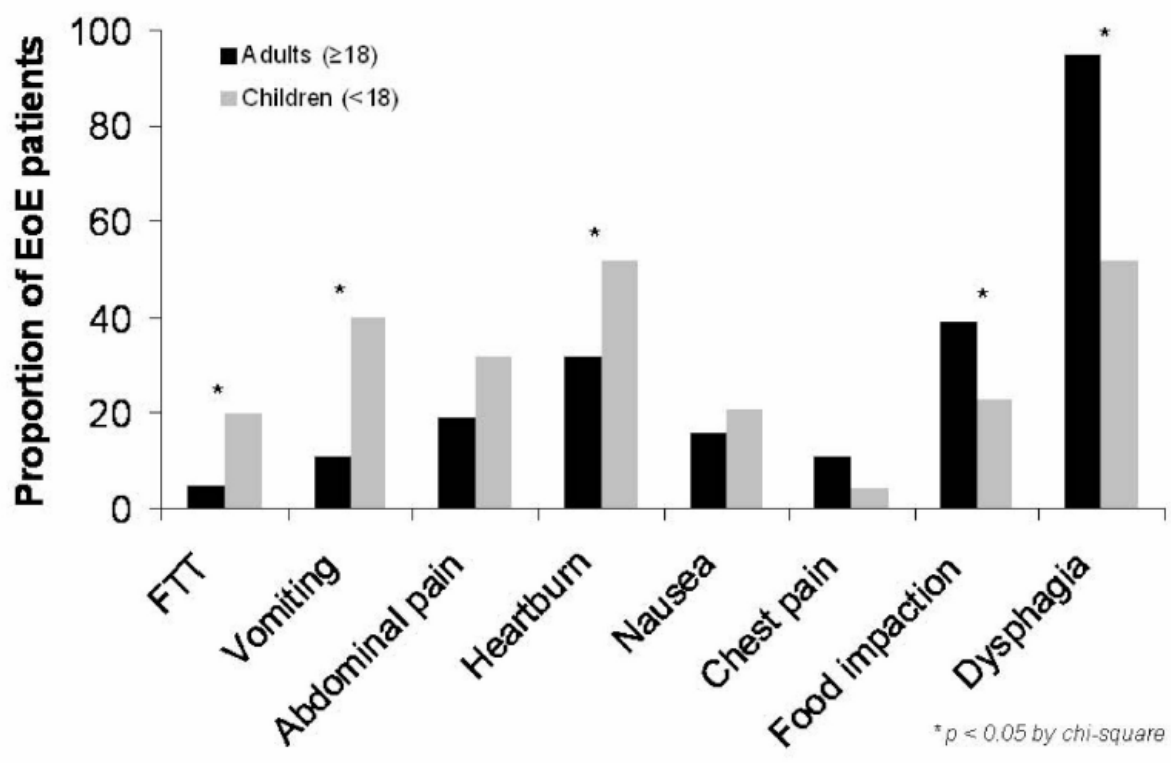
10-20% van alle patiënten met dysfagie

30-50% in geval van voedselimpactie!



