Eosinophilic Esophagitis Diagnosis & Management

2nd Edition

Learning Objectives

Upon completion of this activity, participants should be better able to:

- To define Eosinophilic Esophagitis (EoE) and present the updated 2011 diagnostic guidelines.
- To understand the epidemiology, pathophysiology and genetics of EoE.
- To identify the clinical symptoms, allergic manifestations, endoscopic and histologic features of EoE.
- To list and define the treatments of EoE which include dietary restriction, pharmacologic therapy and esophageal dilation.
- To understand how to manage patients with EoE.
- To provide information regarding ongoing and future research on EoE.

Disclosures

Educational support for the ***Eosinophilic Esophagitis Diagnosis and Management*** slide set was provided by Abbott Nutrition.

NASPGHAN FOUNDATION and **NASPGHAN** do not endorse any commercial product. Any products named in this slide set are presented as part of the scientific evidence being cited and are used only to illustrate teaching points. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Audience members are required to critically evaluate any product that they will use in clinical care.

Presenter Disclosure

- Put your disclosure here

Background & Natural History

Background

- Rare cases suggestive of eosinophilic esophagitis (EoE) were described in the 1970's
- Began to be described in early 1990's
- Appreciated as a distinct entity in 1995
- Initially, unclear if EoE was part of the spectrum of eosinophilic gastroenteritis
- Since the mid 1990's the number of reported cases has greatly increased worldwide

Kelly et al. *Gastroenterology.* 1995; 109:1503-1512.
Straumann et al. *Schweiz Med Wochenschr*. 1994 20;124(33):1419-29.
Attwood et al. *Dig Dis Sci.* 1993; 38(1):109-16.

1995 Distribution of EoE

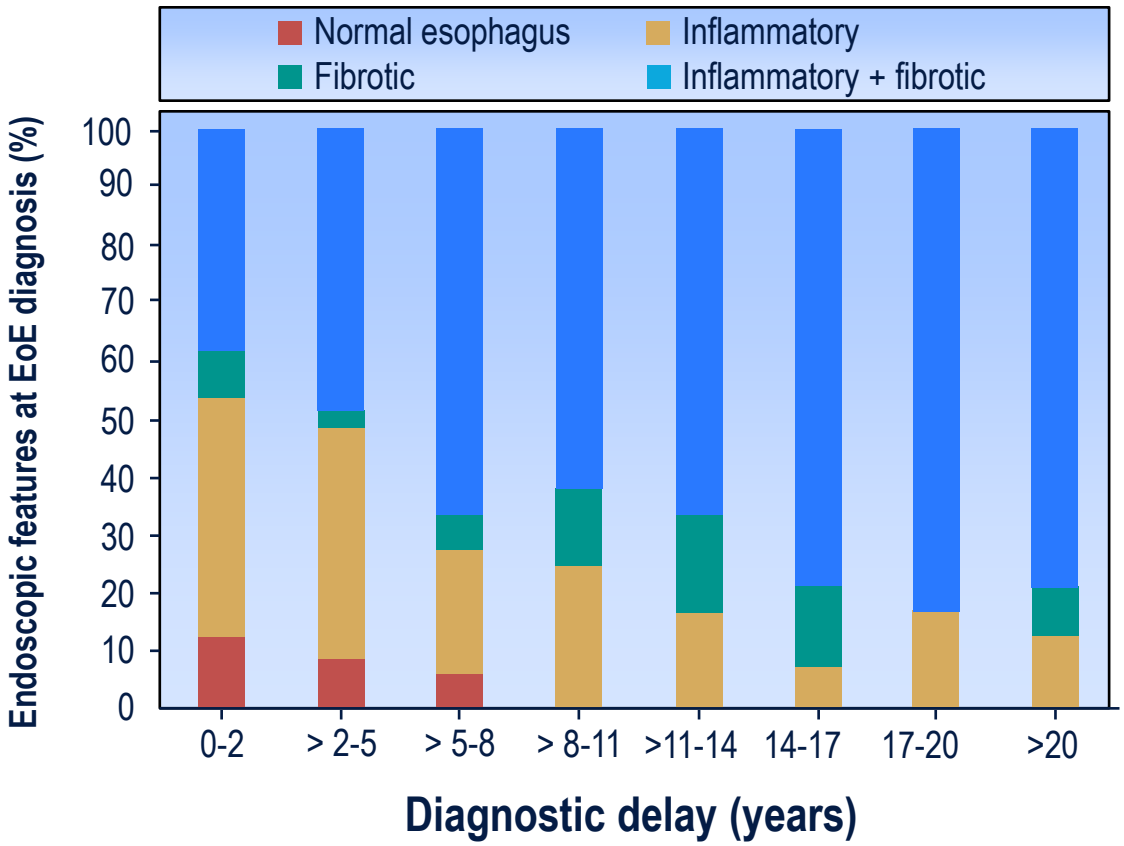
2013 Distribution of EoE

Natural History

- In a prospective case series of 30 adults with EoE (followed for a mean of 7.2 years)
  - 29/30 persistent dysphagia
  - 11/30 underwent at least one dilatation procedure
  - Deeper biopsy tissue was available in 7, and 6 exhibited evidence of fibrosis in the lamina propria
  - Although variable in number, all had a persistent, severe esophageal eosinophilia

Straumann et al. *Gastroenterology.* 2003; 125:1660-1669.

Natural History – Adult Study



Schoepfer et al. *Gastroenterol.* 2013:145;1230-6.

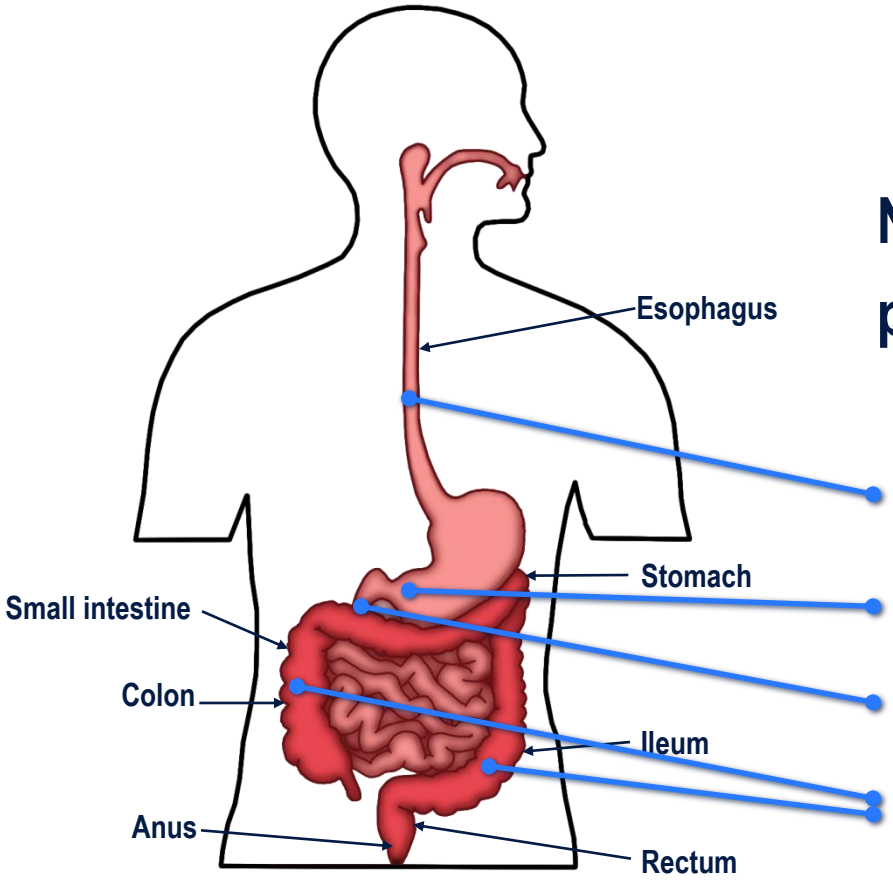
Natural History Adults

- There is still an incomplete understanding of the natural history of EoE

- Long term associated morbidity has now been reported to include the formation of esophageal strictures; either short or long segments of the esophagus, which is the result of chronic esophageal inflammation and remodeling resulting in fibrosis of the esophagus

Definition

Gastrointestinal Eosinophils



Normal eosinophil values, per high power field (hpf):

- **Esophagus (0)**
- **Gastric antrum (2-10)**
- **Duodenum (10-20)**
- **Colon (15-30)**

Average accepted values

DeBrosse CW et.al. *Pediatr Dev Pathol*. 2006;9(3):210-8.

Esophageal Eosinophilia

Differential Diagnosis

- Eosinophilic Esophagitis
- Gastroesophageal Reflux Disease
- PPI-responsive esophageal eosinophilia
- Celiac Disease
- Eosinophilic gastroenteritis
- Crohn's Disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue disease
- Infection
- GVHD

2007 Consensus Recommendations

Clinico-pathologic diagnosis

- Presence of clinical symptoms related to esophageal dysfunction
  - Vomiting, abdominal pain, heartburn, dysphagia, reflux symptoms, feeding difficulty, etc.
- Isolated esophageal eosinophilia
  - > 15 eosinophils per 40X HPF
  - Histology of remainder of GI tract normal
- Exclusion of other GI disorders
  - Absence of pathologic GERD
    - Lack of response to PPI therapy or normal pH probe
  - Infection, Crohn's disease, hypereosinophilic syndrome

Furuta et al. *Gastroenterology.* 2007; 133:1342-63.

2007 -2011

- Scientific publications on EoE doubled
- Increasing recognition of patients with EoE
  - Poor use of the 2007 Recommendations
  - Survey by AAAAI and NASPGHAN revealed only 1/3 of physicians followed 2007 guidelines to make diagnosis
  - Many investigators still not using clinico-pathologic diagnosis - any patient with esophageal eosinophilia or food impaction and endoscopic findings = EoE

Dellon et al. *Am J Gastroenterol.* 2007;(102)*:2300-2313.*

2011 Consensus Report

- Panel of 33 physicians (6 months)
- Conceptual Definition
  - *"Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation"*
- Pediatric and adult EoE likely the same disease

Liacouras et al. *J Allergy Clin Immunol.* 2011; 128:3–20.

2011 Consensus Report

Diagnostic Guideline

- EoE is a clinico-pathologic disease
- Clinically characterized by esophageal dysfunction
- Pathologically 1 or more biopsies show eosinophil predominant inflammation (15+ eosinophils in peak hpf)
- Isolated to esophagus (need for other GI biopsies)
- Other causes need to be excluded
  - Distinguish between “EoE” and “esophageal eosinophilia”
  - “PPI responsive esophageal eosinophilia”
- EoE diagnosis made by clinicians
- Rarely < 15 eos/hpf (if other path features are present)

Liacouras et al. *J Allergy Clin Immunol.* 2011; 128:3–20.

PPI-Responsive Esophageal Eosinophilia

PPI-Responsive Esophageal Eosinophilia

- PPI-REE currently considered to be “distinct” from EoE
- Etiology
  - Gastroesophageal reflux responsive to acid suppression
  - Possible anti-inflammatory effect of PPI
  - Subset of EoE
  - Combination of GERD and EoE
- Important to make distinction
- Further research needed

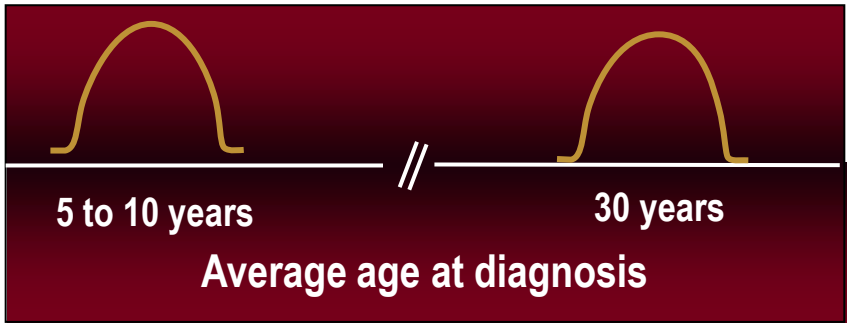
PPI-REE – Estimates

Author	Year	Population	Design	# of patients with eosino-philia treated with PPI	PPI-REE (n, %)
Dranove	2009	Peds	Retro.	43	17 (40)
Sayej	2009	Peds	Retro.	36	14 (39)
Molina-Infante	2011	Adult	Prospective	35	26 (74)
Peterson	2010	Adult	RCT*	12	4 (33)
Moawad	2011	Adult	RCT*	20	7 (35)
Dellon	2013	Adult	Prospective	65	24 (37)
Schroeder	2013	Peds	Retro.	7	5 (71)

Dohil et al. *Dig Dis Sci*. 2012:1413-9.

Epidemiology of Eosinophilic Esophagitis

Age of Onset of EoE



Mean age (N=30)		Range
At first diagnosis	33	6-65
At first manifestation	29	6-52

Mean age (N=31)		Range
At first diagnosis	34	14-77
Years "incorrect diagnosis"		
7		2-12

Liacouras CA et al. Clin Gastroenterol Hepatol. 2005;12:1198-206
Straumann et al. *Gastroenterology.* 2003; 125:1660-1669.
Croese et al. *Gastrointest Endosc.* 2003; 58:516-522.

Incidence and Prevalence of EoE

Region	Δ	Incidence*	Prevalence*	Years
US				
Ohio (Pediatrics)	⇑	1.3	6.9	'00-'05
Minnesota (Mixed)	⇑	.9	10.5	'76-'05
Australia				
Pediatrics	⇑	Not done	.09	'95-'04
Adults	⇑	.6	1.5	'81-'02
Switzerland				
Adults	⇑	.15	2.9	'00-'06

* (all per 10,000 population)

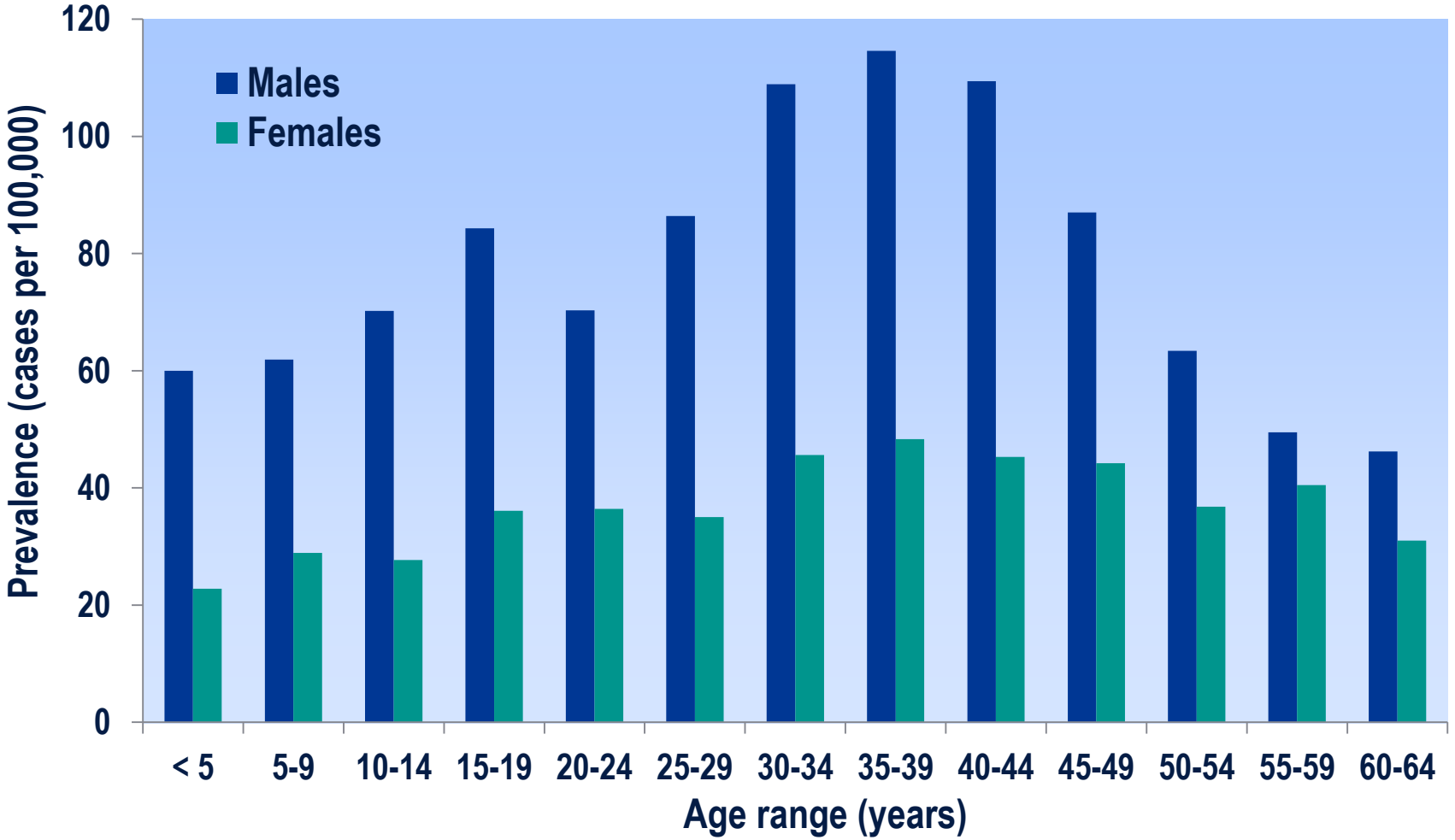
Noel et al. *N Engl J Med*. 2004; 351:940-941.
Straumann et al. *J Allergy Clin Immunol.* 2005; 115:418-419.
Cherian et al. *Arch Dis Child*. 2006; 91:1000-1004.
Croese et al. *Gastrointest Endosc.* 2003; 58:516-522.
Prasad et al. *Gastroenterology*. 2008; 134 (Suppl): S1977.

Prevalence of EoE in the U.S.

		EoE case definition (at least one 530.13 code)	
	Source population	EoE cases	Prevalence (per 100,000)
Age group			
<20	3,587,571	1,813	50.5
20-64	7,981,646	4,700	58.9
Sex			
Male	5,544,574	4,257	76.8
Female	6,024,643	2,256	37.4
Region			
East	2,226,470	1,054	47.3
South	4,529,151	2,507	55.4
Midwest	3,569,432	2,567	71.9
West	1,244,164	385	30.9
Overall	11,569,217	6,513	56.3

Dellon et al. *Clin Gastroenterol Hepatol*. 2013; S1542-3565(13)01304-9.

Prevalence of EoE by Age & Sex



Dellon et al. *Clin Gastroenterol Hepatol.* 2013; S1542-3565(13)01304-9.

Pediatric Incidence of EoE

Frequency of EoE in a Single County‡

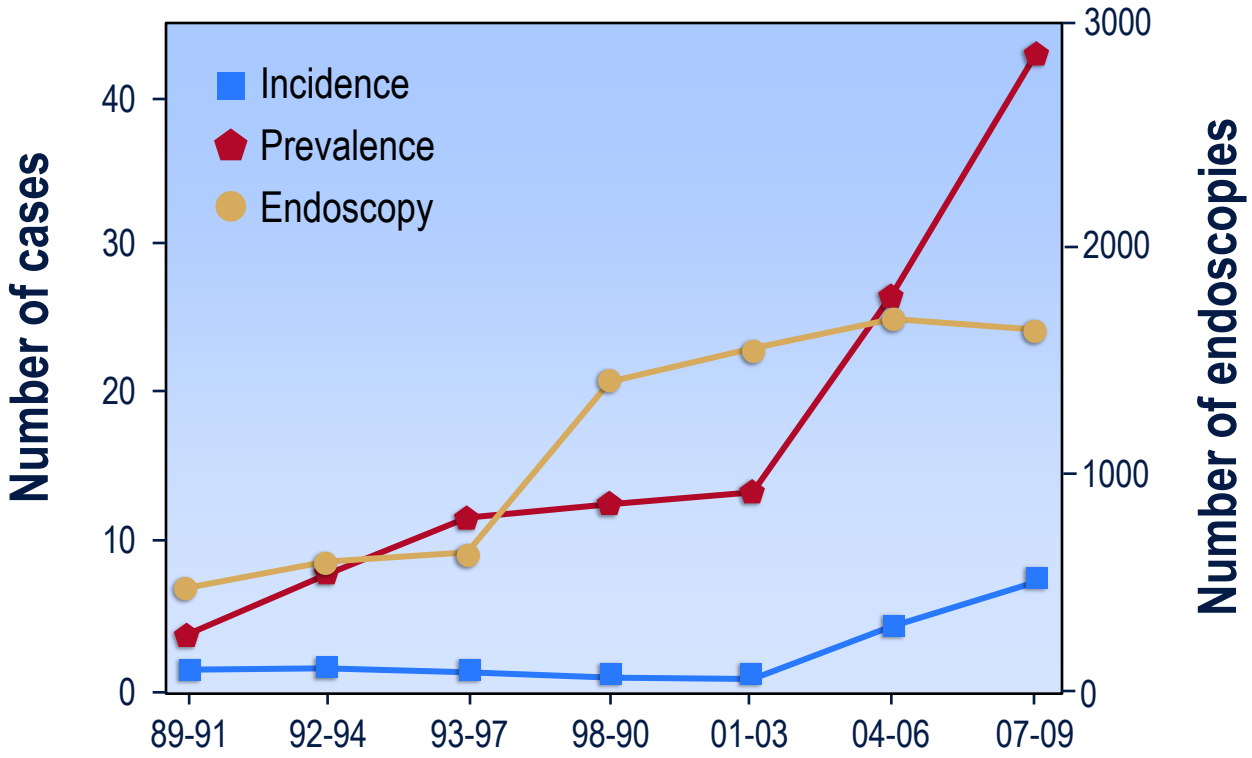
	2000	2001	2002	2003
Cases	22	24	24	31
Incidence*†	0.909	0.991	1.033	1.281
Prevalence*	0.991	1.983	3.016	4.296

‡ Hamilton County, OH
* per 10,000 population age 0-19 years
† Chi-square test for trend NS

Noel et al. *N Engl J Med.* 2004; 351:940-941.

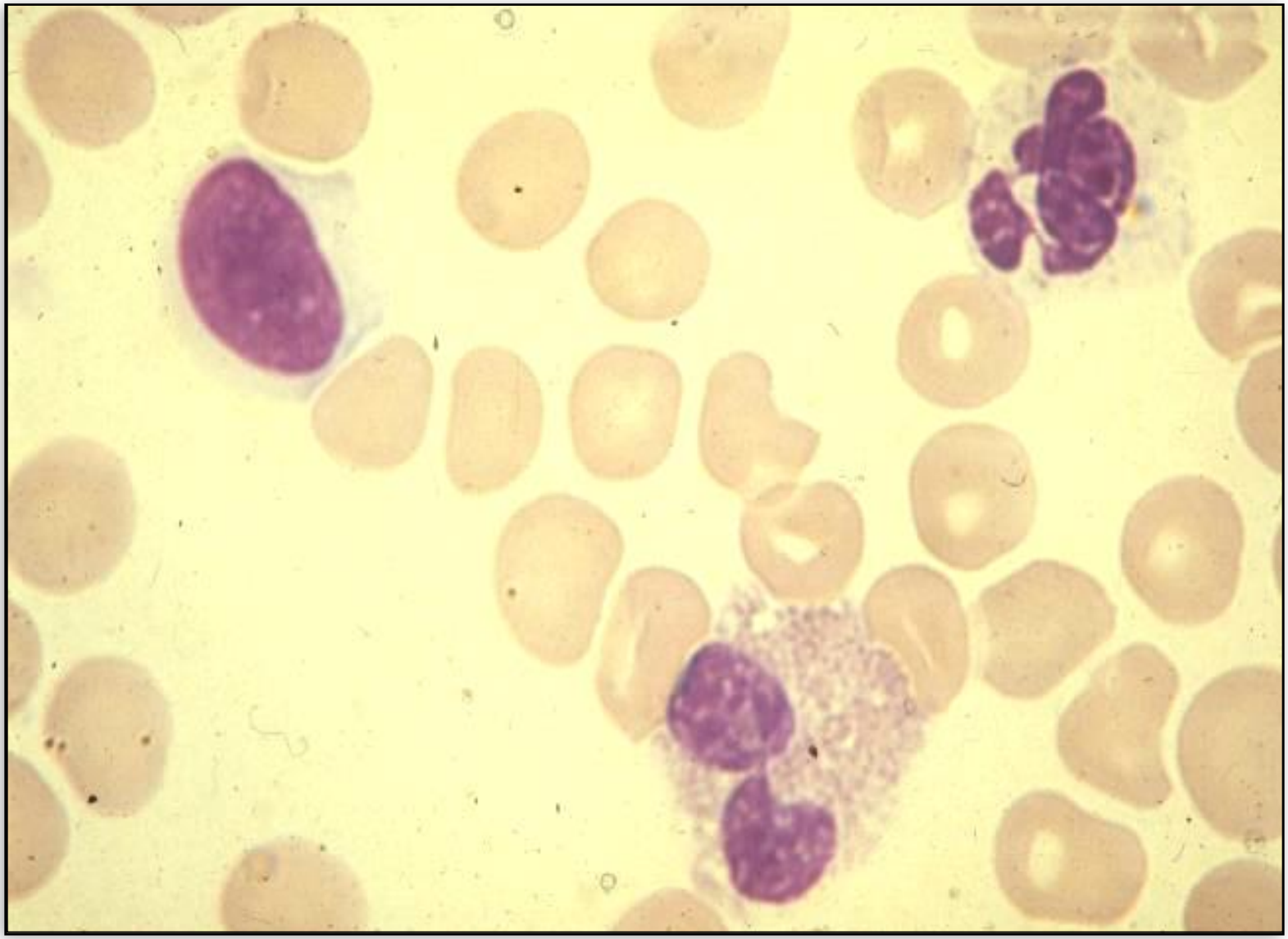
Adult Incidence of EoE

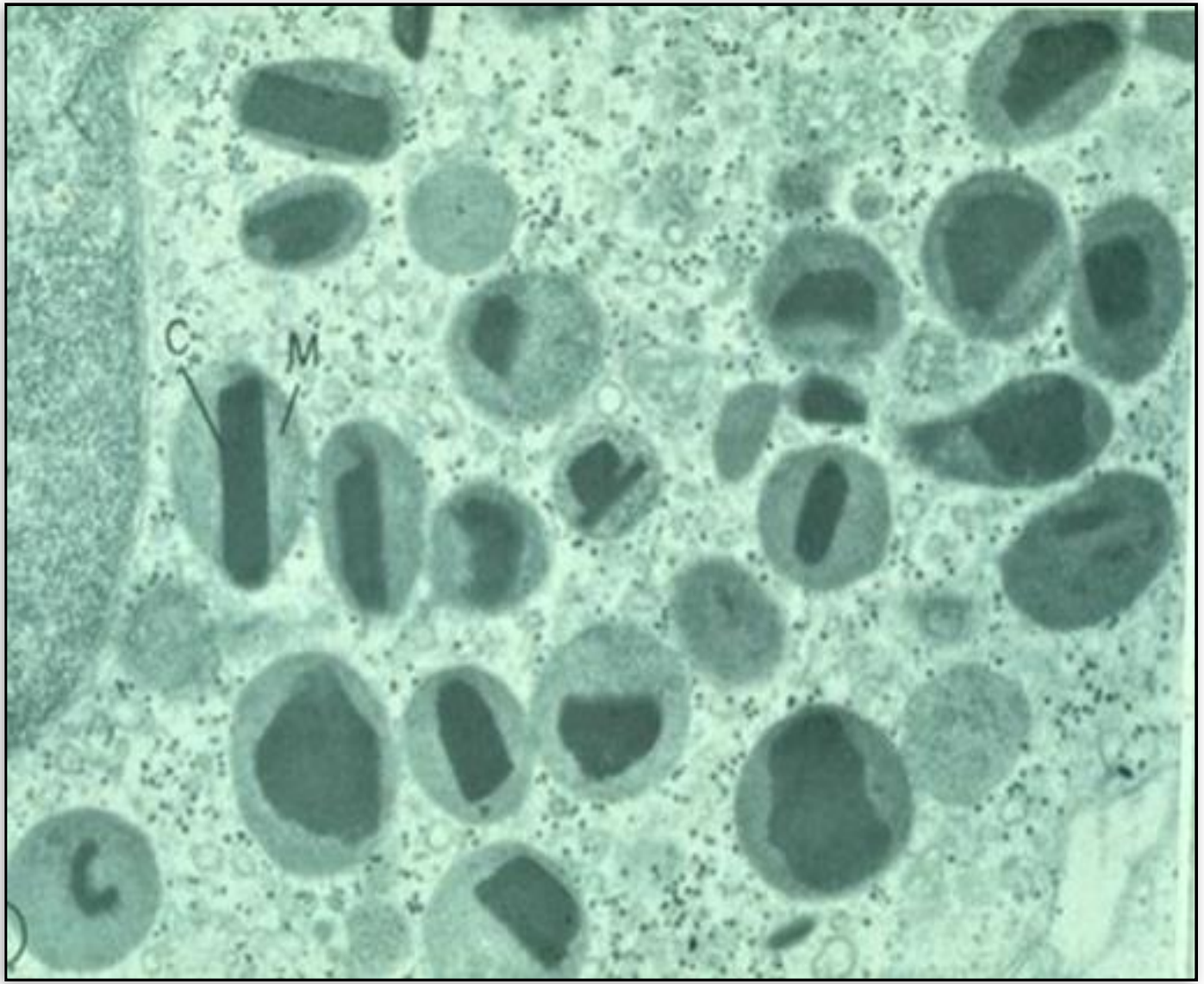
Incidence and Prevalence of EoE in Olten-County Switzerland



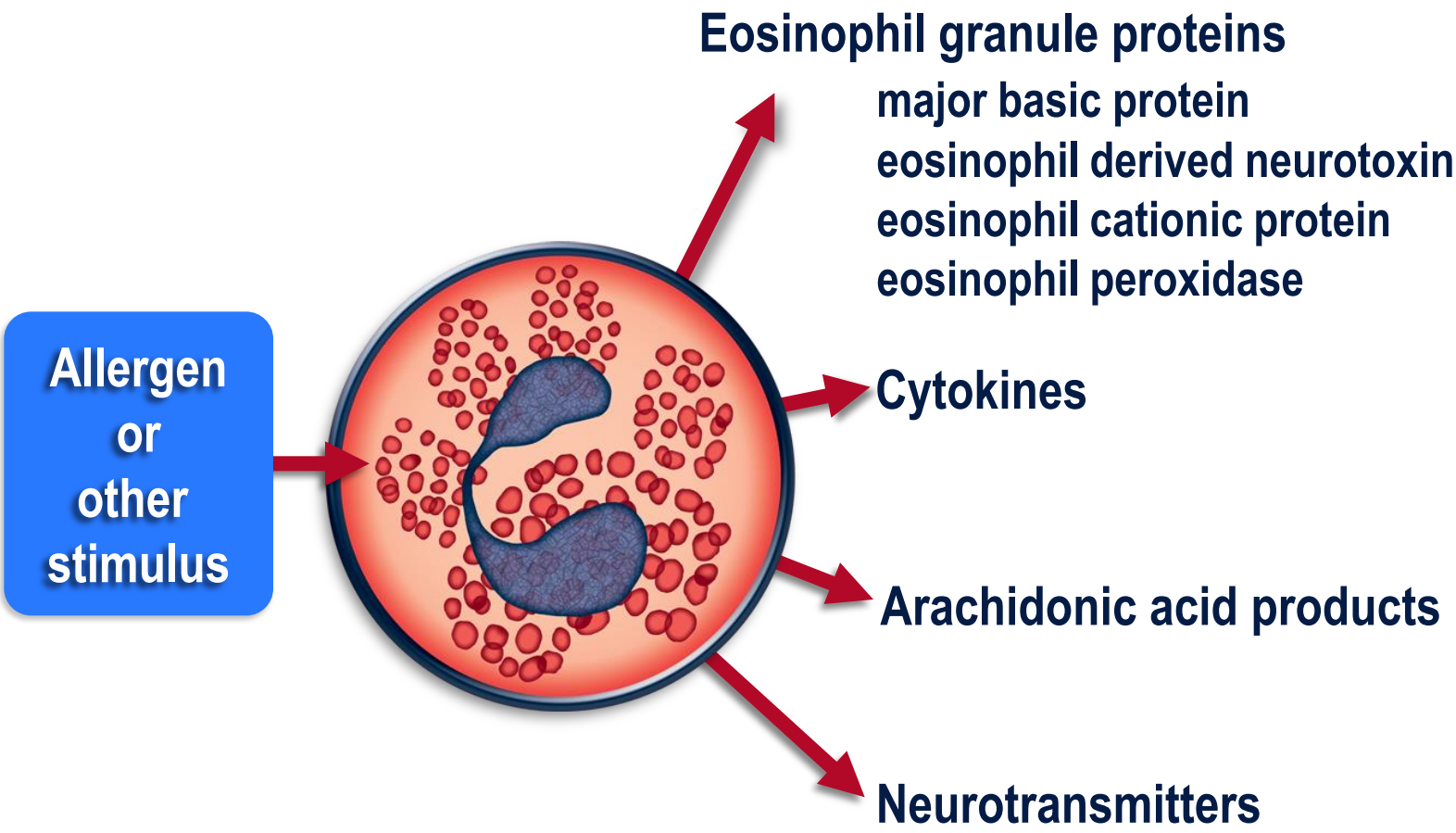
Hruz et al. *J Allergy Clin Immunol*. 2011; 128:1349-50.

Biology of the Eosinophil





Eosinophil Biology



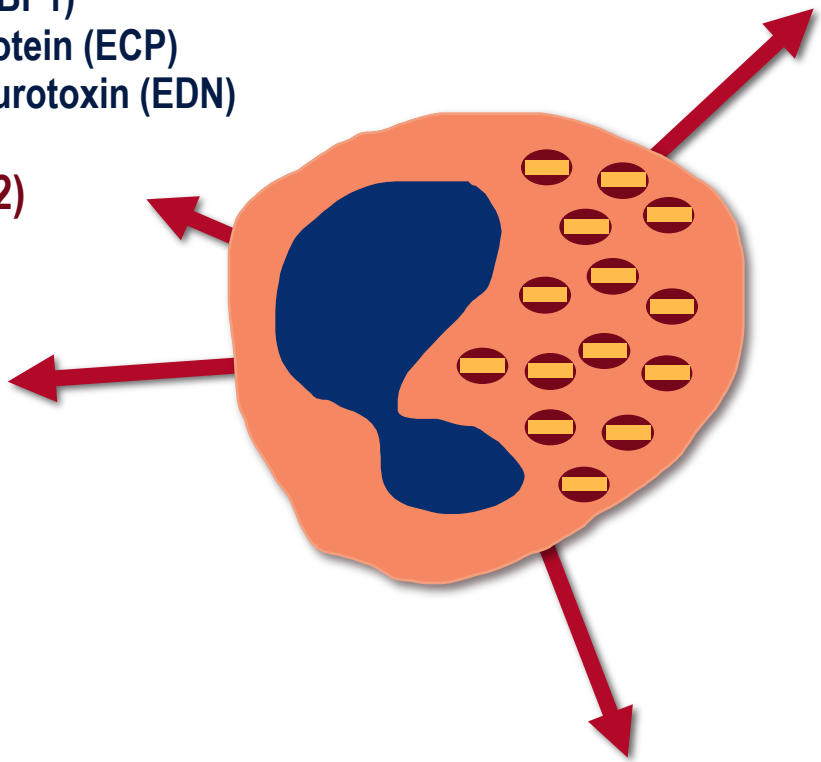
Secretory Products of Eosinophils

Granule-derived proteins

Major basic protein (MBP1)
Eosinophil cationic protein (ECP)
Eosinophil-derived neurotoxin (EDN)
Eosinophil peroxidase
MBP homolog(MBP2)

Reactive oxygen intermediates

Oxygen and peroxide
Hydroxyl radicals
Singlet oxygen



Lipid mediators

Leukotriene C4/D4
Platelet activating factor
5-HETE
5,15- and 8,15-diHETE
Prostaglandin E_1 E_2
Thromboxane B2

Cytokines

Eosinophils & Tissue Damage

Granule proteins:

- Cationic toxins able to disrupt membranes
- Toxic to helminths & bacteria
- Toxic to cells from numerous organs, including bronchial epithelium, keratinocytes, pneumocytes, gut epithelium
- Potent stimuli to resident cells for the production of inflammatory cytokines

Eosinophils & Tissue Damage

- Eosinophil granule proteins activate cells, including eosinophils themselves, basophils, neutrophils, mast cells & bronchial epithelial cells
- In turn, many of these activated cells produce new molecules

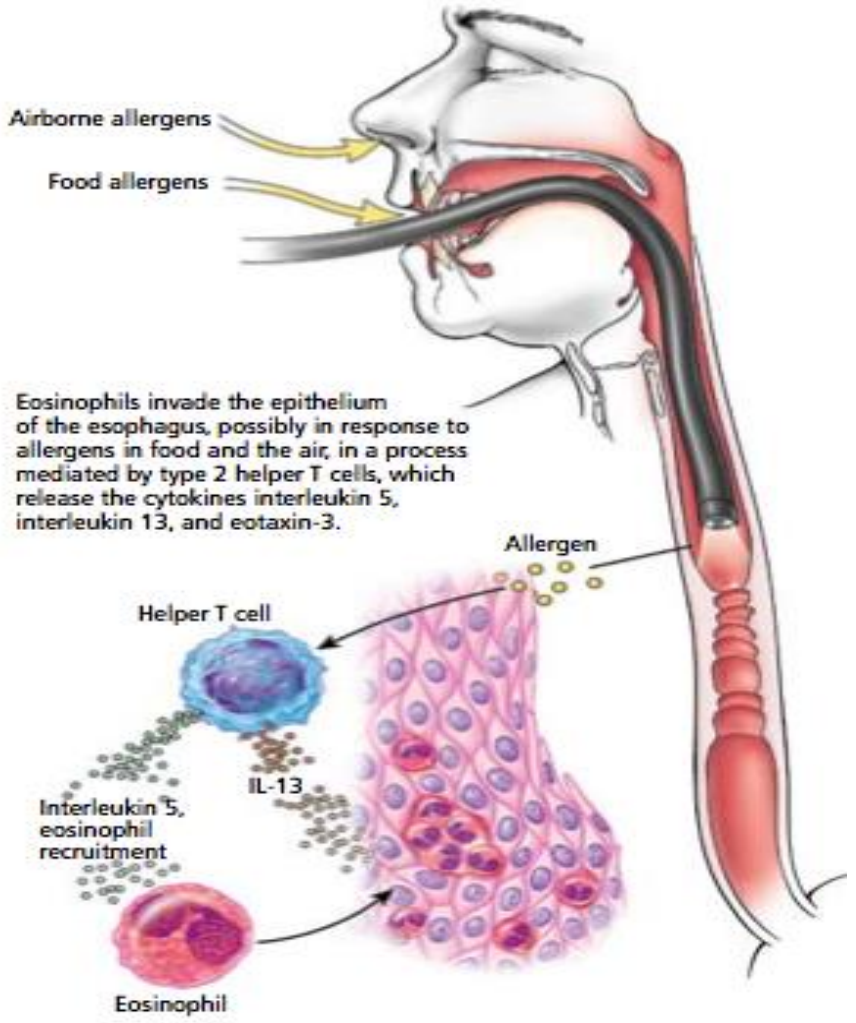
Granule Proteins

- Alter the function of molecules (M2 muscarinic receptors, clotting and complement components)
- Neutralize viruses by possession of Rnase activity
- Toxic concentrations of granule proteins present at sites of tissue injury (heart, skin, GI tract)
- Can occur in absence of intact eosinophils

Pathophysiology of EoE

Potential Pathophysiology of EoE

- Intraluminal allergen exposure
  - Predominately food antigens
- Mucosal production of eosinophilic chemoattractants
- Influx of eosinophils
- Release of inflammatory mediators
- Esophageal dysfunction

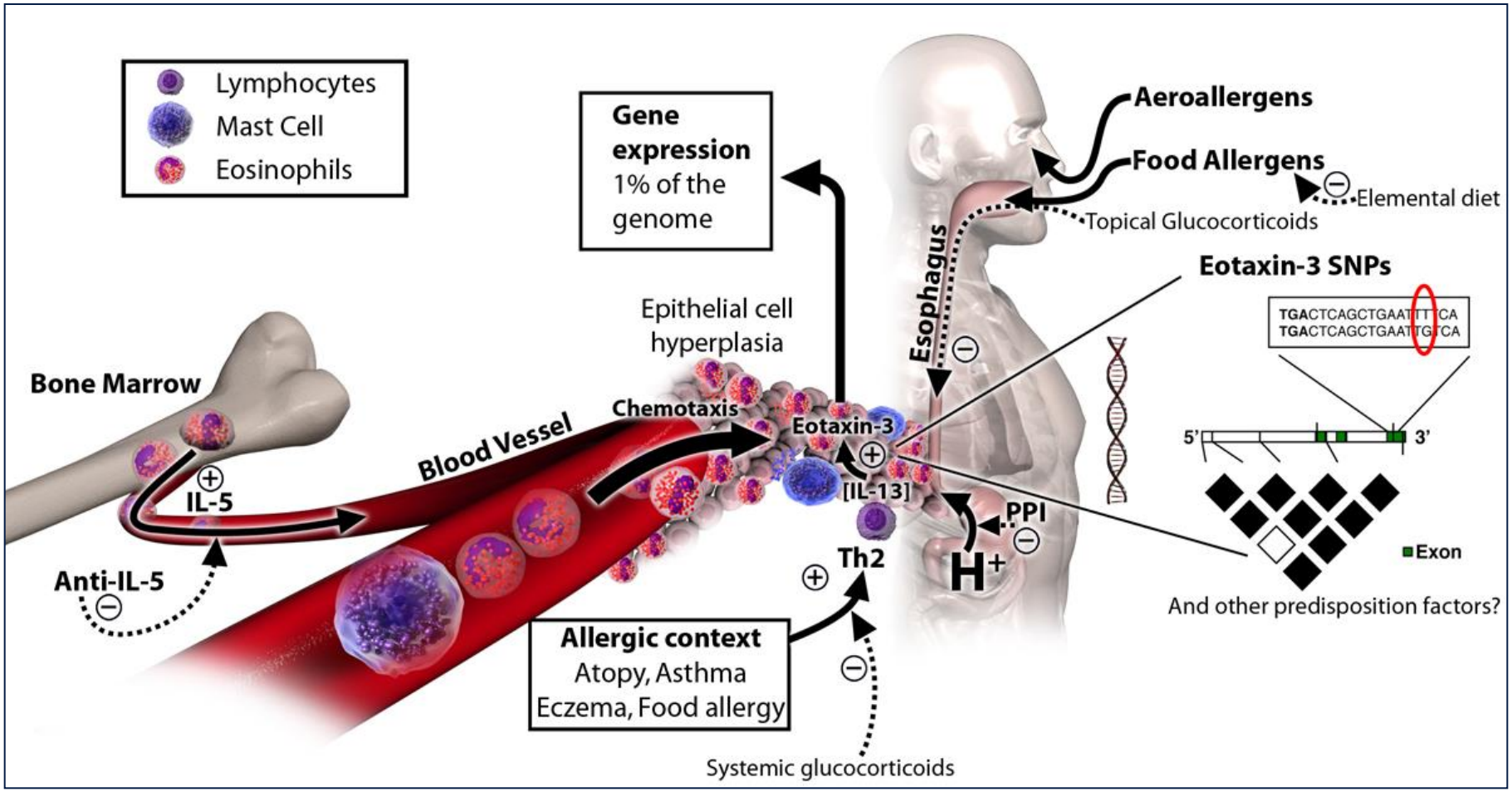


Noneveski et al; *Clev Clin J.* 2008:75(9):623-633.