Dellon and Hirano. Gastroenterology 2018

Symptomen



Dellon et al. Clin Gastroenterol Hepatol 2009

Symptomen

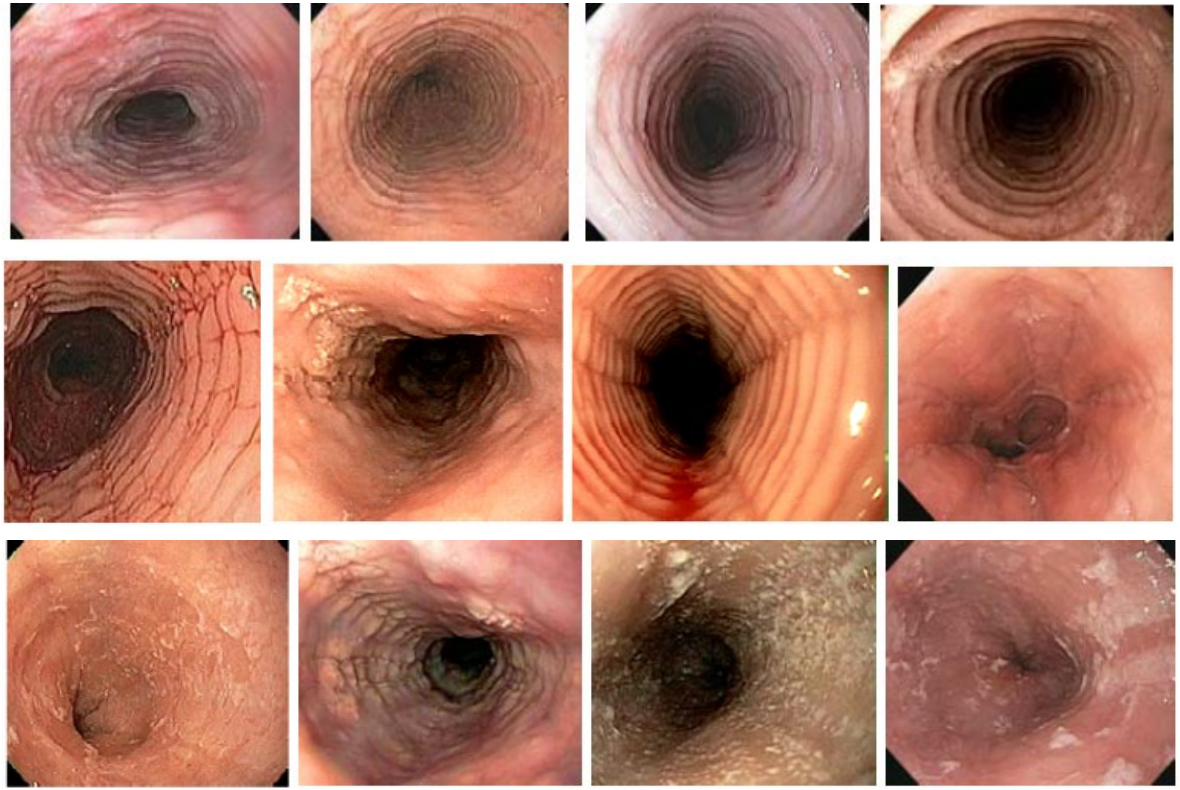








Diagnose: Endoscopie



Ringen
‘trachealisatiie’
‘feline esophagus’

Furrows
= ‘tramsporen’

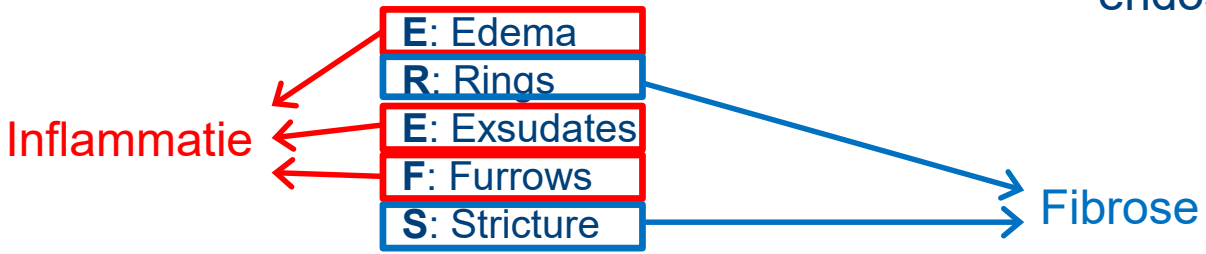
Exsudaten
= eosinofiele inflammatie +
micro-abcessen
DD candidiase

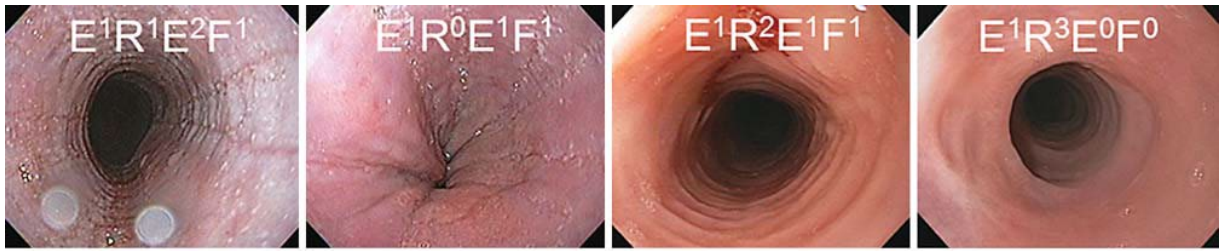
Hirano et al. Gut 2012

Diagnose: Endoscopie

EREFS: **EoE Endoscopic Reference Score**

7% hebben normale endoscopie!