Cells Related to EoE

- Esophageal eosinophils
- An expansion of Th2 cells are found
- Both Th2 cells and eosinophils play a critical role in the pathogenesis of EoE
- Other cells
  - Esophageal mast cells
  - Esophageal basophils

Schematic Representation of EoE Pathogenesis

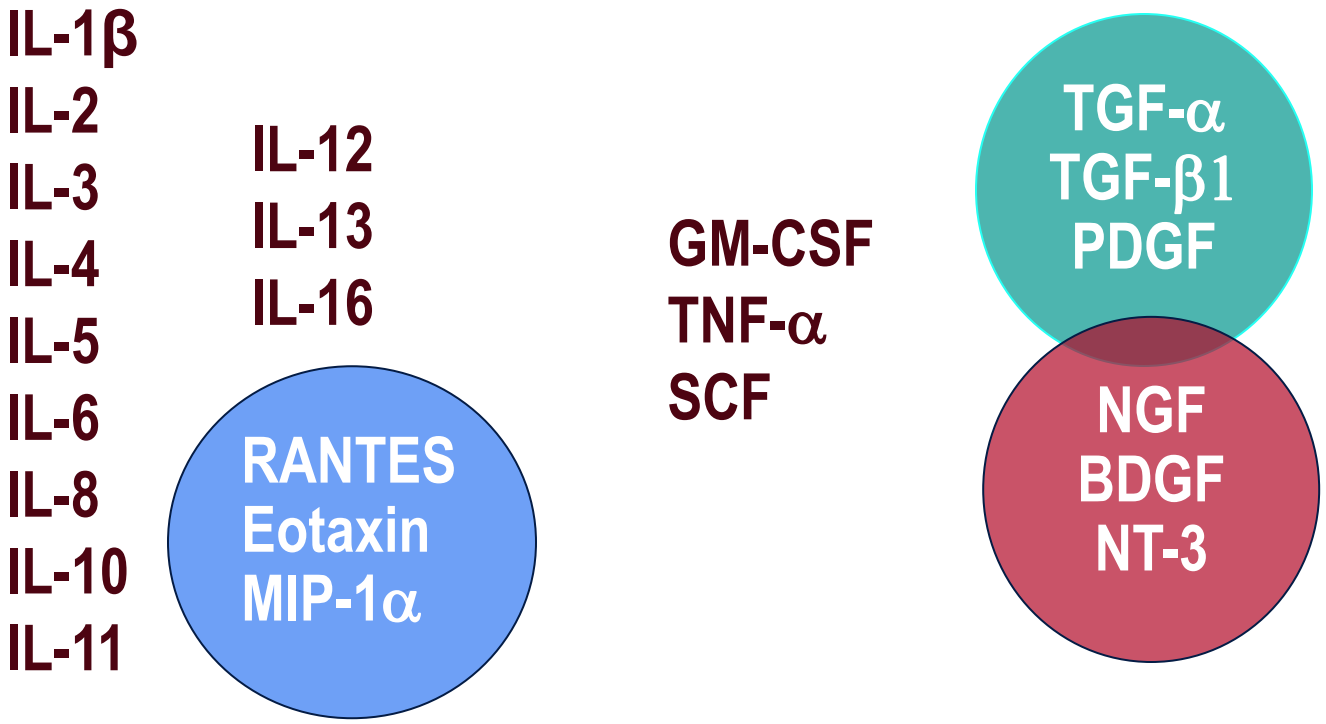


Blanchard et al. *J Clin Invest.* 2006;116(2):536-547.

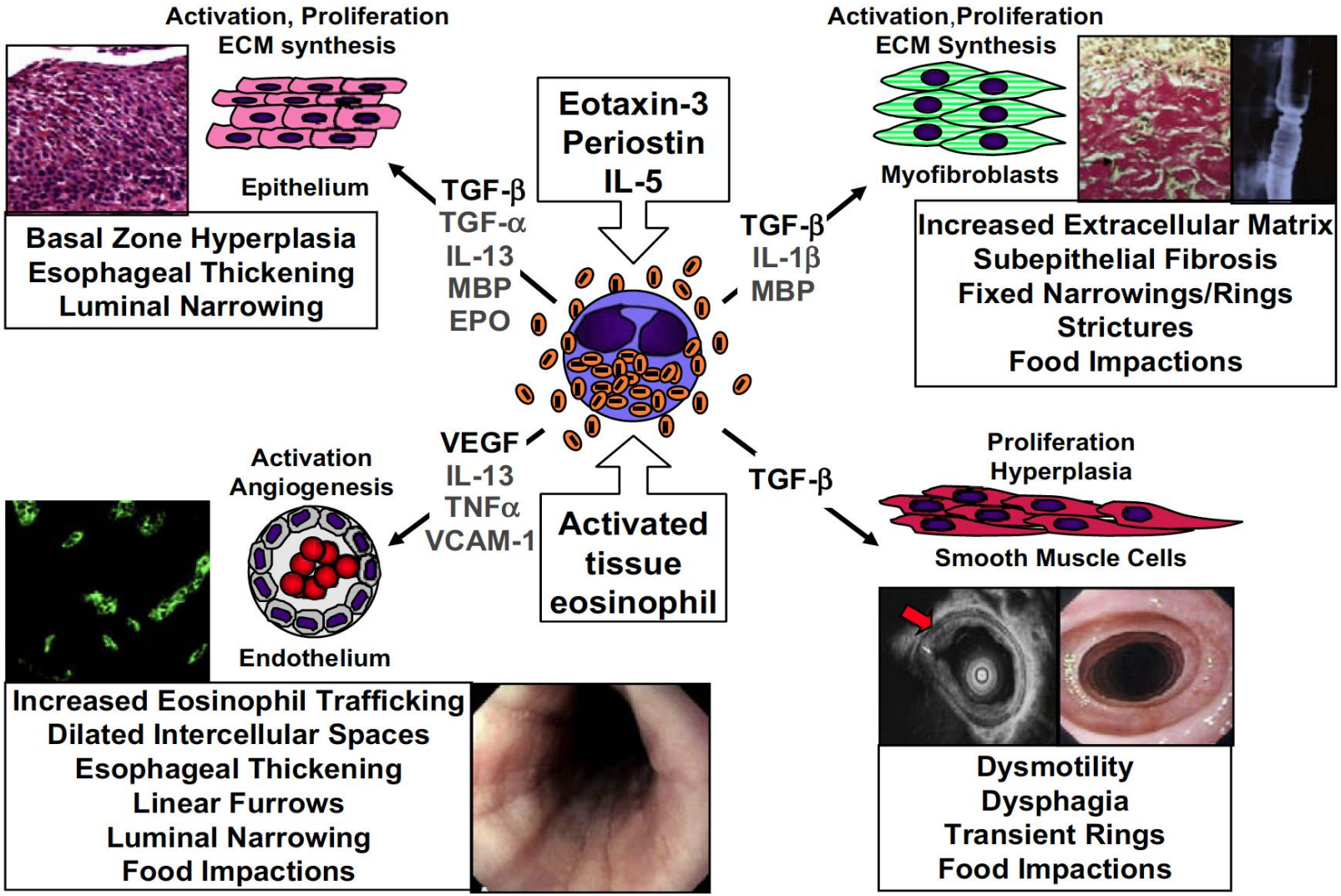
Cytokines Related to EoE

- Increased expression of human eotaxin-3 and interleukin-5
- Murine inflammation is dependent on interleukin-5 and interleukin-13
- Murine collagen deposition dependent on interleukin-5
- Secretion of cytokines (IL-5 and IL-13) that favor both IgE synthesis and eosinophilia.
- Human fibrosis associated with increased collagen deposition, TGFβ and pSMAD

Cytokines and Growth Factors



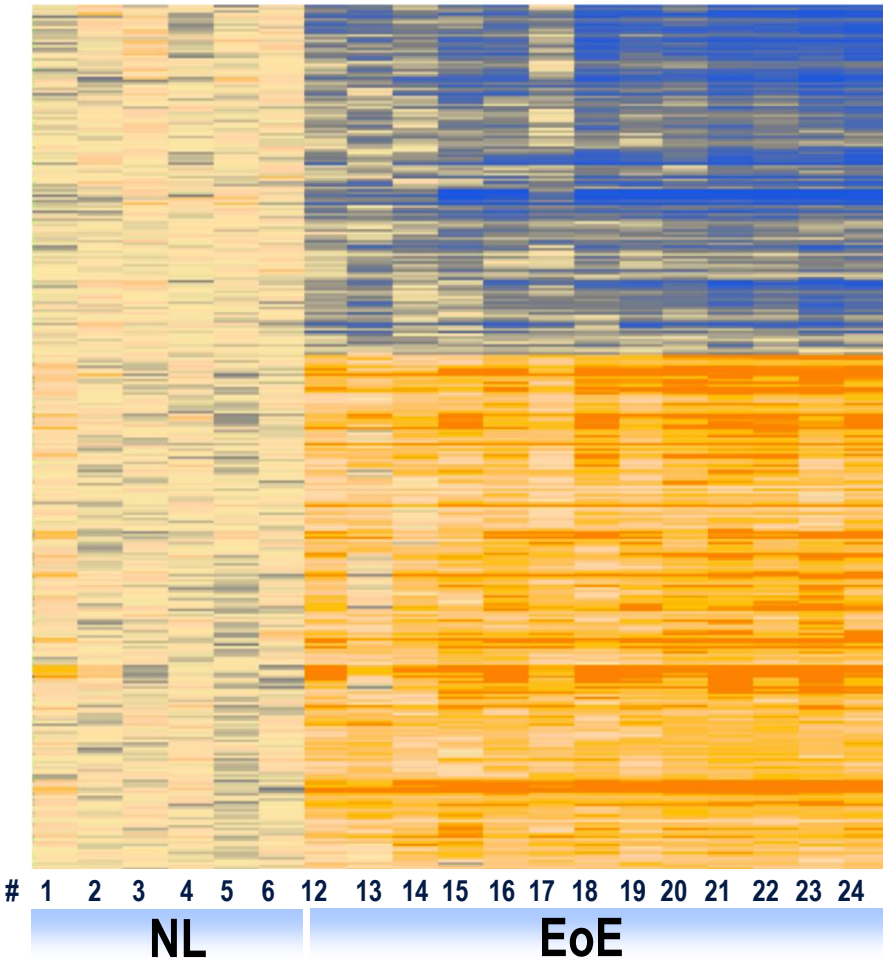
Molecular Microenvironment in EoE



Ackerman et al. *Immunol Allergy Clin North Am.* 2009;29(1):197-211.

Genetics

Gene Expression Profile of EoE



EoE patients have a unique gene expression profile

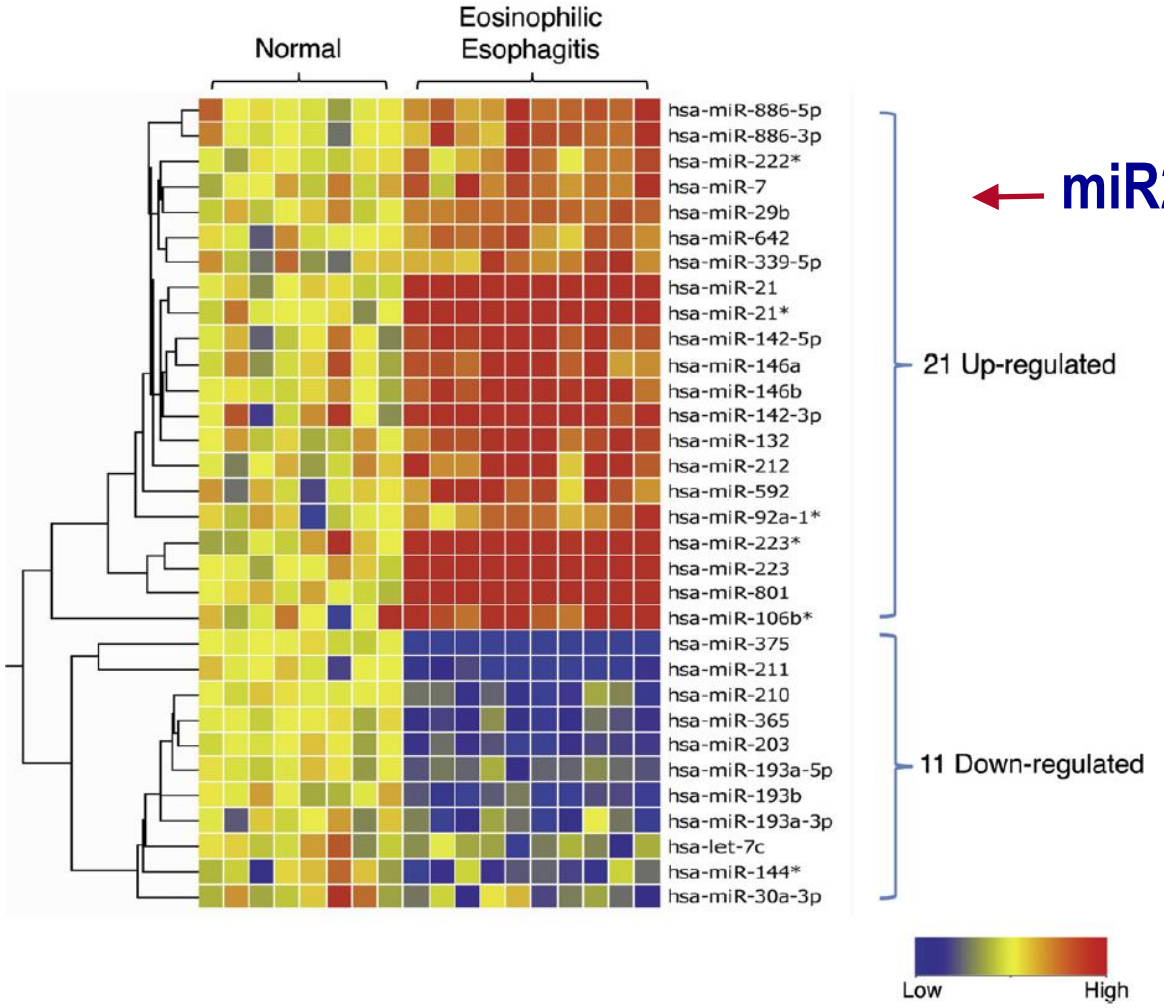
Blanchard et al. *J Clin Invest.* 2006; 116(2):536-547.

EoE - Genetics

- Increased incidence in siblings and 1st degree relatives
- Identified gene locus at chromosome 5q22
- TSLP gene (Thymic Stromal Lymphopoetin Protein)

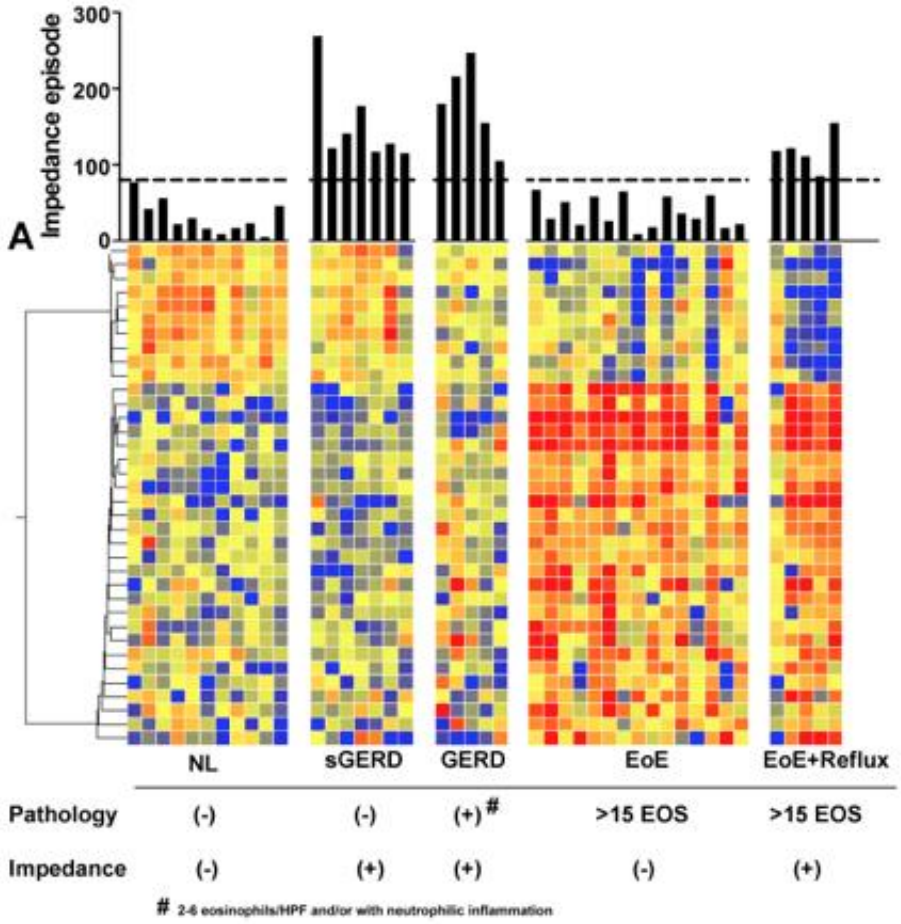
Rothenberg et al. *Nat Genet*. 2010; 42:289-10.

MicroRNA (miR) Expression in Human Allergic and Control Tissue



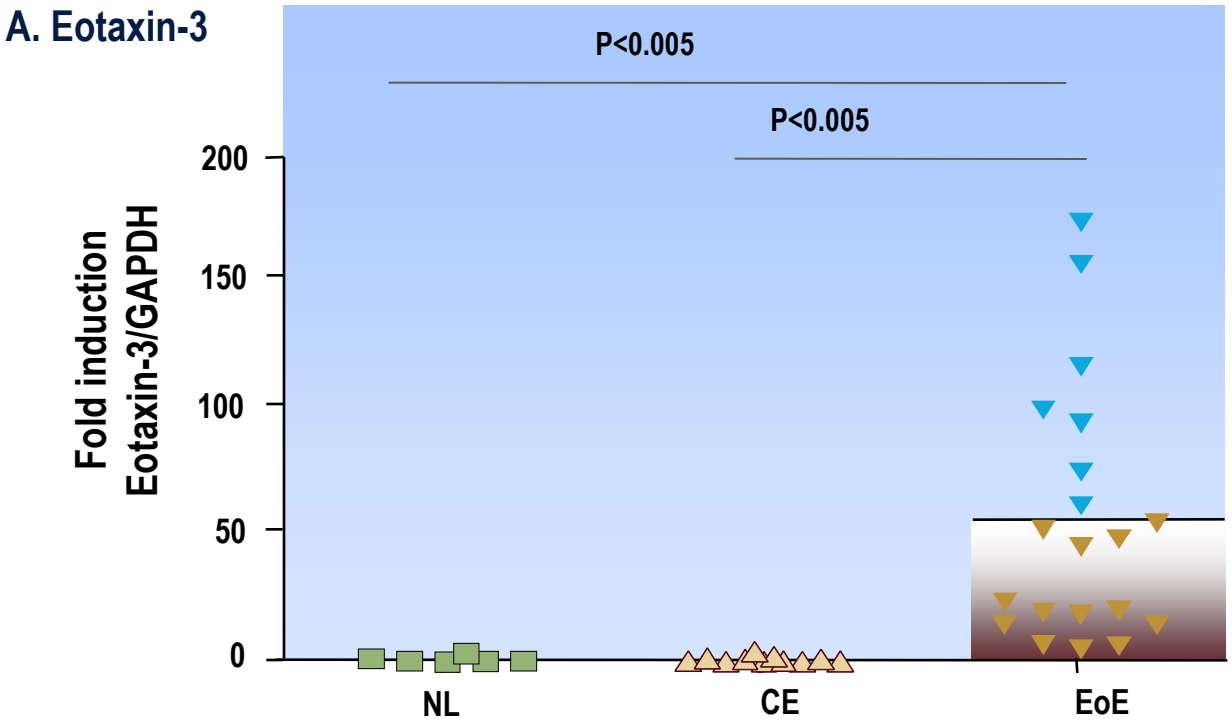
Lu et al; *J Immunol.* 2011; 187(6): 3362–3373.