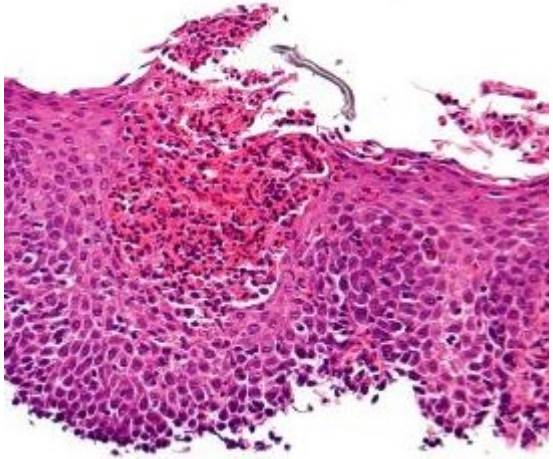


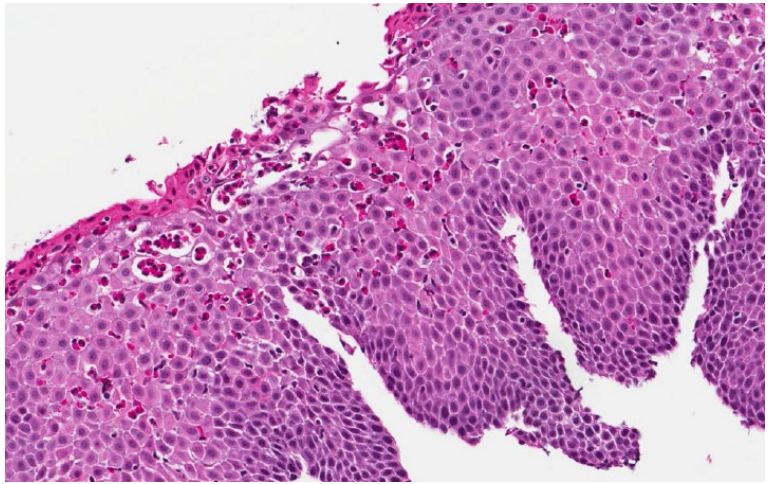
Hirano et al. Gut 2012

Diagnose: Pathologie

Minstens 6 biopten (3 proximal en 3 distaal)

Diagnose: >15 eo/HPF





	≥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

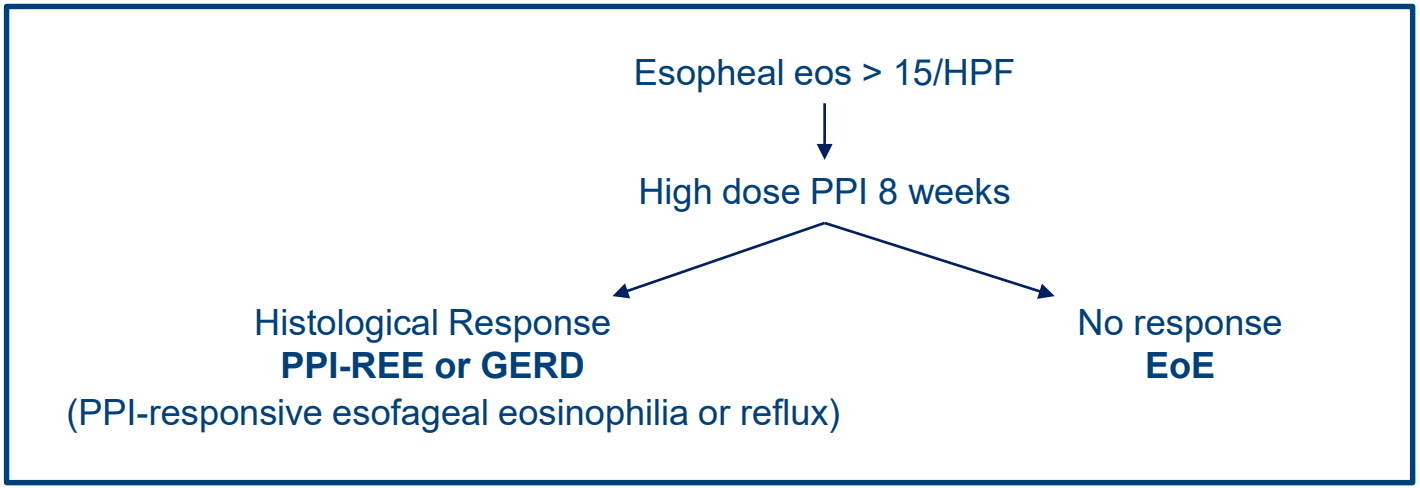
Dellon et al. Mod Pathology 2015
Dellon et al. Clin Gastroenterol Hepatol 2012