EoE Diagnostic Panel Analyzed as a Function of Impedance Guided Analysis



Wen et al. *Gastroenterology.* 2013; 145(6):1289-1299.

Eotaxin-3 Expression in EoE Tissues



Strong expression of eotaxin-3 in esophageal biopsies of EoE patients vs NL and CE patients

Blanchard et al. *J Clin Invest.* 2006; 116(2):536-547.

Fibrosis

Esophageal Fibrosis

- Occurs in adults
- Occurs in animal model
  - In response to allergen challenge
- Occurs in pediatric patients
  - With dysphagia
  - With strictures and EoE

Straumann et al. *Gastroenterol.* 2003; 125(6):1660-1669.
Parfitt et al. *Mod Pathol.* 2006; 19:90-96.
Mishra et al. *Gastroenterology.* 2008; 134(1):204-214.
Chehade et al, *J Pediatr Gastroenterol Nutr.* 2007; 45(3):354-357.
Aceves et al. *J Allergy Clin Immunol.* 2007; 119(1):206-2012.

Role of Eosinophils in Fibrosis

- Elevated eosinophils in the lamina propria of EoE patients
- Human esophageal eosinophils express TGFβ_1
- Mice lacking eosinophils have decreased esophageal fibrosis
- Mice lacking IL-5 have decreased esophageal fibrosis

Parfitt et al. *Mod Pathol.* 2006; 19:90-96.
Aceves et al. *J Clin Gastroenterol.*2007; 41(3):252-256.
Aceves et al. *J Allergy Clin Immunol.* 2007; 119(1):206-2012
Mishra et al. *Gastroenterology.* 2008; 134(1):204-214.

Esophageal Tissue Remodeling

- Components of EoE remodeling
  - Fibrosis
  - Collagen deposition
  - Pro-fibrotic factors
  - Pro-fibrotic signaling molecules
  - Angiogenesis
  - Vascular activation

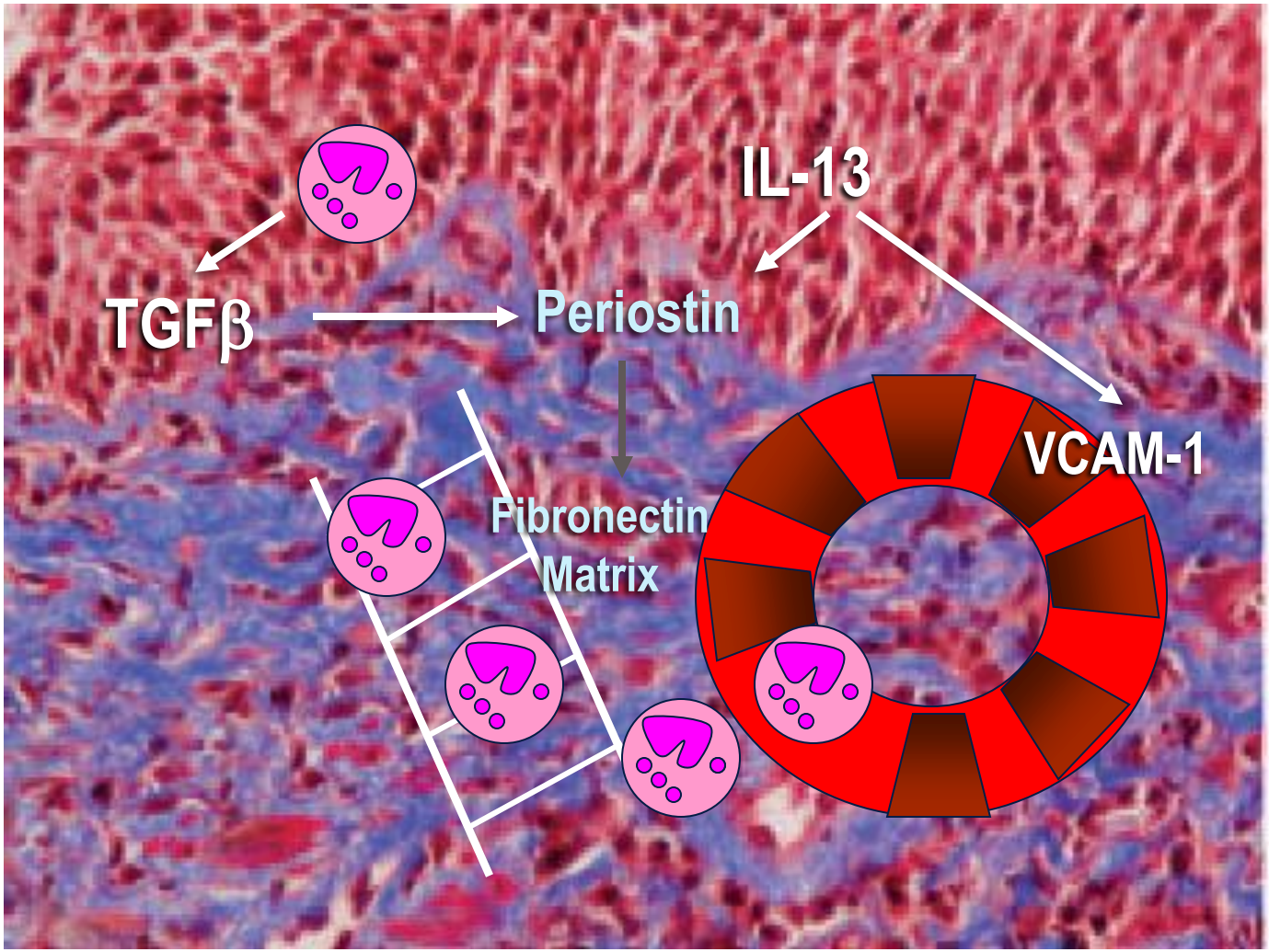
Straumann et al. *Gastroenterol.* 2003; 125(6):1660-1669.
Parfitt et al. *Mod Pathol.* 2006; 19:90-96.
Mishra et al. *Gastroenterology.* 2008; 134(1):204-214.
Chehade et al, *J Pediatr Gastroenterol Nutr.* 2007; 45(3):354-357.
Aceves et al. *J Allergy Clin Immunol.* 2007; 119(1):206-2012.

Pro-Fibrotic Factors

- **TGFβ**
  - Increased in pediatric EoE as compared to normal and GERD
  - **Phosphorylated Smad2/3**
    - Downstream transcription factor for TGFβ_1
    - Increased in EoE as compared with normal and GERD
- **Periostin**
  - Increased in animals following allergen challenge
  - Increased in pediatric EoE
  - Increases eosinophil adhesion to fibronectin

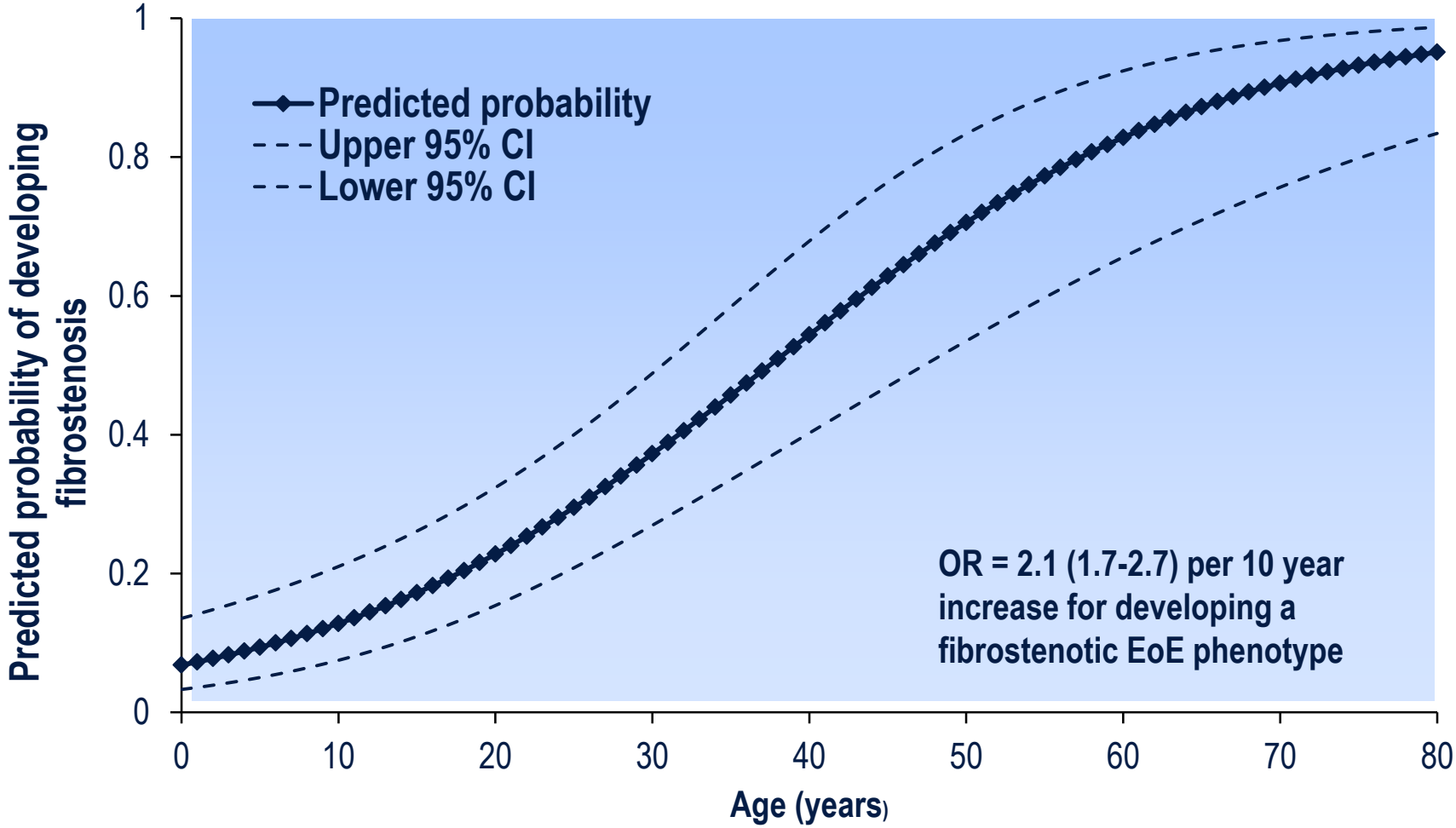
Blanchard et al. *Mucosal Immunol.* 2008; 1:289-296.

Fibrosis and Eosinophil Trafficking



Chehade et al. *J Pediatr Gastroenterol Nutr.* 2007;45:319–328.
Aceves and Ackerman. *Immunology Clin North America.* 2009;29(1):197.

EoE as a Progressive Disease



Dellon et al. *Gastrointest Endosc*. 2013.

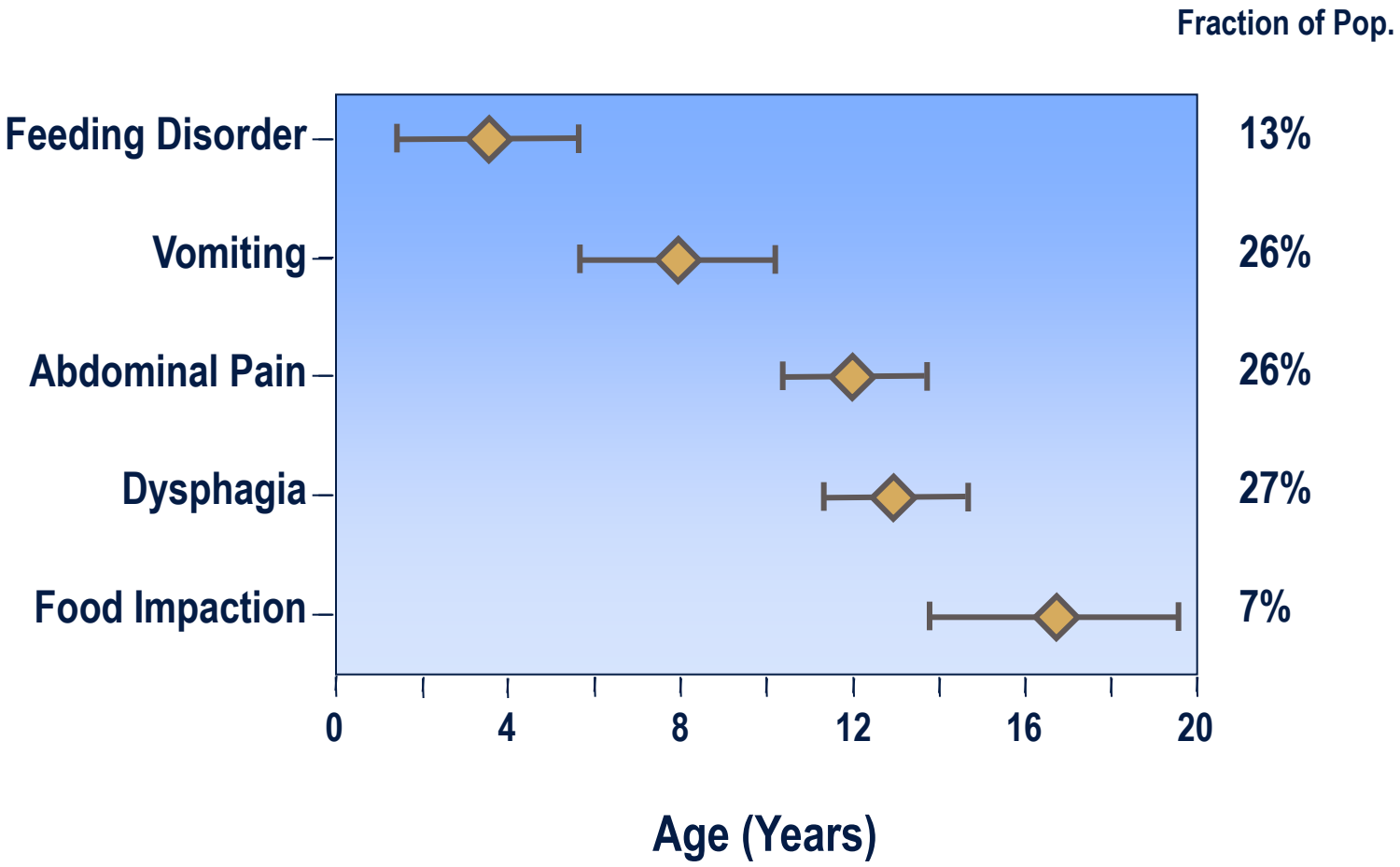
Pediatric Clinical Symptoms

Clinical Features

- Male predominance (about 3:1)
- Multiple reports of familial clustering (within and across generations)
- Association with food allergy and atopy
- Chronic condition in adults and children

Furuta et al. *Gastroenterology.* 2007; 133:1342-1363.

EoE Presentation by Age



Noel et al. *N Engl J Med.* 2004; 351:940-941.

Clinical Symptoms - Pain

- Present in 5-68% of children
- Frequent, but not universal complaint
- May be chest pain or abdominal pain (epigastric or generalized)
- GERD-like symptoms in 5-82% of children
- Odynophagia is not typical
- May be responsive to acid suppression therapy

Clinical Symptoms - Vomiting

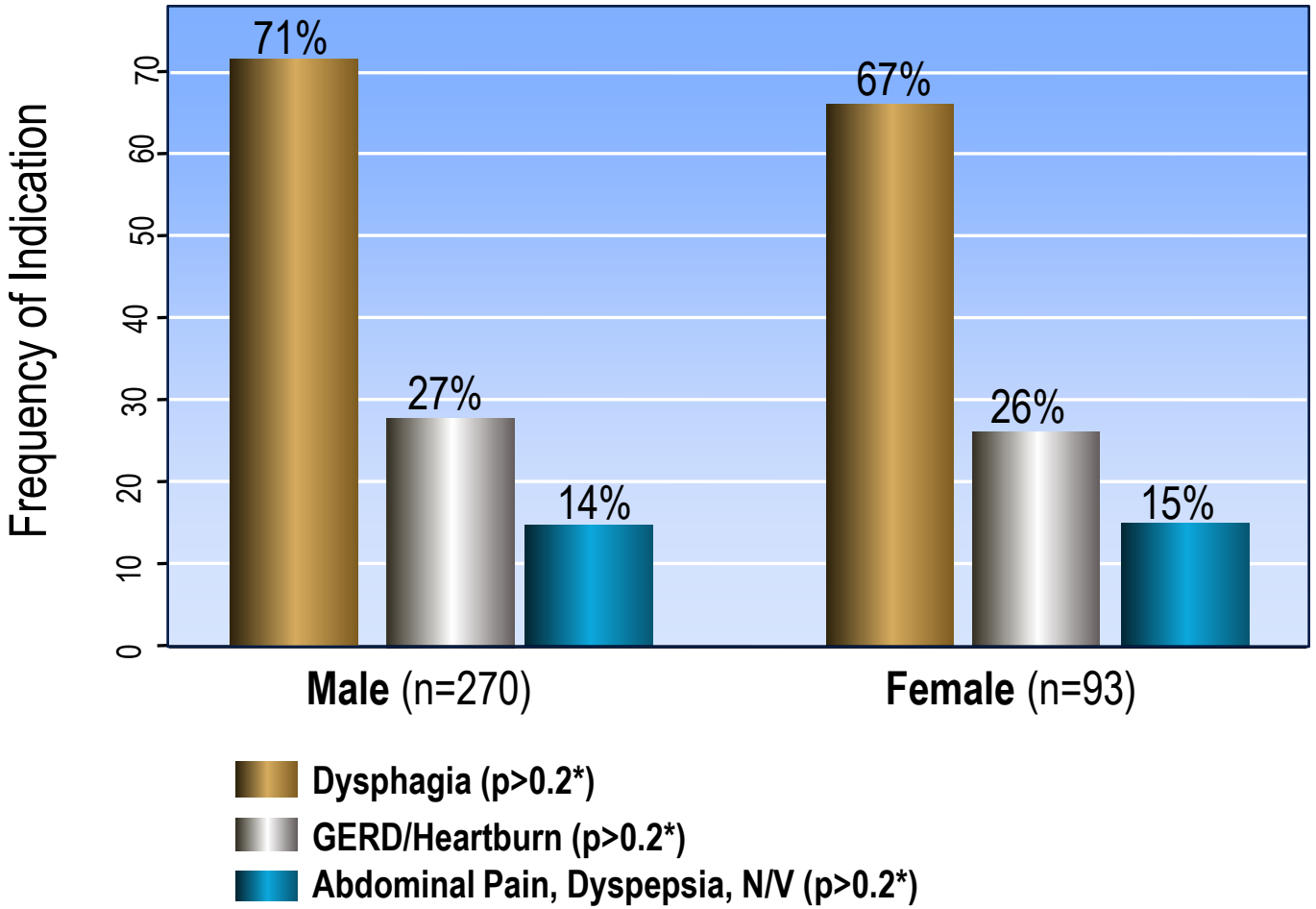
- Present in 8-100% of children with EoE
- Not clinically distinguishable from other causes of vomiting
- Symptom frequently misclassified as GERD and there is often a delay in diagnosis
- Typically true vomiting over effortless regurgitation
- Chronic, episodic and unpredictable
- May not occur immediately after food ingestion

Clinical Symptoms- Dysphagia

- The most common symptom of EoE in adults
- In children, dysphagia manifests in several ways:
  - Choking, gagging, food refusal
  - The sensation of food sticking or going down slowly
  - Food impaction
- Often occurs even in the absence of esophageal stricture or small caliber esophagus

Adult Clinical Symptoms

Presenting Symptoms of EoE in Adults

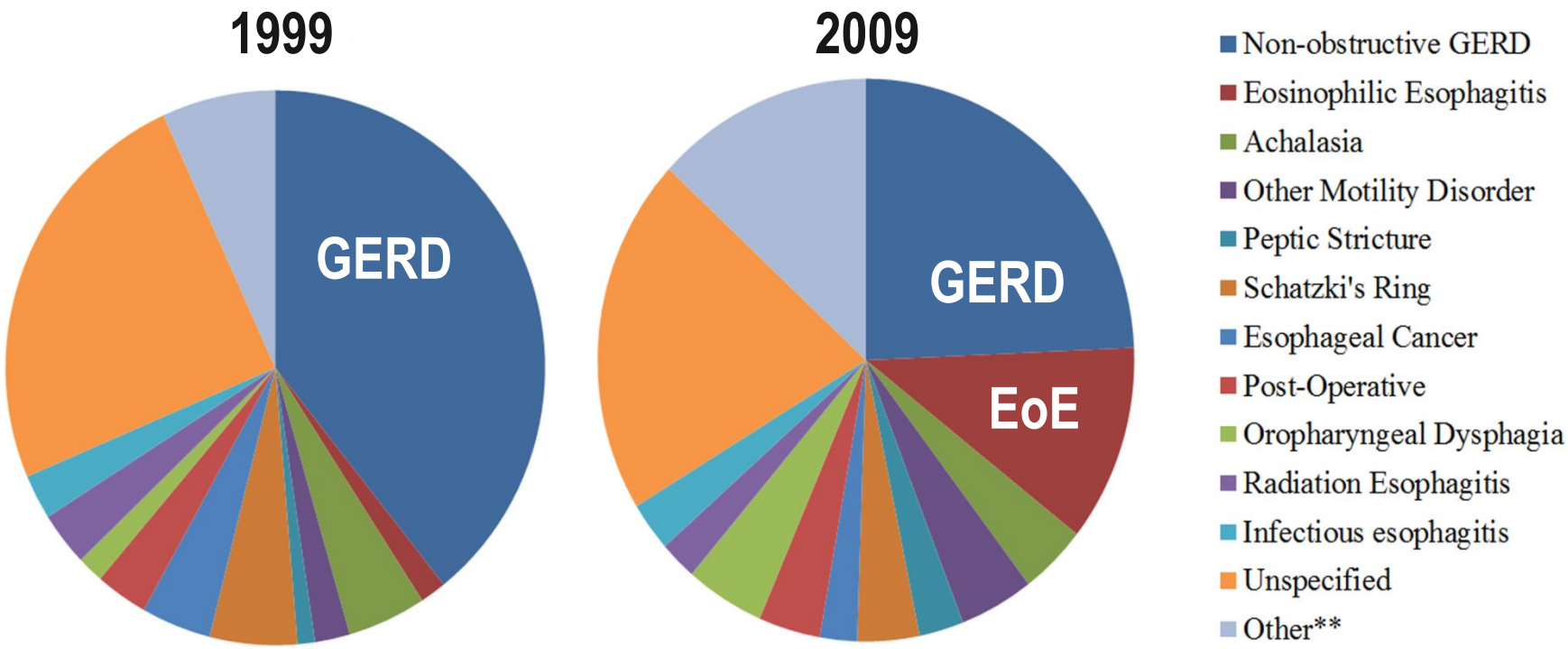


* P value for χ^2 comparing the proportion of males vs. females

Kapel et al. *Gastroenterology.* 2008; 134:1316-1321.

Etiology of Dysphagia

Retrospective Study 1371 Adults Undergoing EGD for Dysphagia



Kidambi et al. *World J. Gastroenterol. 2012*;18(32):4335-4341.

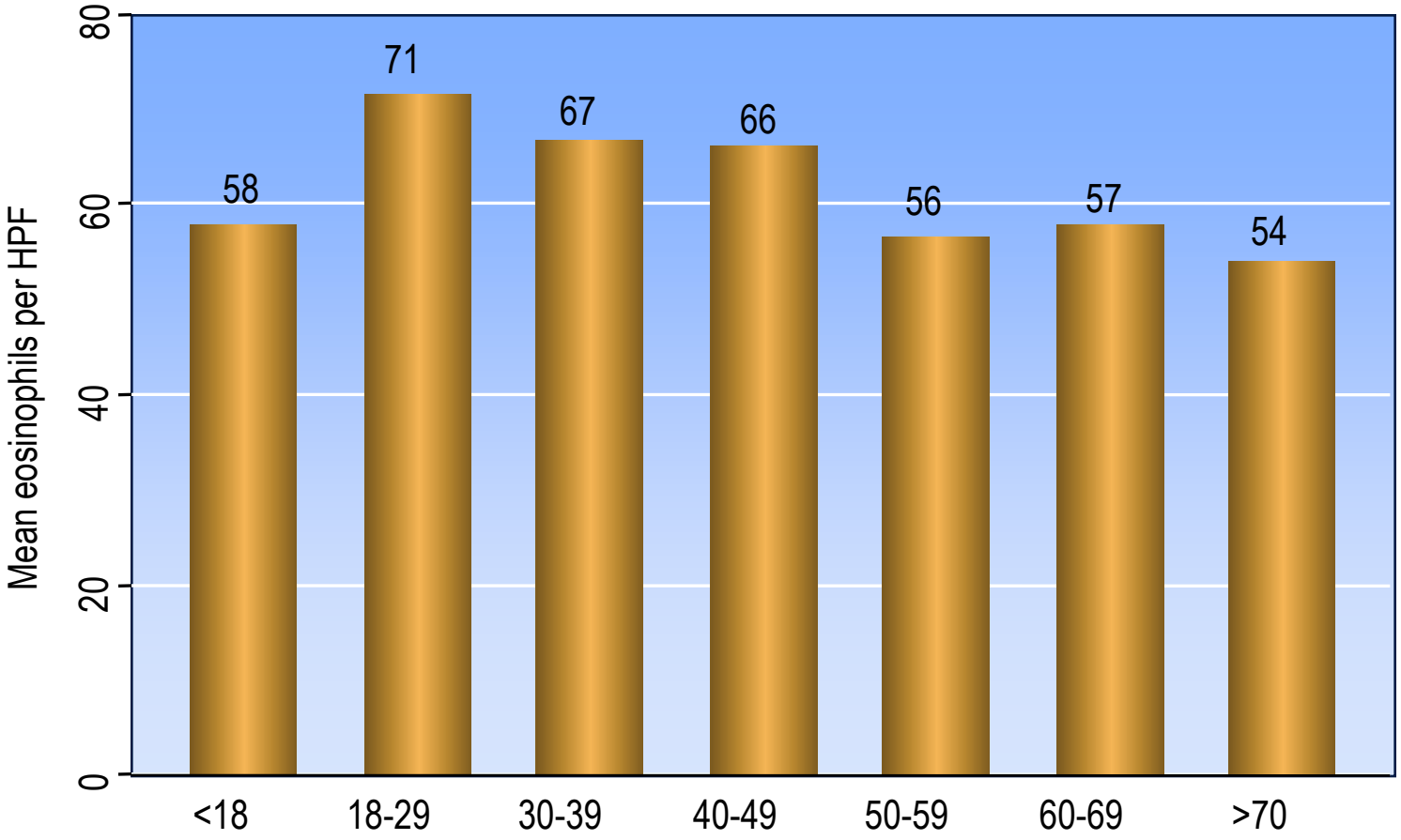
Gender in Adult EoE

	Male	Female	Total
Cases of EoE	270	93	363
Patients in the Cohort*	35083	35947	71030‡
Relative Risk (Unadjusted)	3.0		
95% CI	2.4 - 3.8 (p<.001)		

* Patients in the Caris pathology database with at least one esophageal biopsy

Kapel et al. *Gastroenterology.* 2008; 134:1316-1321.

EoE Histology by Age



Kapel et al. *Gastroenterology.* 2008; 134:1316-1321.

EoE and Atopy

Prevalence of Atopic Disease in EoE

- Asthma, allergic rhinitis, atopic dermatitis and IgE mediated food allergies are common and increasing in the general population
- Patients with eosinophilic gastrointestinal disorders have a higher prevalence of all atopic disorders
- Studies report between 50% to 93% of EoE patients have some type of atopic disorder
  - Rise in EoE mirrors rise in atopy
  - Atopy much more common in patients with EoE

Incidence of Atopic Symptoms

Feature	Percentage
Rhinoconjunctivitis	57.4
Wheezing	36.8
Food allergy*	46
Family history atopy	73.5
Family history EoE	6.8

* H/O positive skin-prick, RAST, or clinical response

Noel et al. *N Engl J Med*. 2004; 351:940-941.

Prevalence of Atopy

Author/population	Number of patients with EoE	Asthma	Allergic Rhinitis	Atopic Dermatitis
Atopy in the General Population		8.5%	25%	10%
Spergel, et al; Philadelphia	620	50%	61%	21%
Assa'ad, et al; Cincinnati	89	39%	30%	19%
Sugnanam, et al; Australia	45	66%	93%	55%
Guajardo, et al; World Wide Registry	39	38%	64%	26%

Spergel et al. *J Pediatr Gastroenterol Nutr.* 2009; 48(1):30-36.
Sugnanam et al. *Allergy*. 2007; 62(11):1257-1260.
Guajardo et al. *J Pediatr.* 2002; 141:576-581.
Assa'ad et al. *J Allergy Clin Immunol*. 2007; 119:731-738.

EoE and IgE Mediated Food Allergy in Children

- Prevalence in U.S. children (Sampson)
  - 2%-8% under 3 years of age
  - 3% aged 3 years and older
- Children with EoE
  - Majority have food allergy
    - Improvement with elimination diets
    - IgE-mediated sensitization
  - Food-induced anaphylaxis
    - 5.7% of 620 children - Spergel (Philadelphia):
    - 9% of 89 children - Assa'ad (Cincinnati):
    - 24% of 45 children - Sugnanam (Australia):

Sampson. J Allergy Clin Immunol. 2004; 113(5):805-819.
Spergel et al. J Pediatr Gastroenterol Nutr. 2009; 48(1):30-36.
Sugnanam et al. Allergy. 2007; 62(11):1257-1260.
Assa'ad et al. J Allergy Clin Immunol. 2007; 119:731-738.

EoE and Atopy in Adults

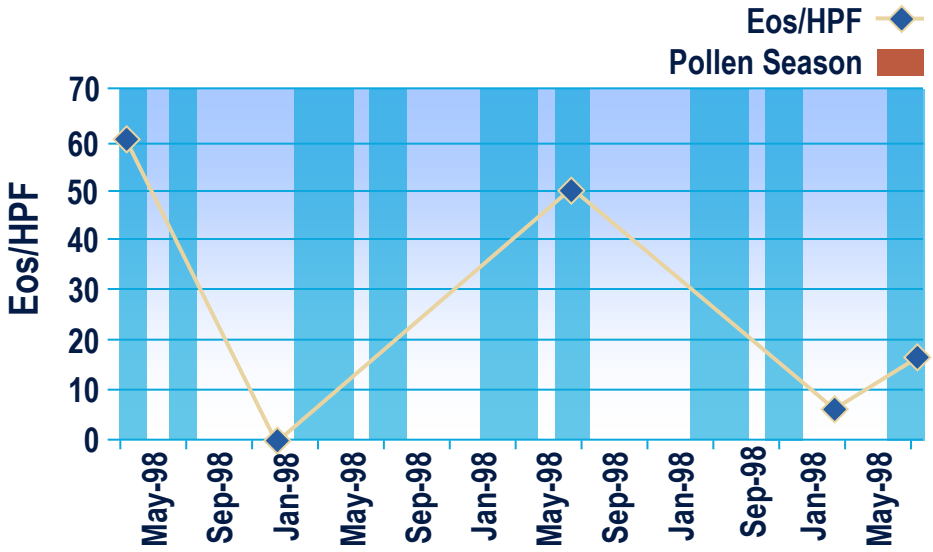
- Adults
  - 20% have allergic rhinitis
  - 6.7% have asthma
  - 4% have food allergy
- Associated atopy with EoE
  - 31 adults, 68% had asthma, atopic dermatitis or allergic rhinitis (Simon)
  - 23 patients, 78% had sensitivity to aeroallergens (allergic rhinitis) and 82% had specific IgE to foods (Roy-Ghanta)

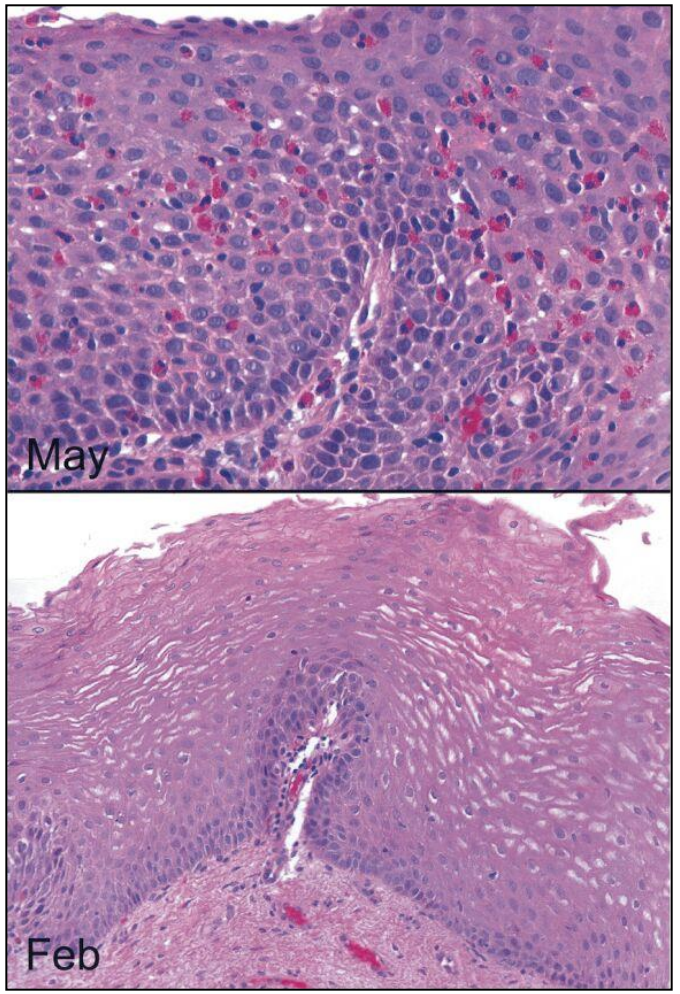
Simon et al. *J Allergy Clin Immunol*. 2005; 115:1090-1092.
Roy-Ghanta et al. *Clin Gastroenterol Hepatol*. 2008; 6:531-535.

Association with Environmental Allergies

Seasonal Variation in EoE

20 year old female, history of multi-sensitization to aeroallergens. Symptoms of allergy and EoE peaked during pollen season.





Fogg et al. *J Allergy Clin Immunol*. 2003; 112(4):796-797.

Seasonal Diagnosis

- New diagnosis of EoE in Iowa
- Decrease in winter (out of pollen season)

TABLE 1. Number of Newly Diagnosed EoE Patients and Number of Eosinophils/hpf Based on Seasons

	SPRING	SUMMER	FALL	WINTER
No. EoE patients	65	69	58	42
Mean*	32.4	39.1	36.7	29.7
Median*	30.0	35.0	30.0	24.5
Standard deviation*	17.1	20.6	17.0	13.9
Range*	15-100	15-100	15-80	15-70

*Eosinophils/hpf.

Wang et al. *J Clin Gastroenterol.* 2007; 41:451-453.

Pollen and EoE

- Study Population
  - 38 patients without GERD but with atopy
    - 16 with allergic rhinitis
    - 22 with allergic rhinitis and asthma
  - 25 controls without GERD without atopy
  - 24 patients with GERD without atopy
- Endoscopy during grass pollen season

Onbasi et al. *Clin Exp Allergy.* 2005; 35:1423-1426.

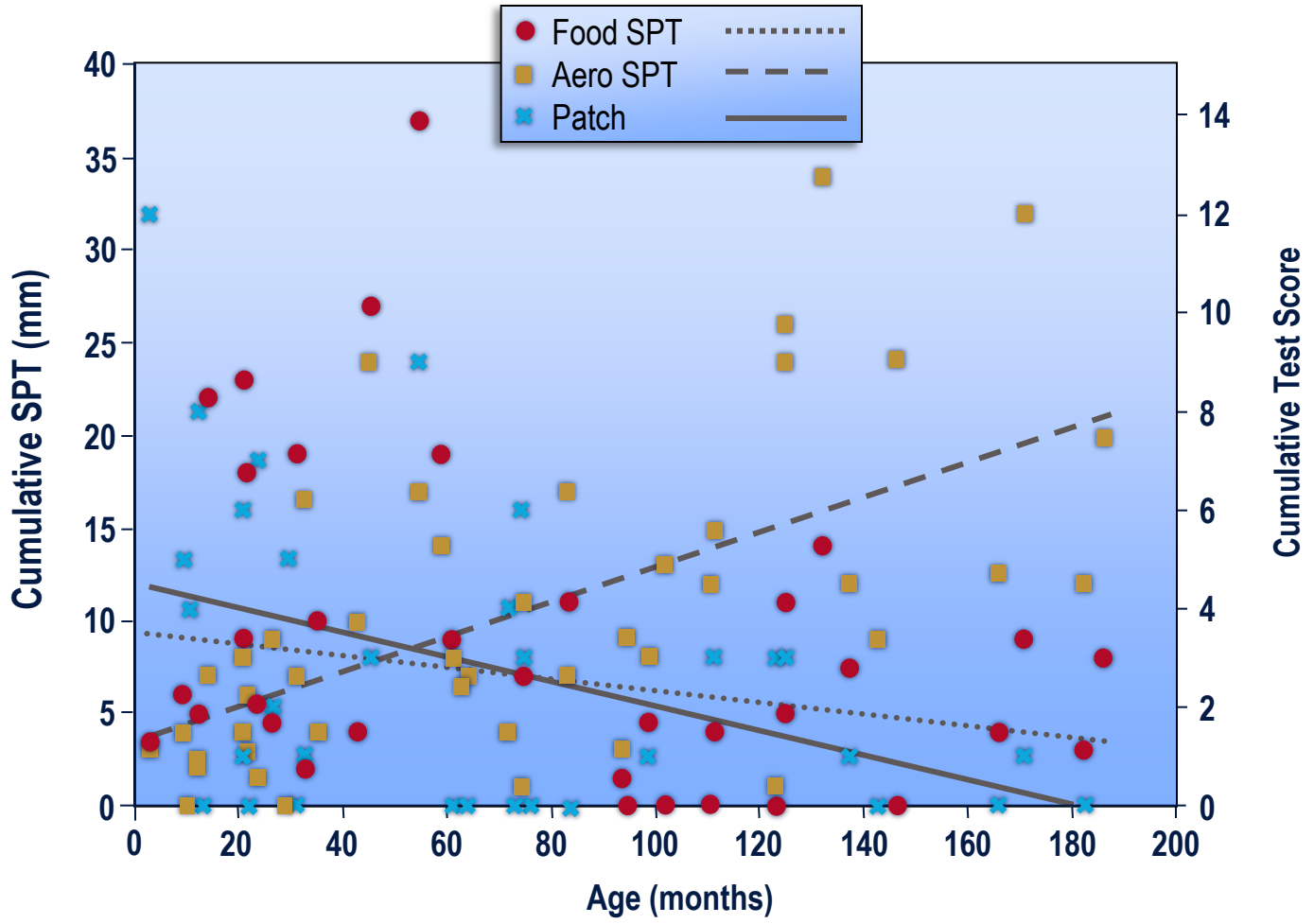
Pollen and EoE

- Esophageal eosinophils were found in
  - 0 control patients
  - 10 (26%) with allergic rhinitis
  - 5 (21%) of GERD patients

- Eosinophils per HPF
  - 5.5 ± 7.3 in allergic rhinitis patients
  - 1.7 ± 1.5 in GERD patients

Onbasi et al. *Clin Exp Allergy*. 2005; 35:1423-1426.

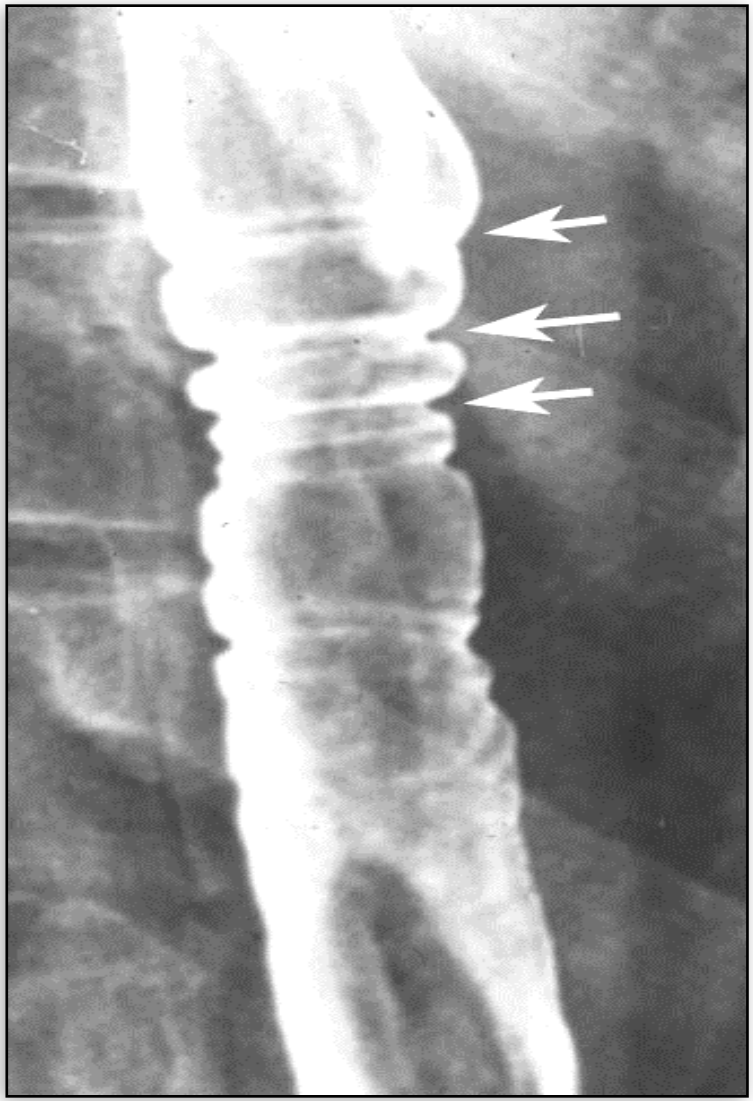
Sensitization to Foods/Inhalants in EoE



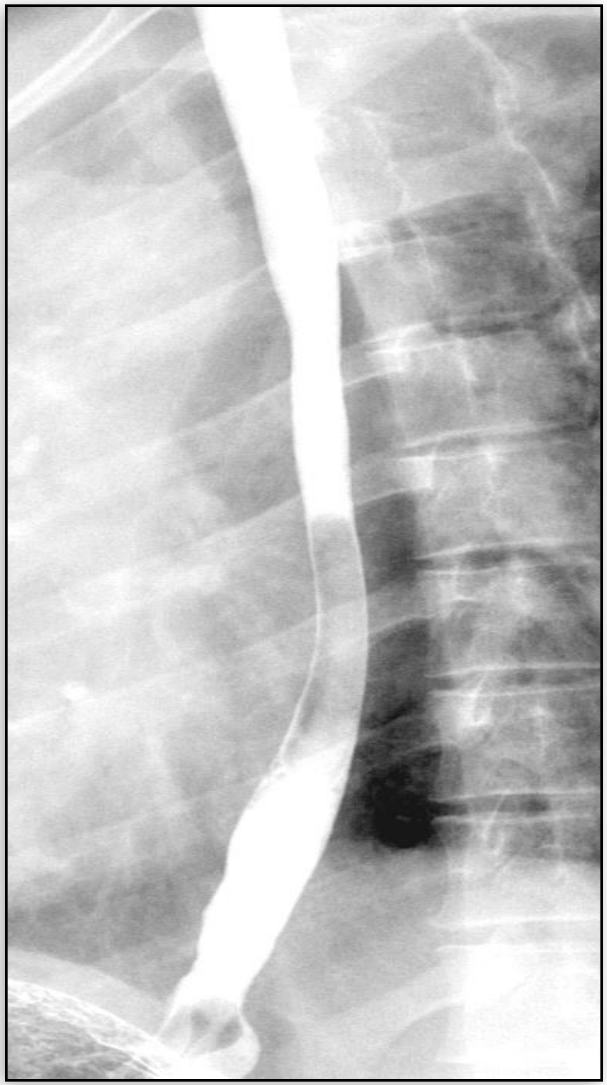
Sugnanam et al. *Allergy*. 2007; 62(11):1257-1260.