Diagnose: uitsluiten andere etiologie van eosinofilie

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

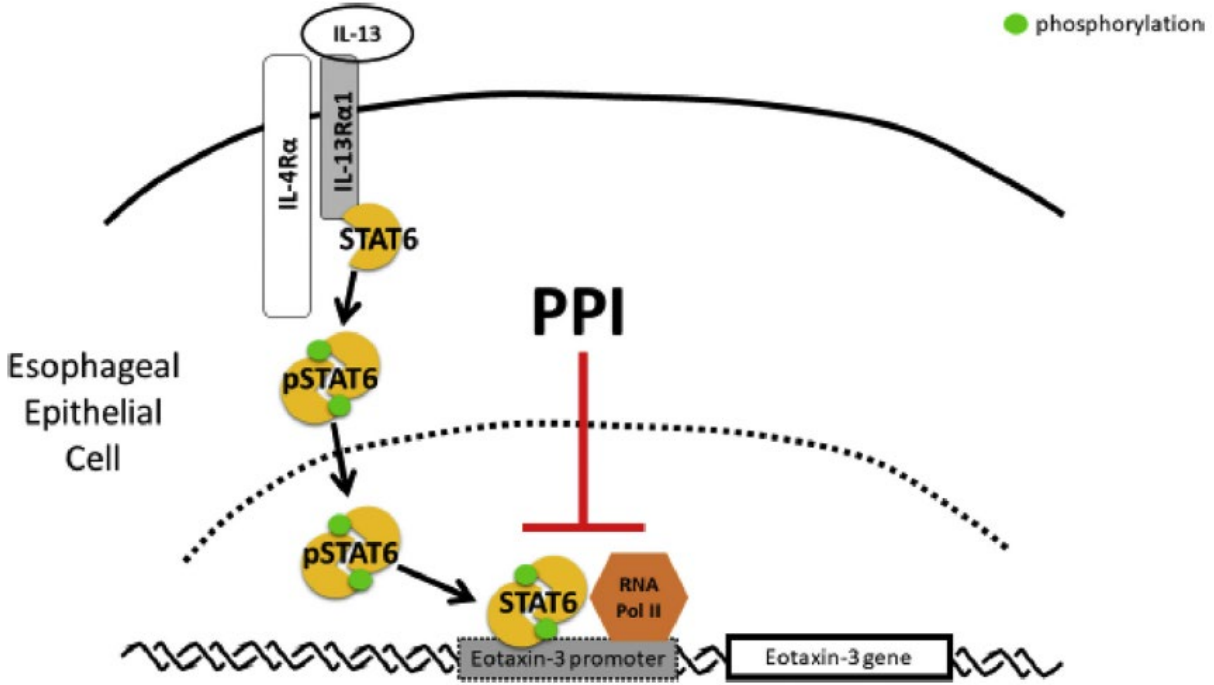
Diagnose: uitsluiten andere etiologie van eosinofilie

The ‘old’ days (2016):



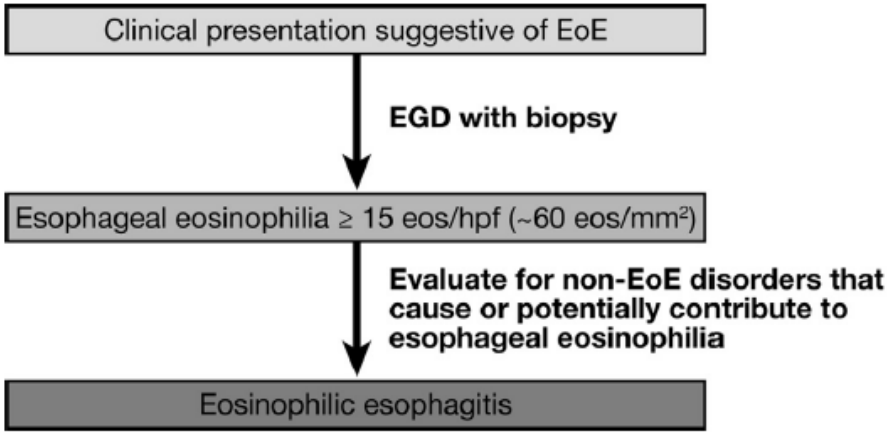
Diagnose: uitsluiten andere etiologie van eosinofilie

PPI's hebben anti-inflammatoire eigenschappen!