Radiologic Findings

Esophageal Rings

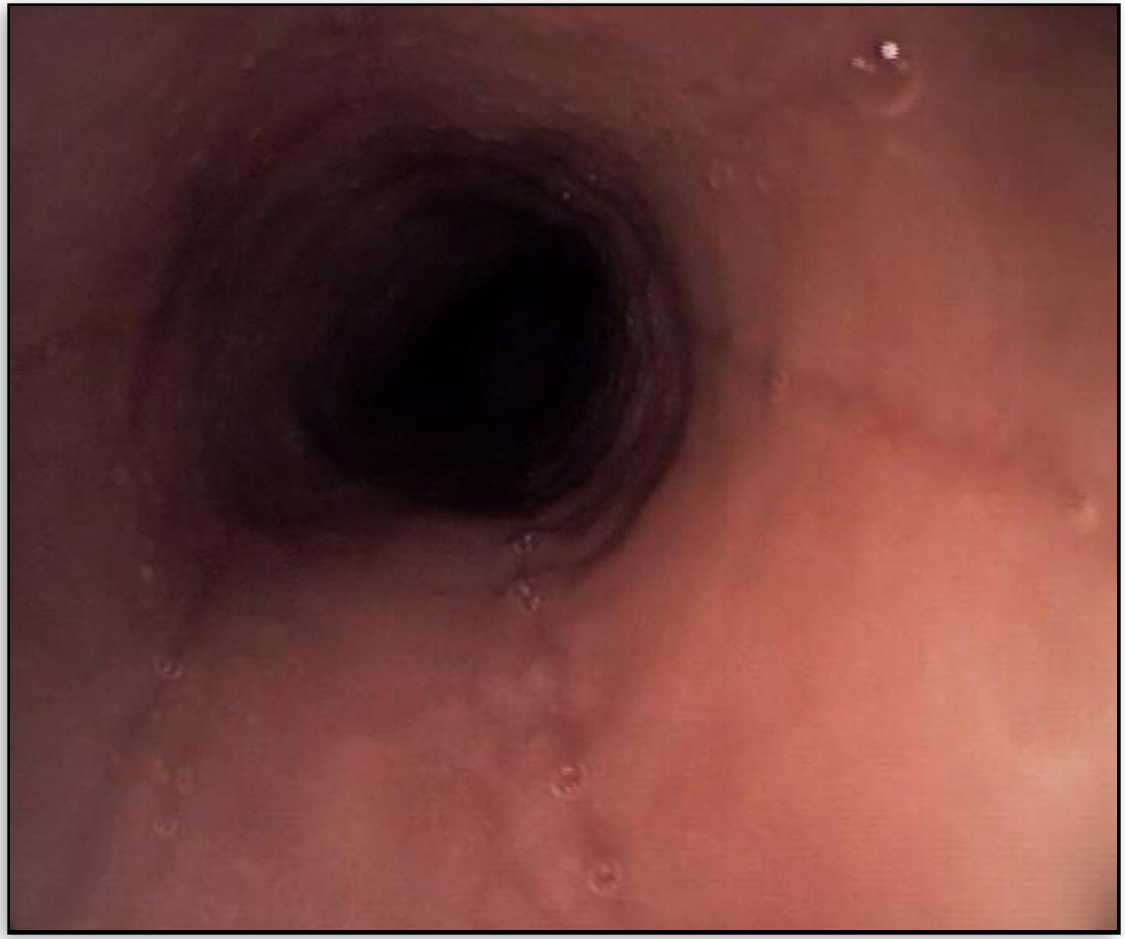


Small Caliber Esophagus

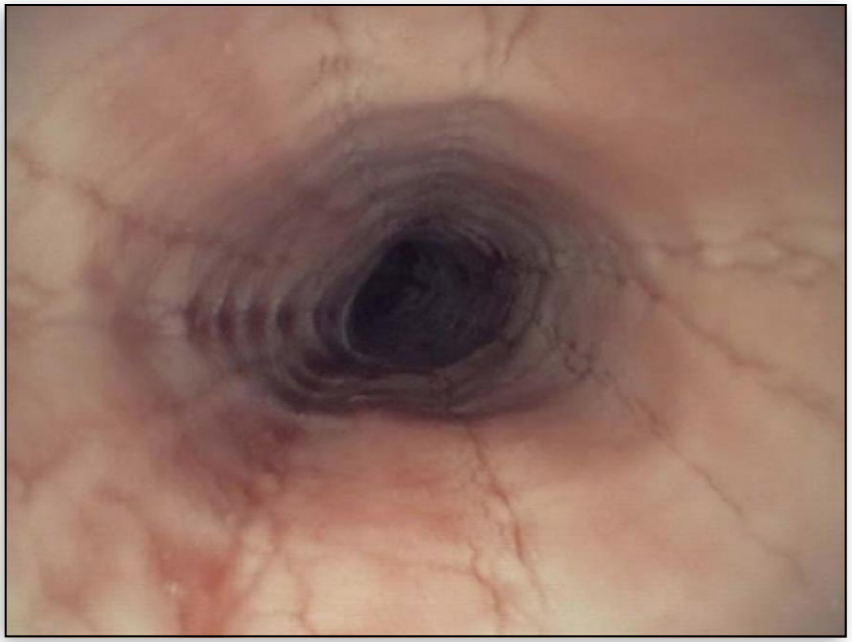


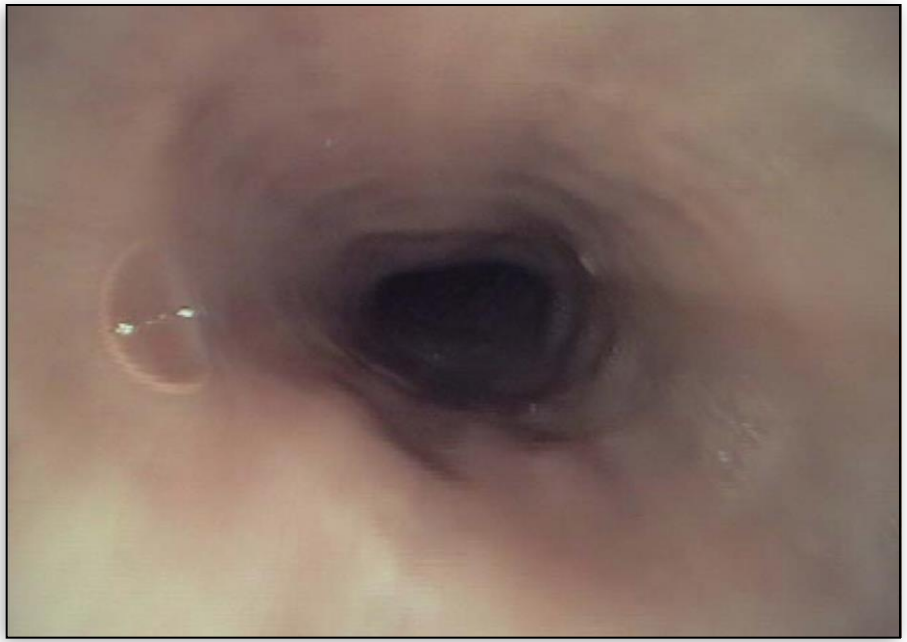
Endoscopic Findings

Esophageal Furrowing

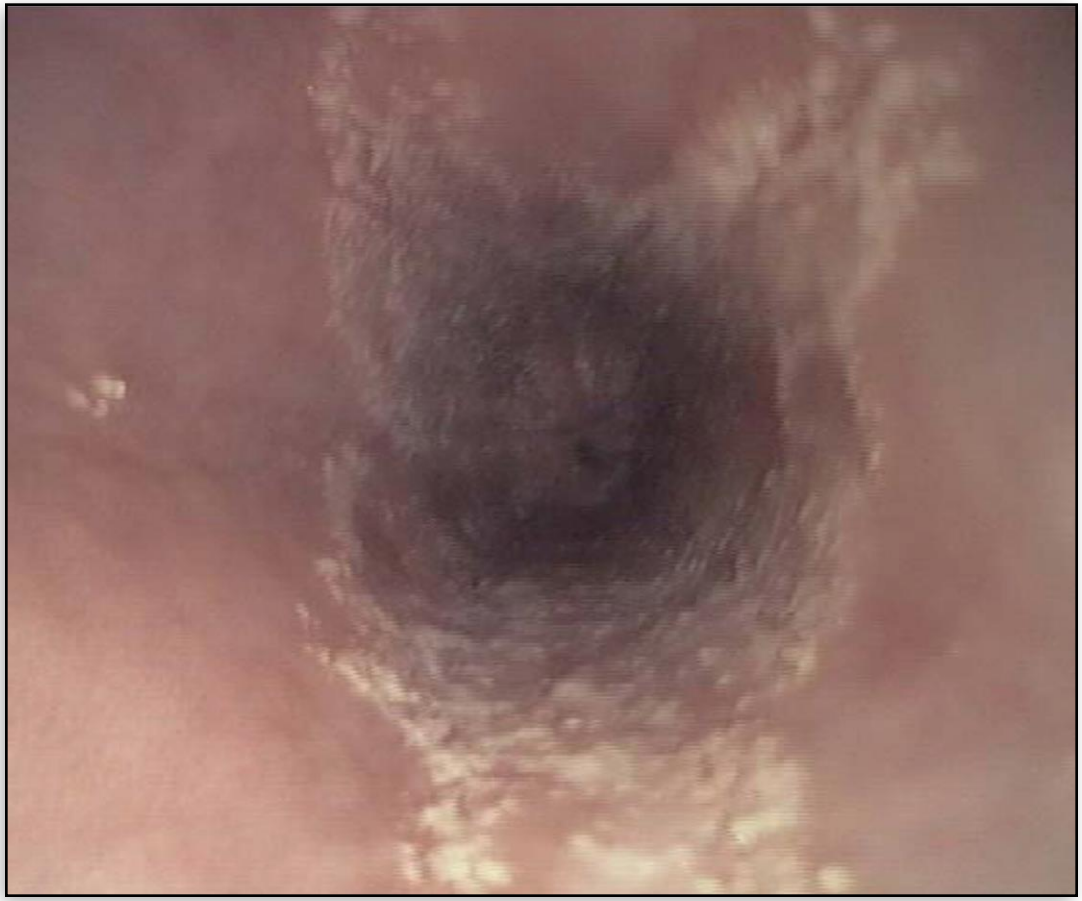


Esophageal Furrowing Before & After Treatment

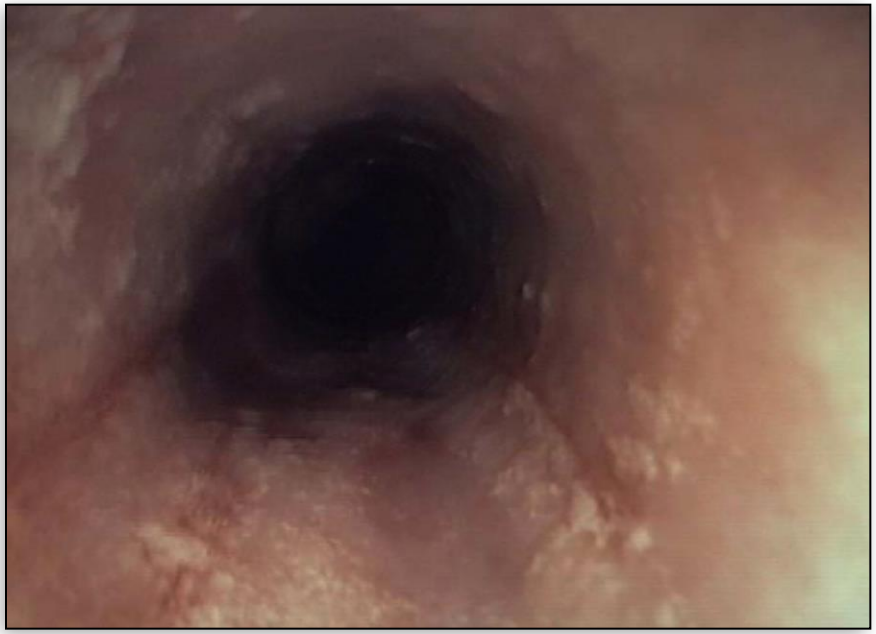


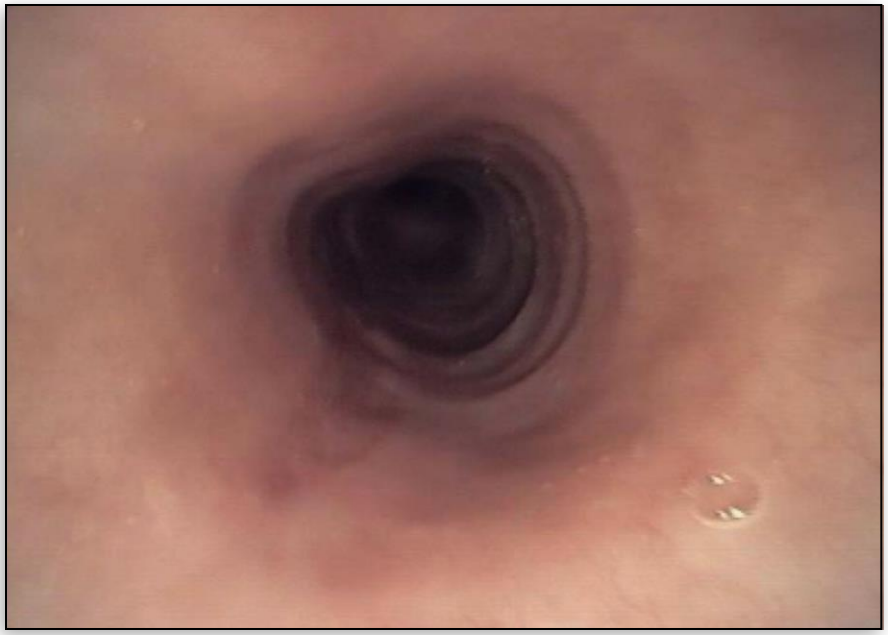


White Plaques

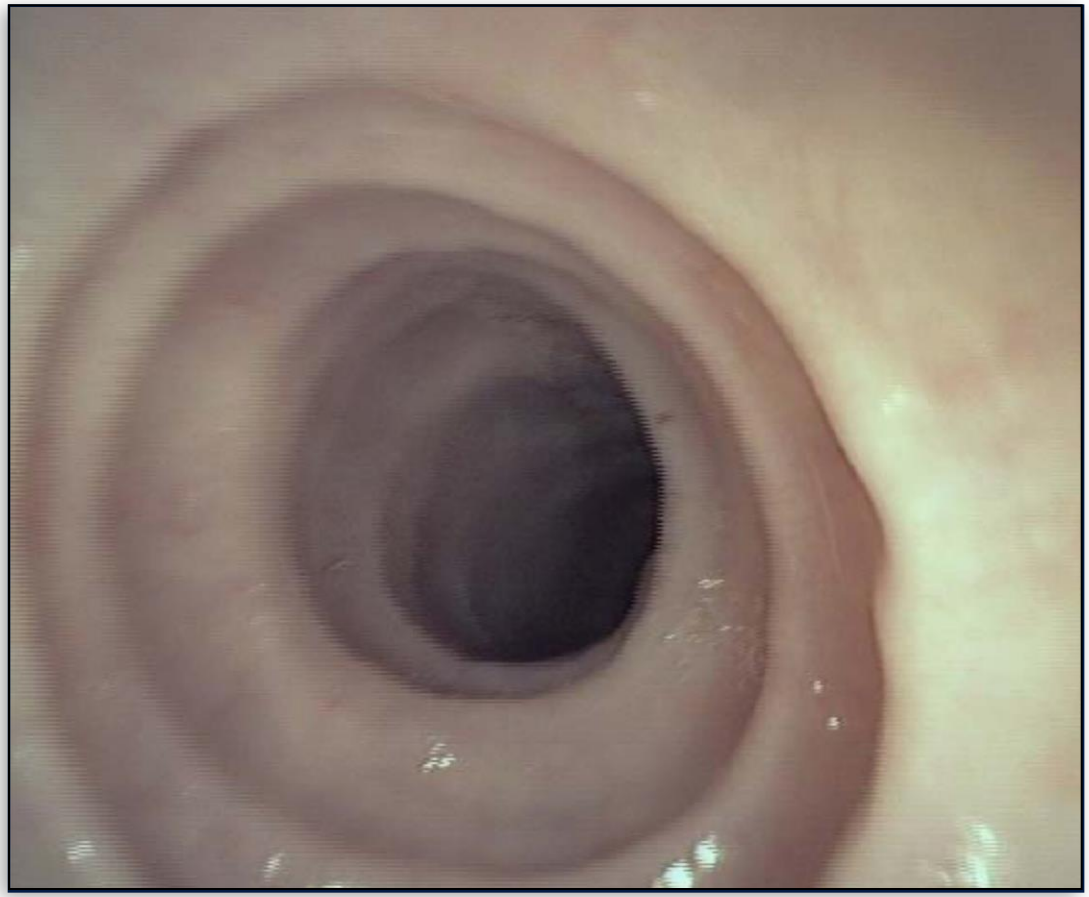


White Plaques
Before and After Treatment

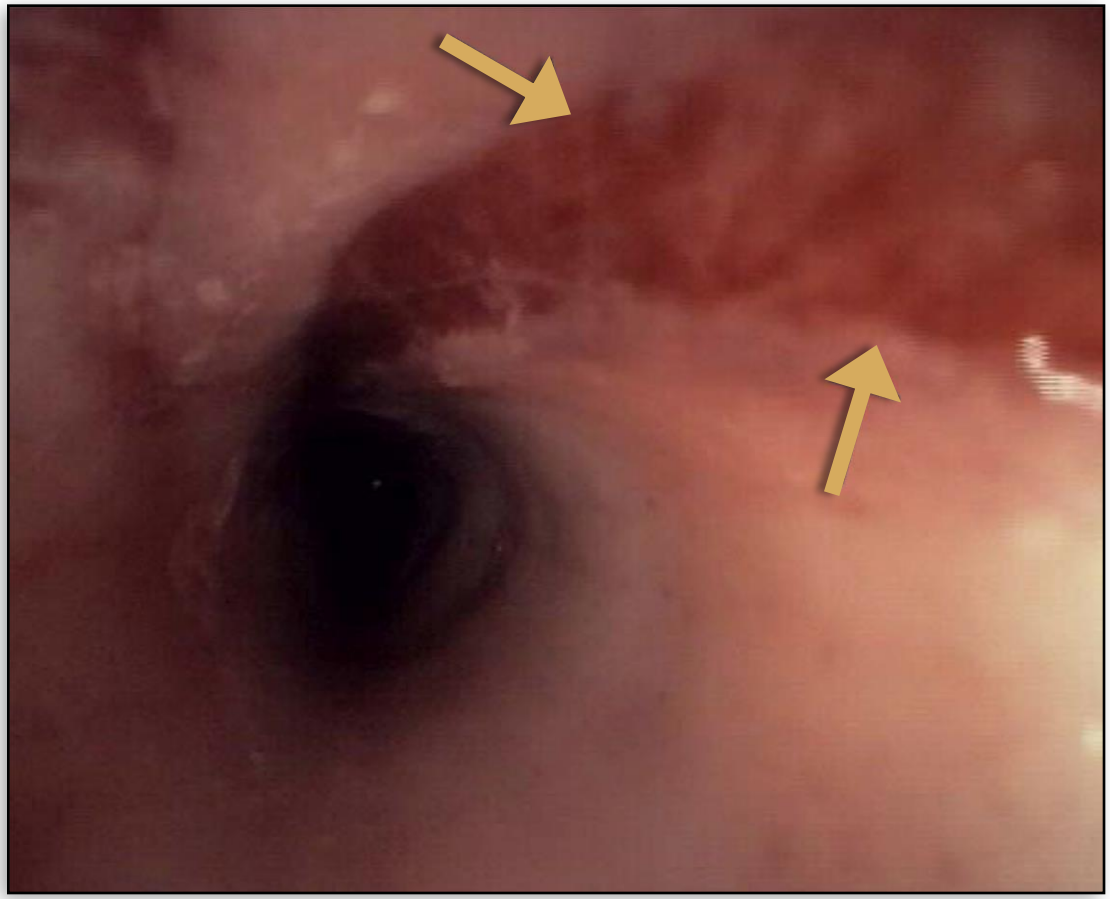




Esophageal Rings



Esophageal Fragility



Prevalence of Endoscopic Findings

Pooled prevalence (%)	Rings	Stricture	Narrow caliber	Linear furrows	White plaques	Decreased vasculature	Normal
All studies	44	21	9	48	27	41	17
Adults	57	25	9	48	19	18	15
Children	11	8	11	46	36	58	21
Retrospective	39	22	9	44	22	36	20
Prospective	59	17	11	61	44	57	7

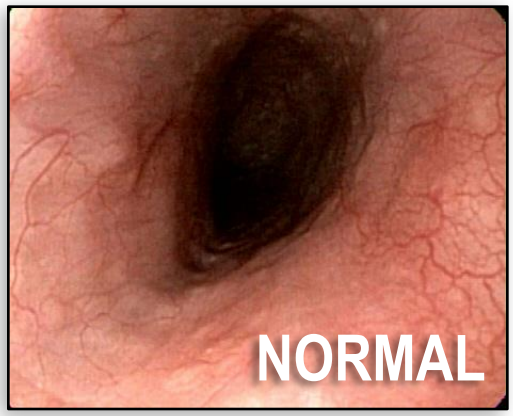
Kim et al. *Clin Gastroenterol Hepatol*. 2012;10(9):988-986.