Dellon et al. Gastroenterology 2018, the AGREE conference

Diagnose: het nieuwe tijdperk



3 D's:
Drugs
Diet
Dilatation

PPI

Topische corticoiden

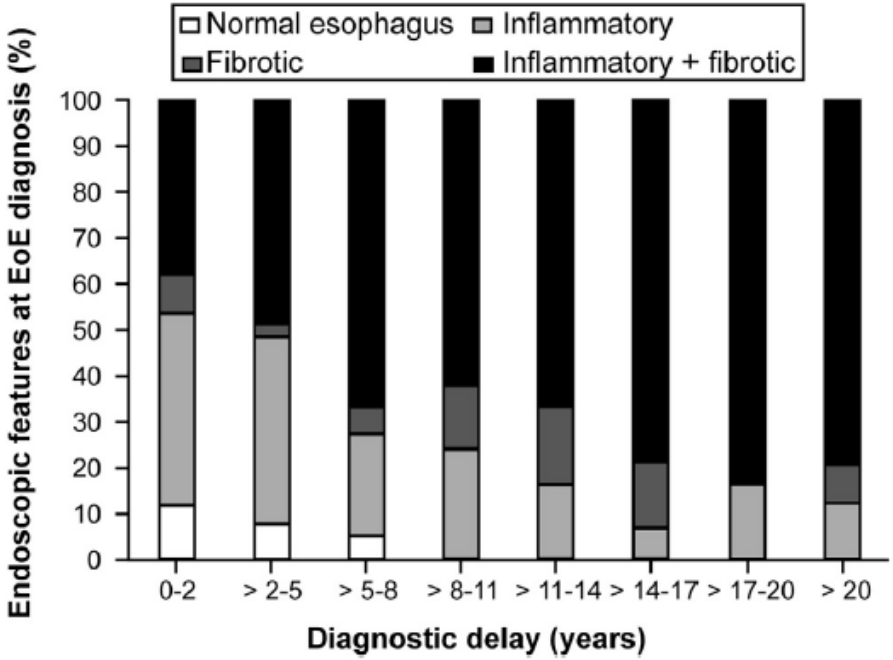
Eliminatie Dieet

Dilatatie

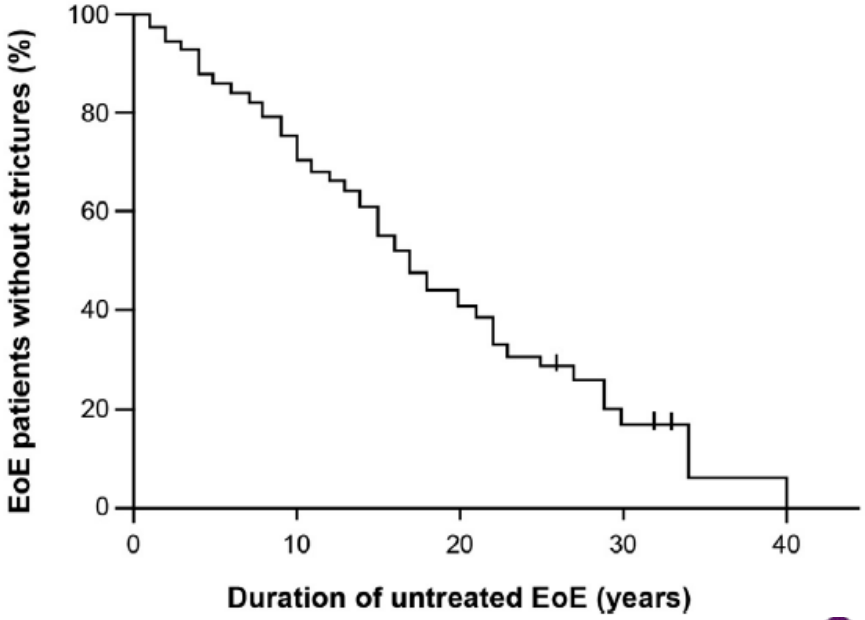
Dellon et al. Gastroenterology 2018, the AGREE conference

Behandeling: waarom?

Tekens van fibrose nemen toe met de tijd



Risico op stricturen bij onbehandelde EoE



Schoepfer et al. Gastroenterology 2013

Behandeling: PPI

Doel = behandeling inflammatie, (meestal) niet behandeling van reflux

Meestal eerstelijnstherapie behalve in het geval van:

- **Fibrostenotische ziekte**: topische corticoiden +/- dilatatie
- Patienten met voorkeur voor **dieet**

Start dubbele dosis: bv. pantoprazole 2x40mg/d gedurende 8 weken

Onderhoudsdosis? Onduidelijk, maar meestal 2x20mg (70% chronische respons)

Behandeling: Topische corticoiden

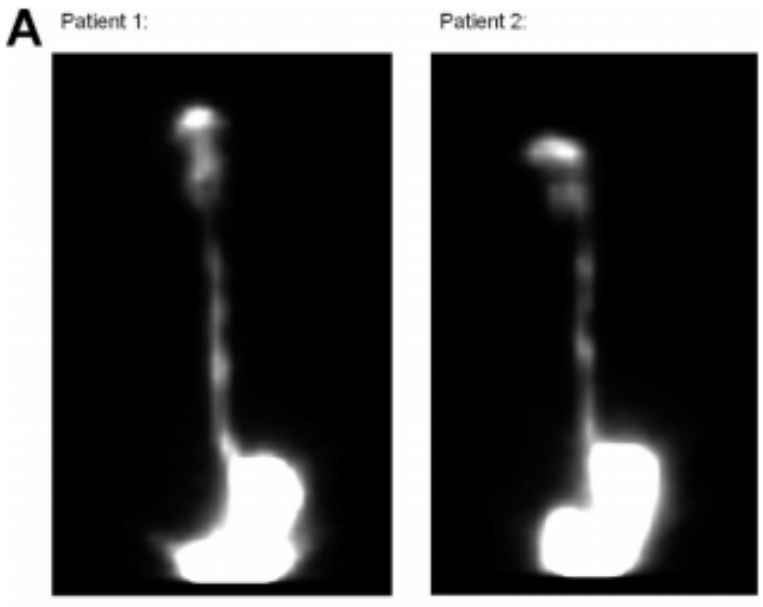
- Fluticasone poeder of puff
  Dosis: 750µg (3 puffs) 2x/d of 1000 µg (2 comp in disk) 2x/d
- Budesonide gel (magistraal)
  Dosis: start aan 2x1mg/d (1mg budesonide + xanthane gum tot 10mL; 2x/d)
- Endoscopische en histologische herevaluatie na 8-12 weken



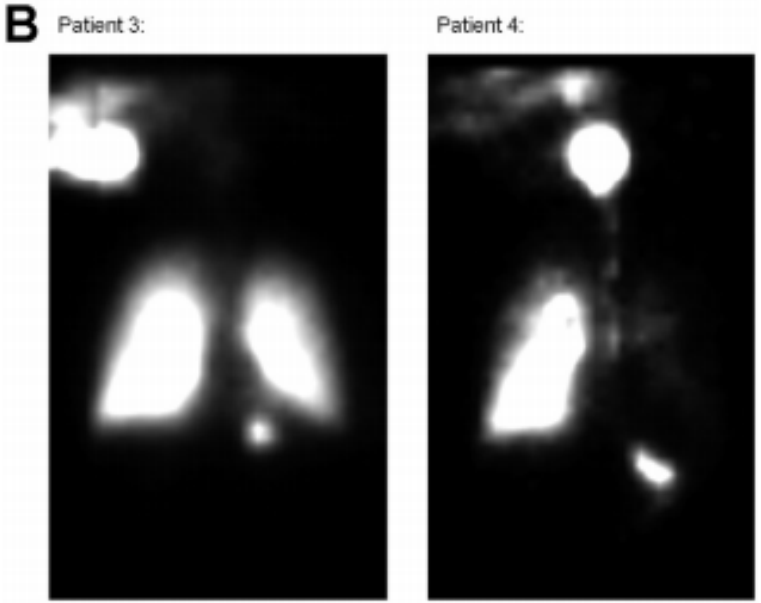
Straumann and Katzka. Gastroenterology 2018

Behandeling: Topische corticoiden

Visceuze oplossing (gel)