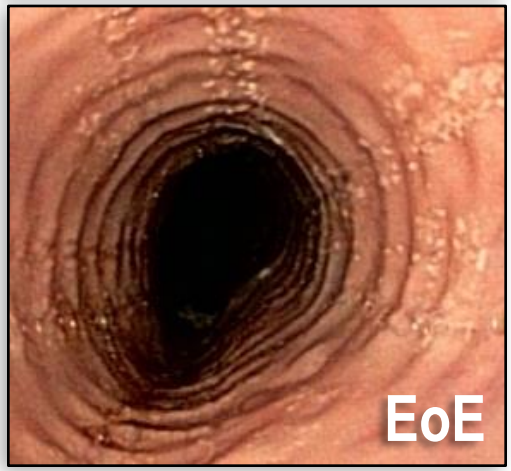
Operating Characteristics

	Rings	Stricture	Linear furrows	White plaques	Decreased vasculature	Abnormal endoscopy
Sensitivity (%)	48	15	40	27	43	87
Specificity (%)	91	95	95	94	90	47
PPV (%)	64	51	73	67	65	42
NPV (%)	84	76	83	74	79	89

Kim et al. *Clin Gastroenterol Hepatol*. 2012;10(9):988-986.

Classification/Grading System for Endoscopically Detected Esophageal Features of EoE -EREFS





Edema (pallor)

Rings ("trachealization")

Exudates (plaques)

Furrows (vertical lines)

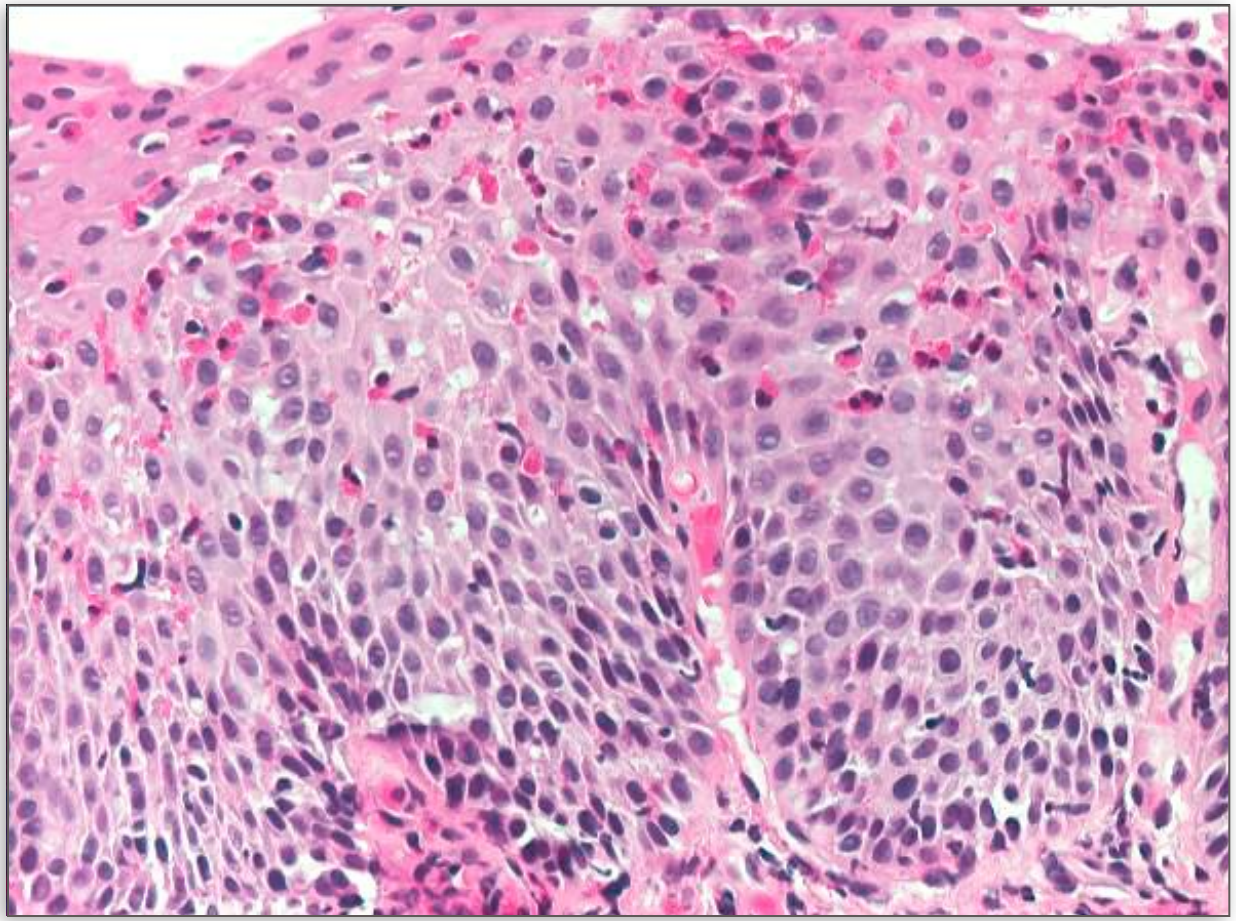
Stricture

- Mucosal fragility
- Narrow caliber esophagus

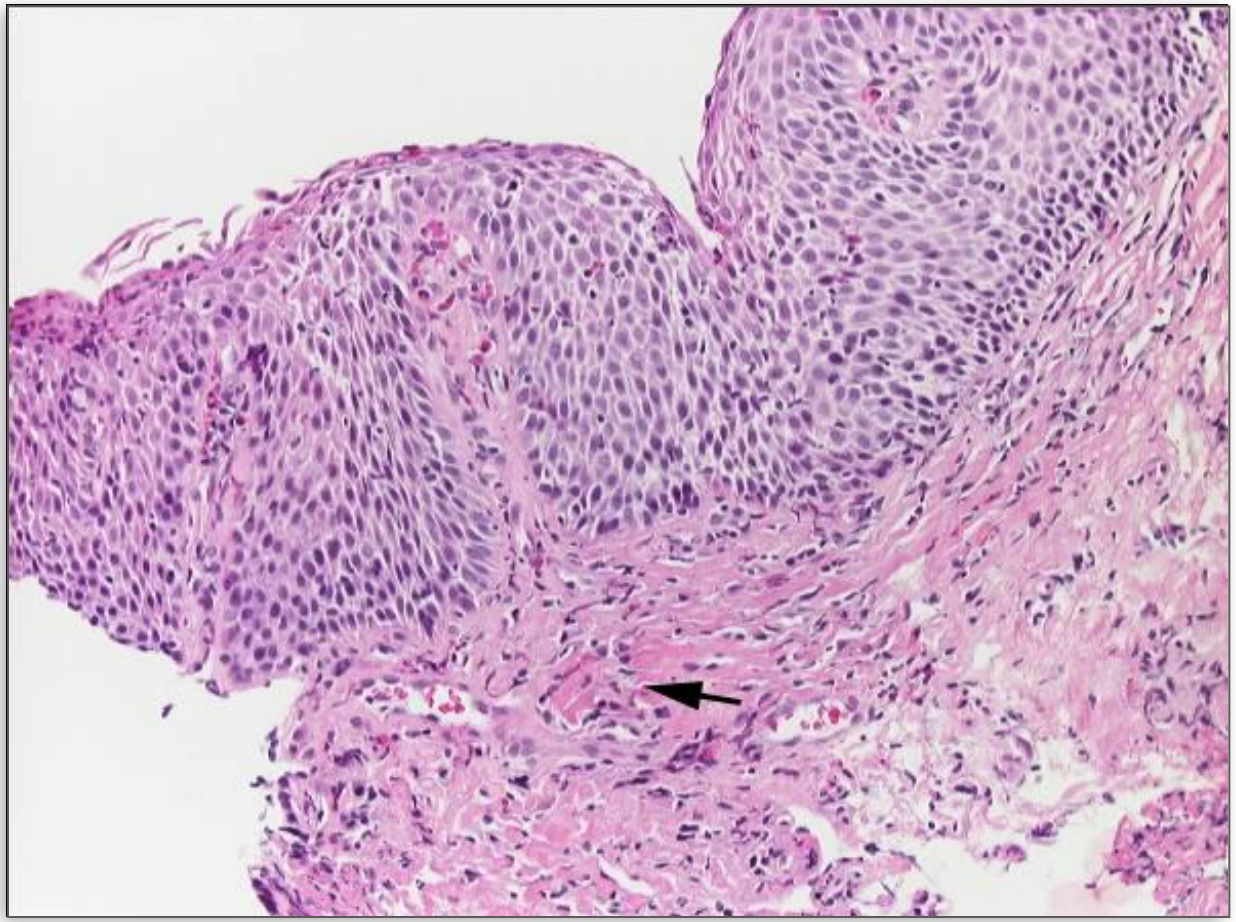
Hirano et al. *Gut*. 2013; 62(4); 489-495.