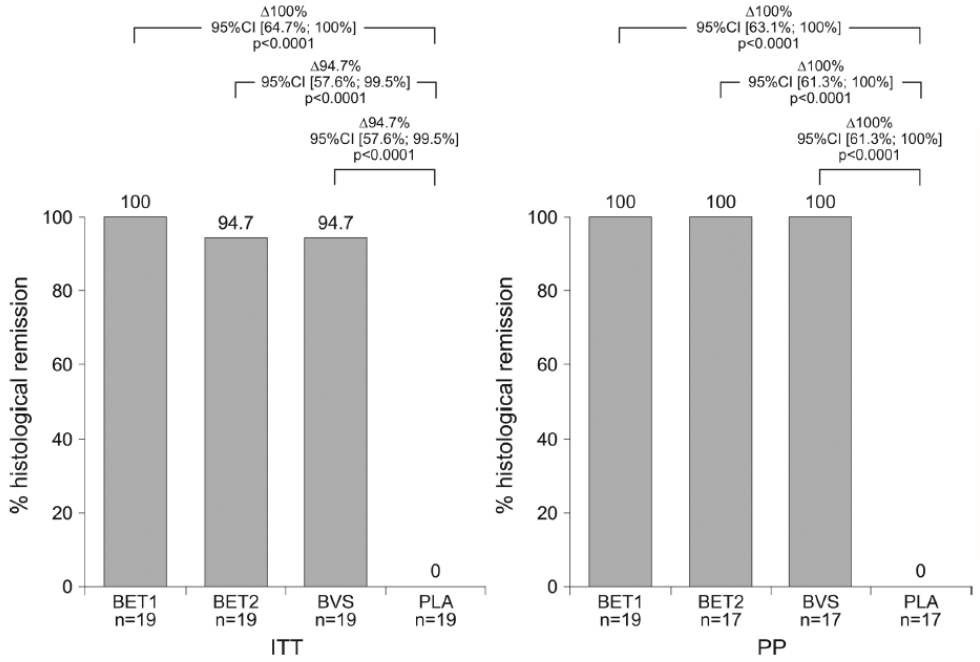


Verstuifd en ingeslikt (‘puff’)



Behandeling: Topische corticoiden

Nieuwe formuleringen: Budesonide smelttabletten 1mg (Jorveza)





Miehlke et al. Gut 2016

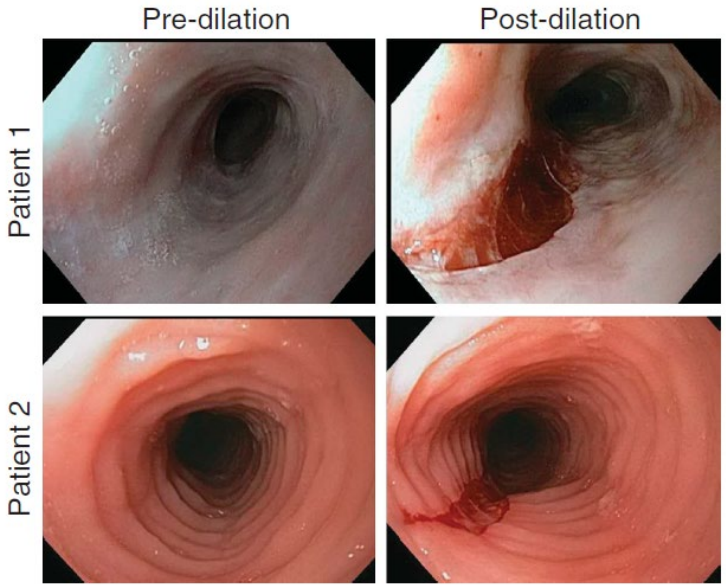
Behandeling: Topische corticoiden

Onderhoudsdosis is nodig! Bv. 2x0,5mg of 1x1mg/d

Corticofobie
bij patienten en artsen!

Greuter et al. Am J Gastroenterol 2017
Greuter et al. Clin Gastroenterol Hepatol 2019

Behandeling: dilatatie



	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)

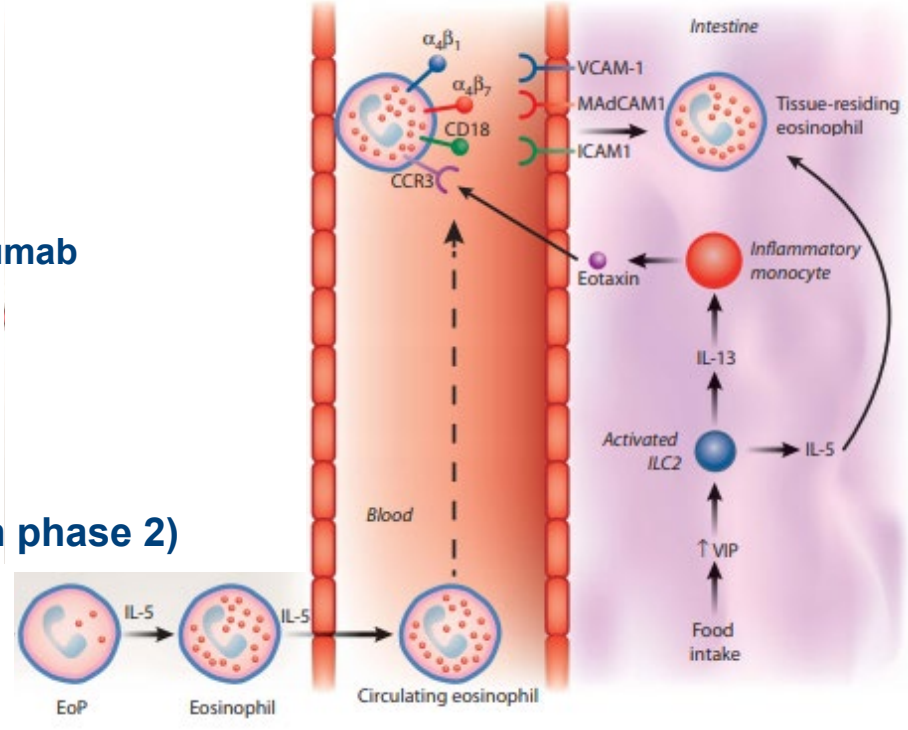
Bij stricturen of belangrijke vernauwingen is dilatatie de eerste therapie, maar steeds gevolgd door dieet of corticoiden indien er actieve inflammatie is

Hirano I. Am J Gastroenterol 2017

Runge et al. Am J Gastroenterol 2016

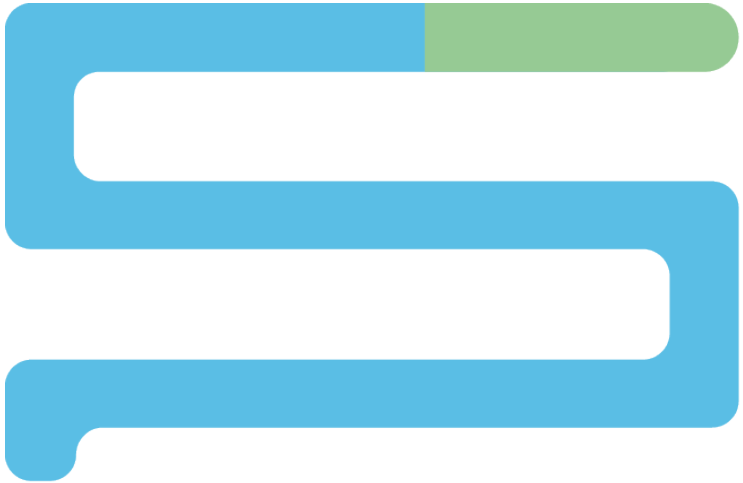
De toekomst: biologicals

- **Infliximab**
  Not effective in open label trial
- **Anti-IL5: Mepolizumab and Reslizumab**
  Effect on eosinophilia but not on symptoms **Omalizumab**
  No effect in RCT
- **Vedolizumab**
  Case series of concomitant IBD – EoE patients
- **Anti IL13: RPC4046 (HEROES; successful in phase 2)**
- **Anti-IL4Rα: Dupilumab**
  Fase 3 trial lopende in UZ Leuven!



Conclusies

- Eosinofiele oesofagitis is een frequente, ‘nieuwe’ aandoening binnen de gastro-enterologie
- Steeds endoscopie met biopten vragen bij patienten met dysfagie, zeker bij (mannelijke) jonge patienten
- Diagnose is een combinatie van klachten en histologie
- PPI is meestal de eerstelijnsbehandeling
- Topische corticoiden of dieet bij falen van PPI (ifv type patiënt)
- Steeds onderhoudstherapie om stricturen te vermijden
- Nieuwe (biologische) therapieën komen eraan



LIFT

LEUVEN INTESTINAL FAILURE
AND TRANSPLANTATION