Histology of EoE

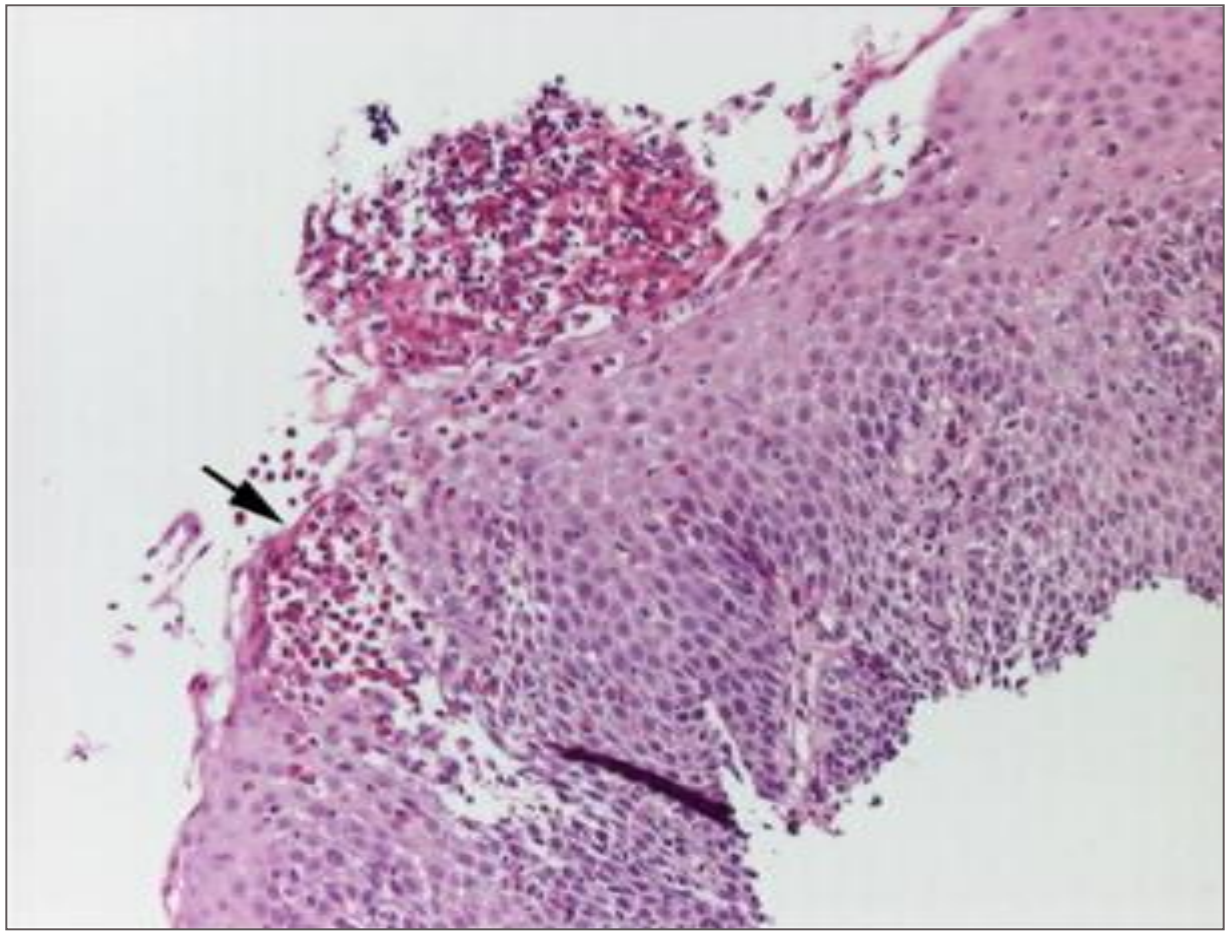
EoE Histology



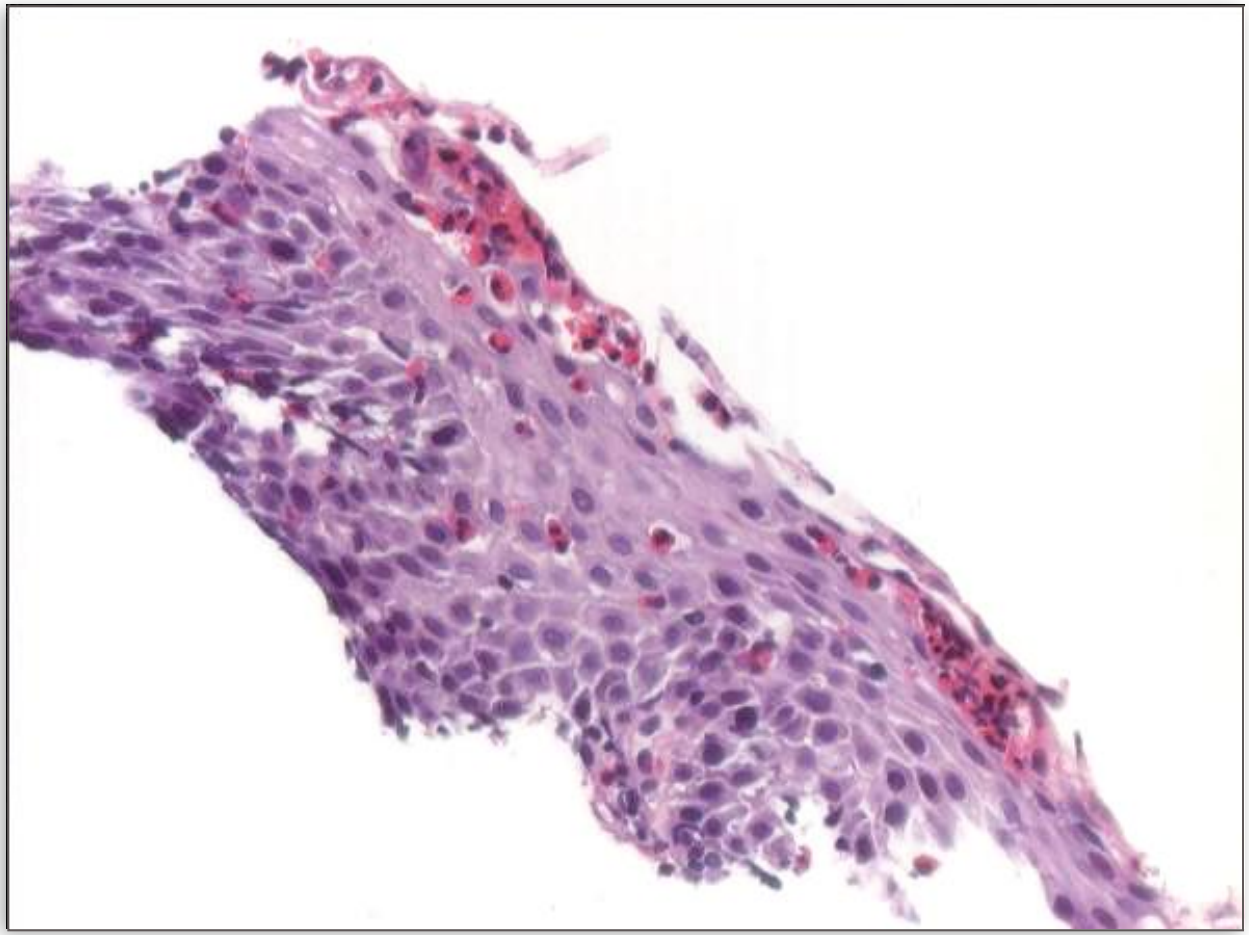
EoE Histology



EoE Histology



EoE Histology

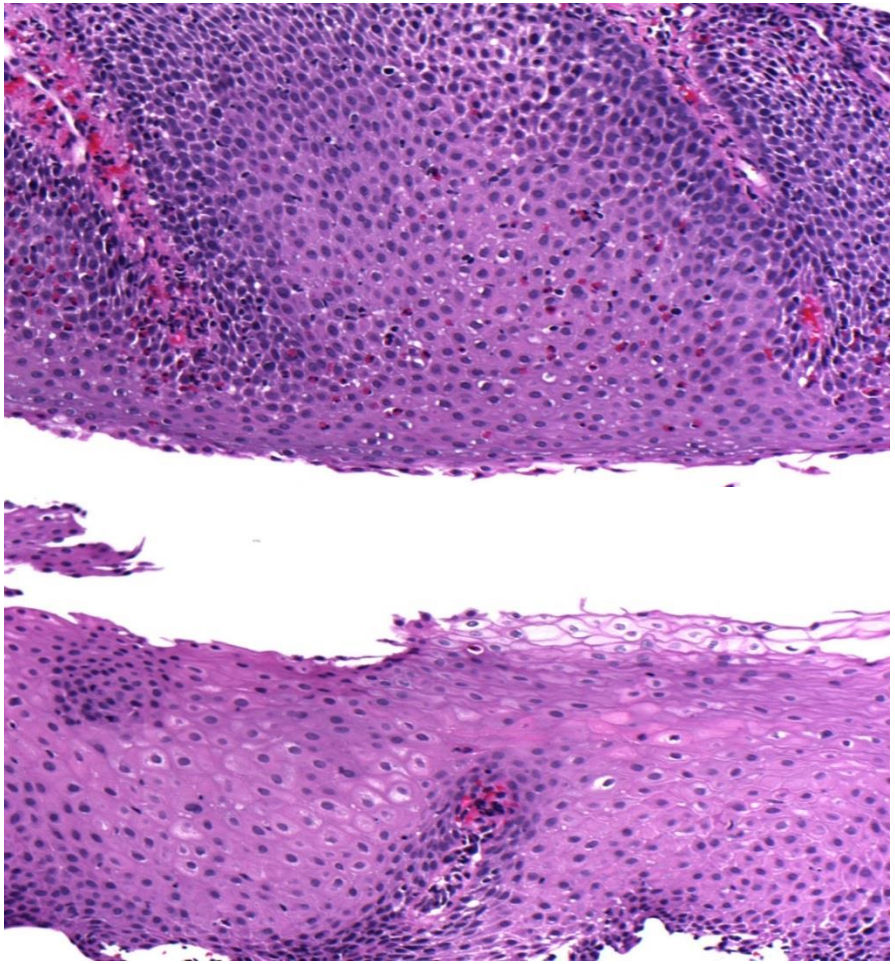


Histology of EoE

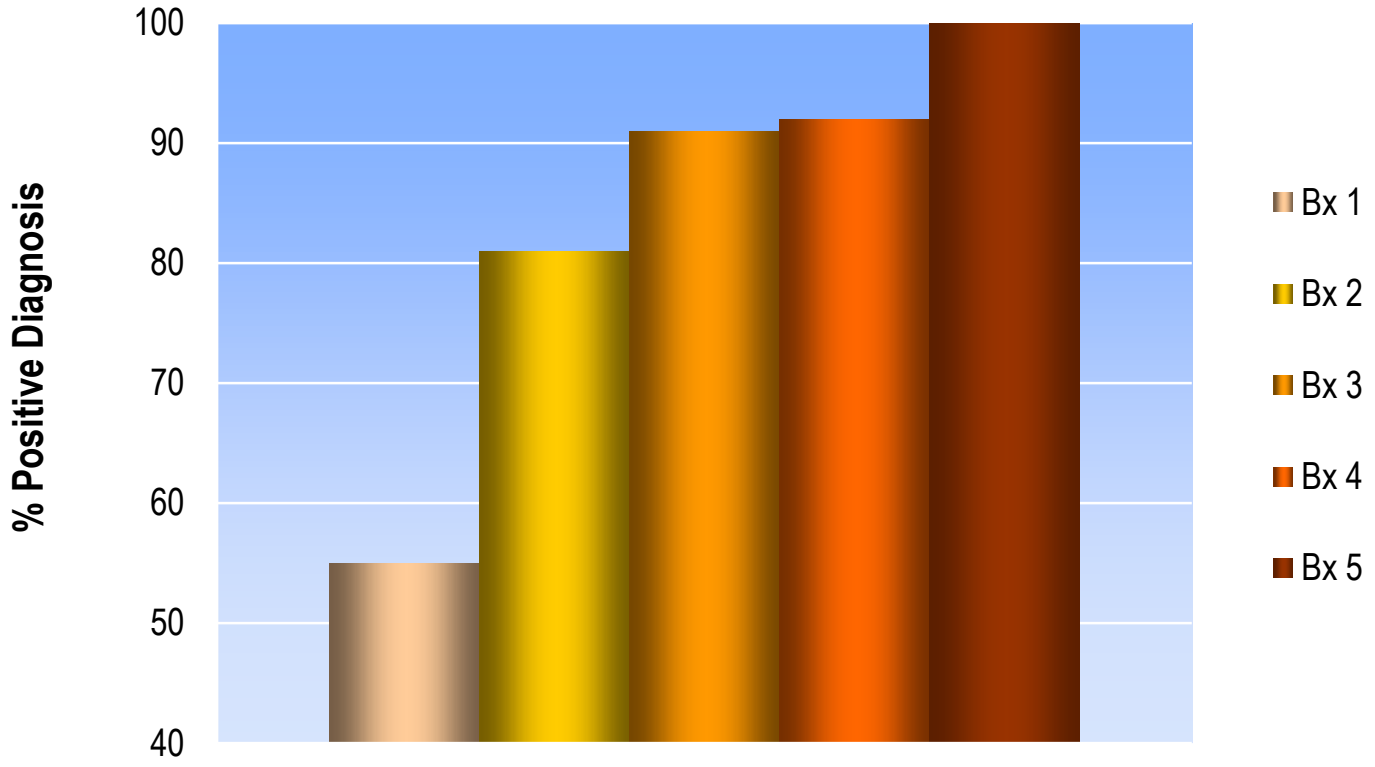
Eosinophilia is often patchy

Multiple biopsies are necessary

EoE currently determined by the number of eosinophils in most affected field

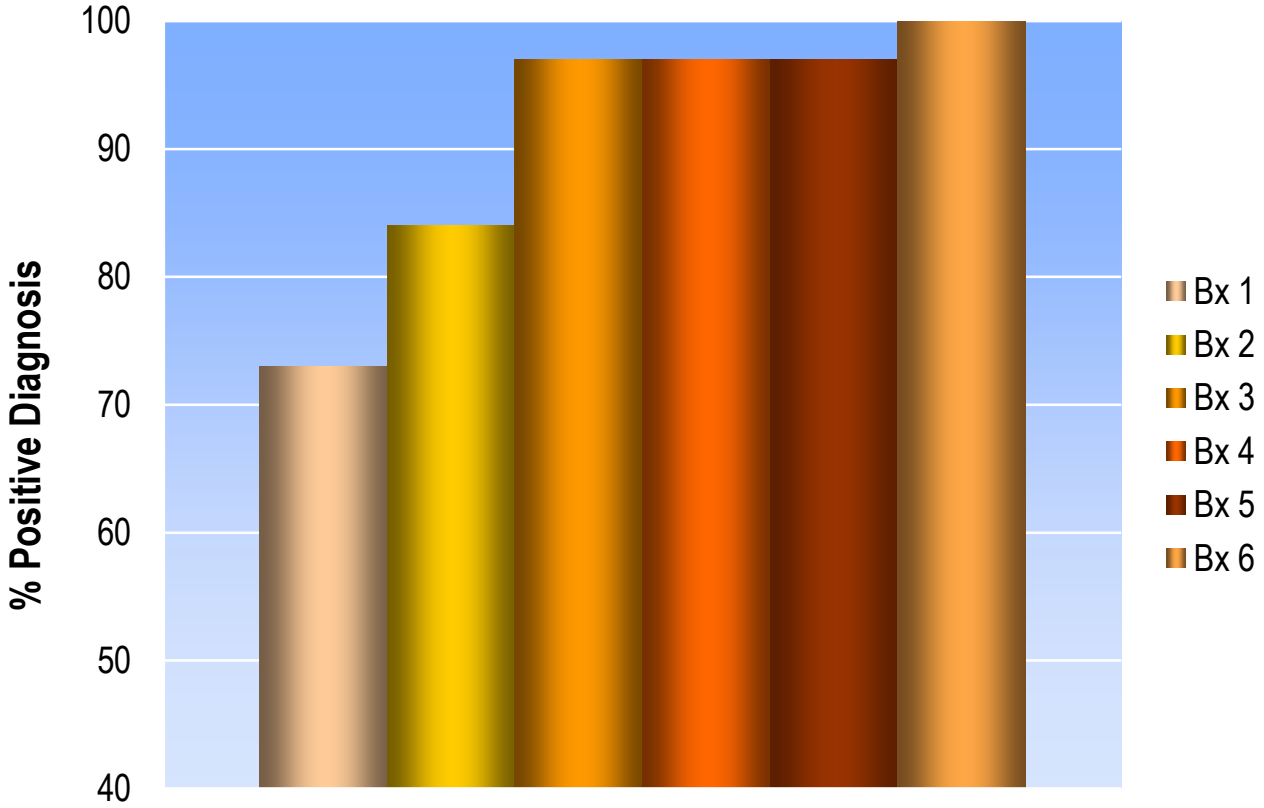


Number of Biopsies to Diagnose Adult EoE



Gonsalves et al. *Gastrointest Endosc.* 2006; 63:13-15.

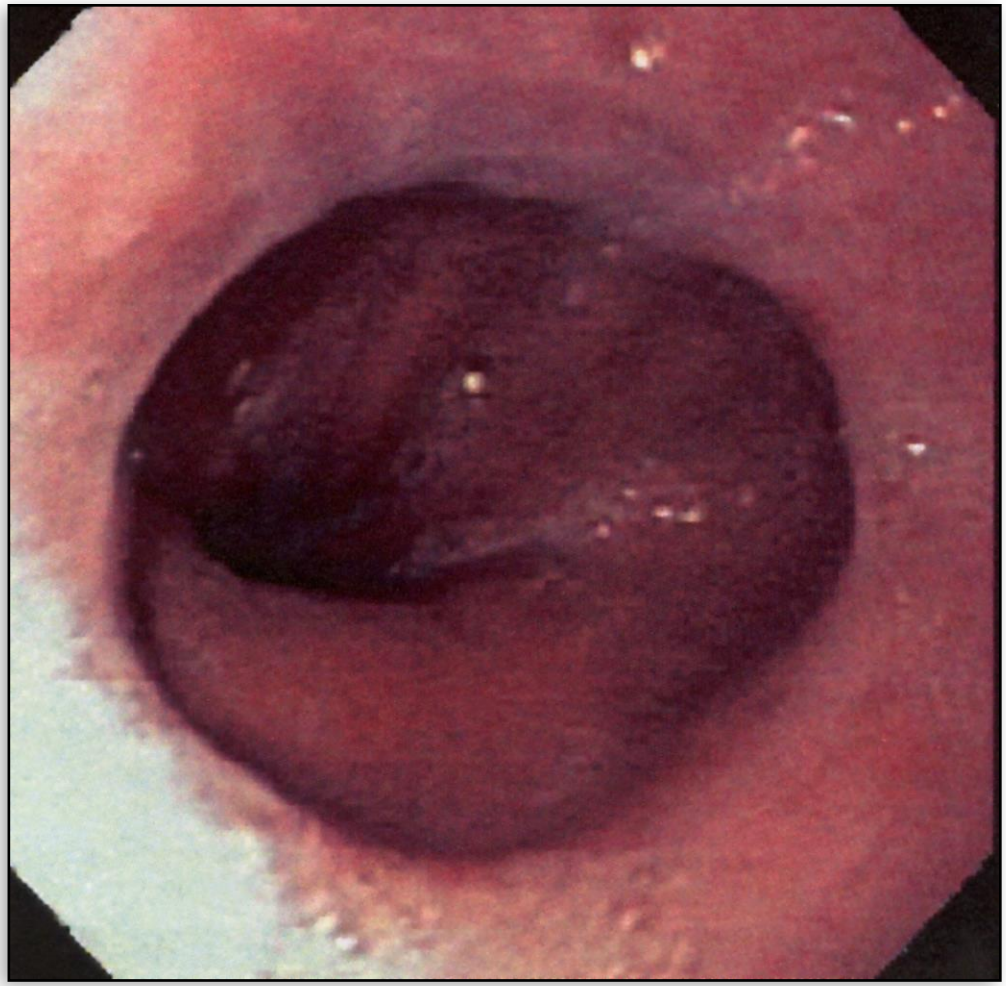
Number of Biopsies to Diagnose Pediatric EoE



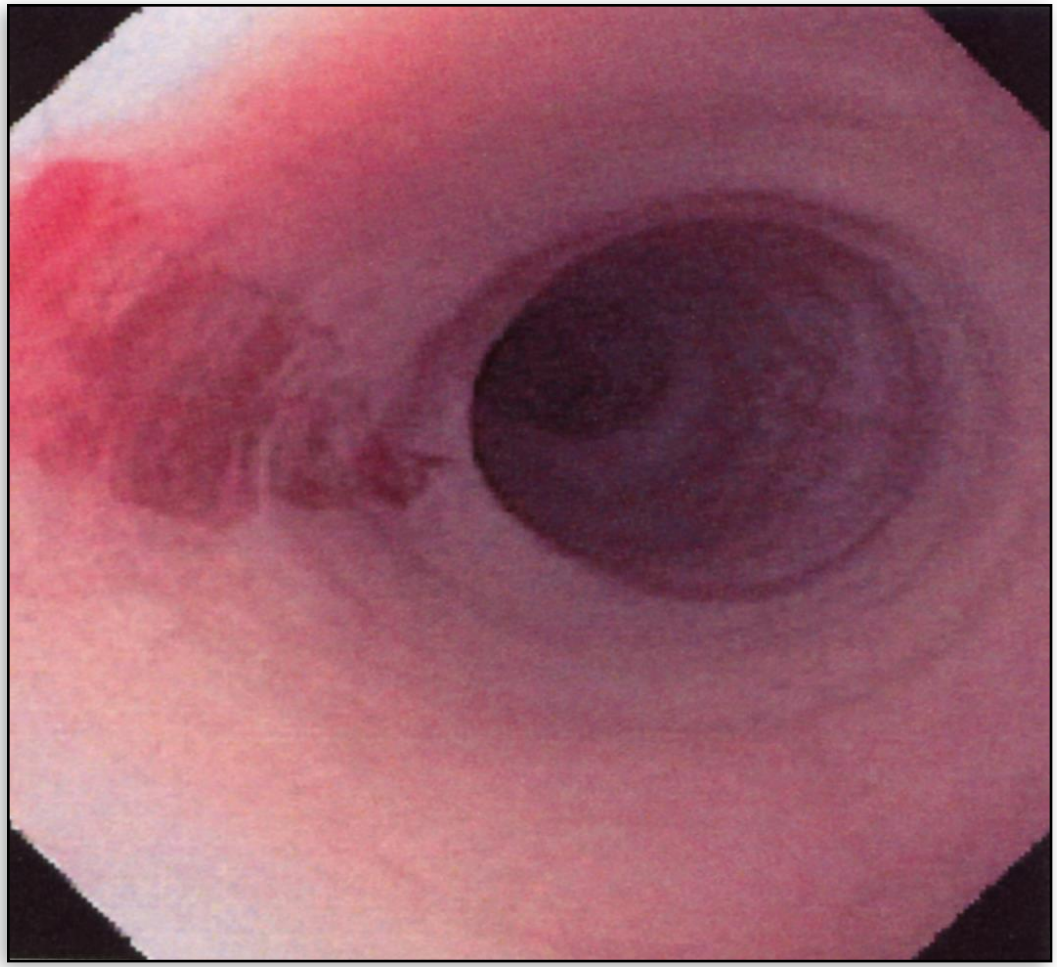
Shah et al. *Am J Gastroenterol*. 2009; 104:716-721.

Complications

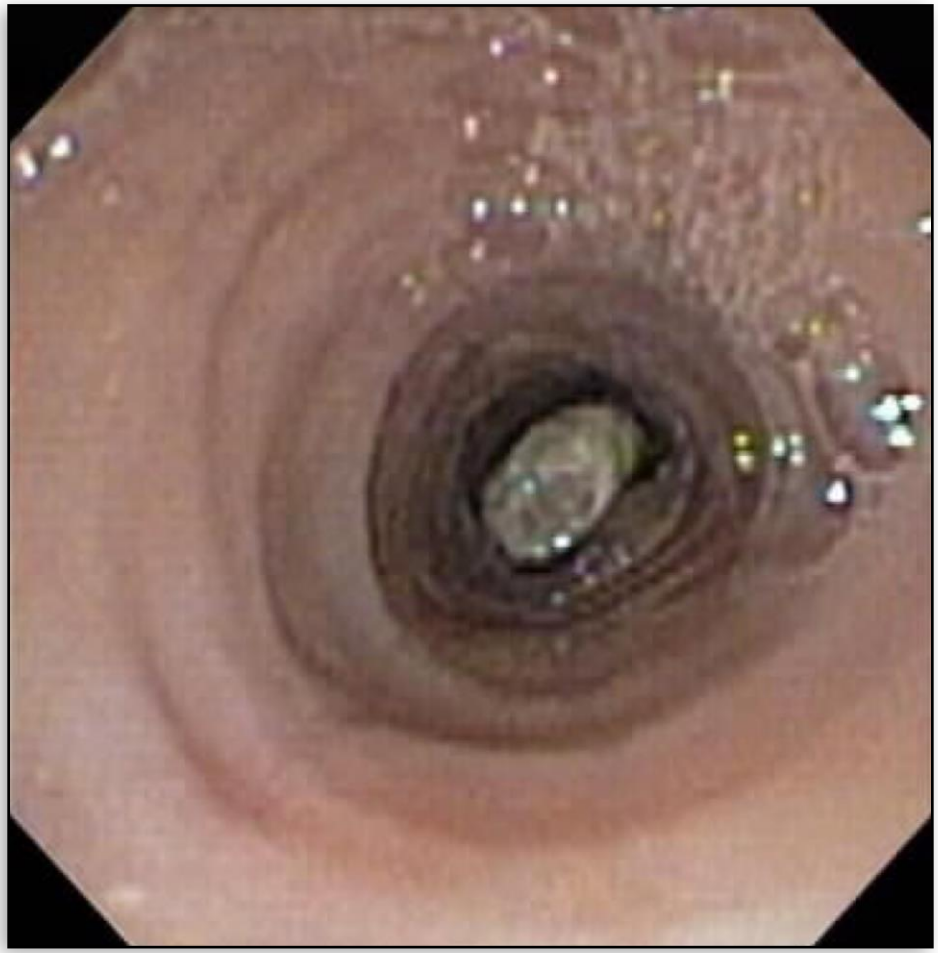
Distal Esophageal Stricture



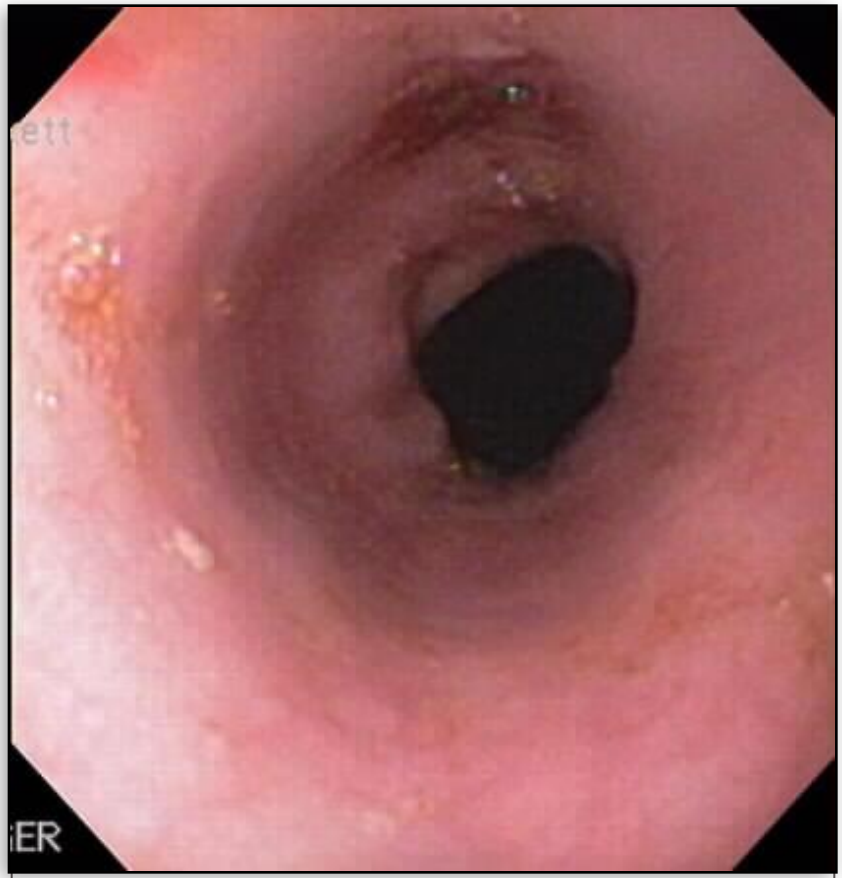
Small Caliber Esophagus

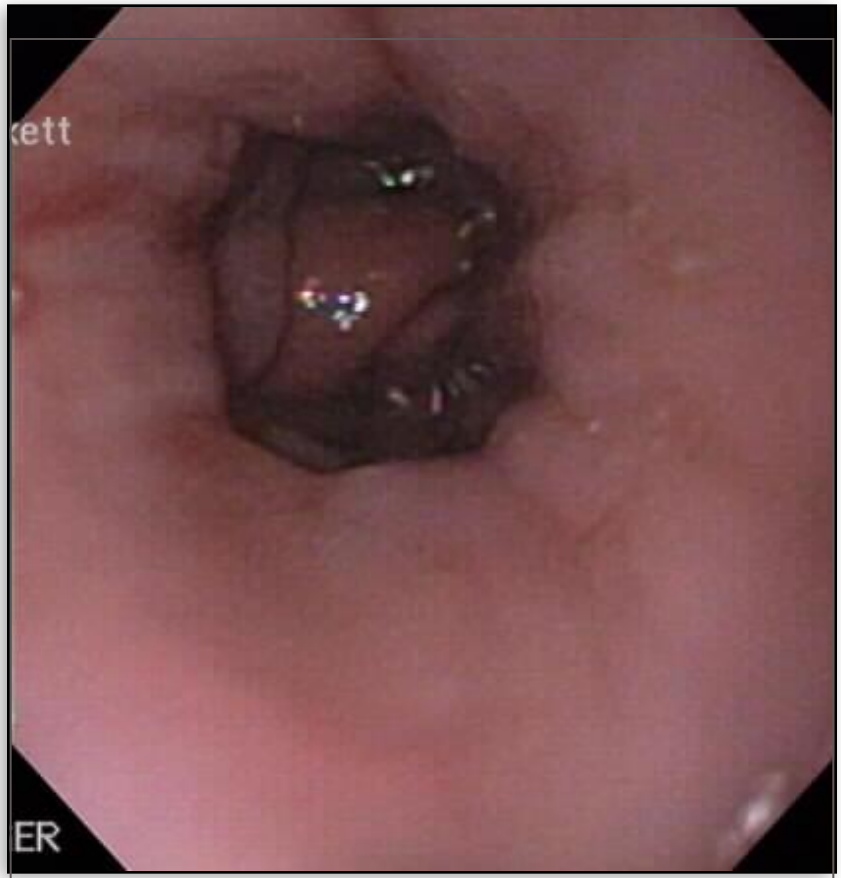


Pill Impaction

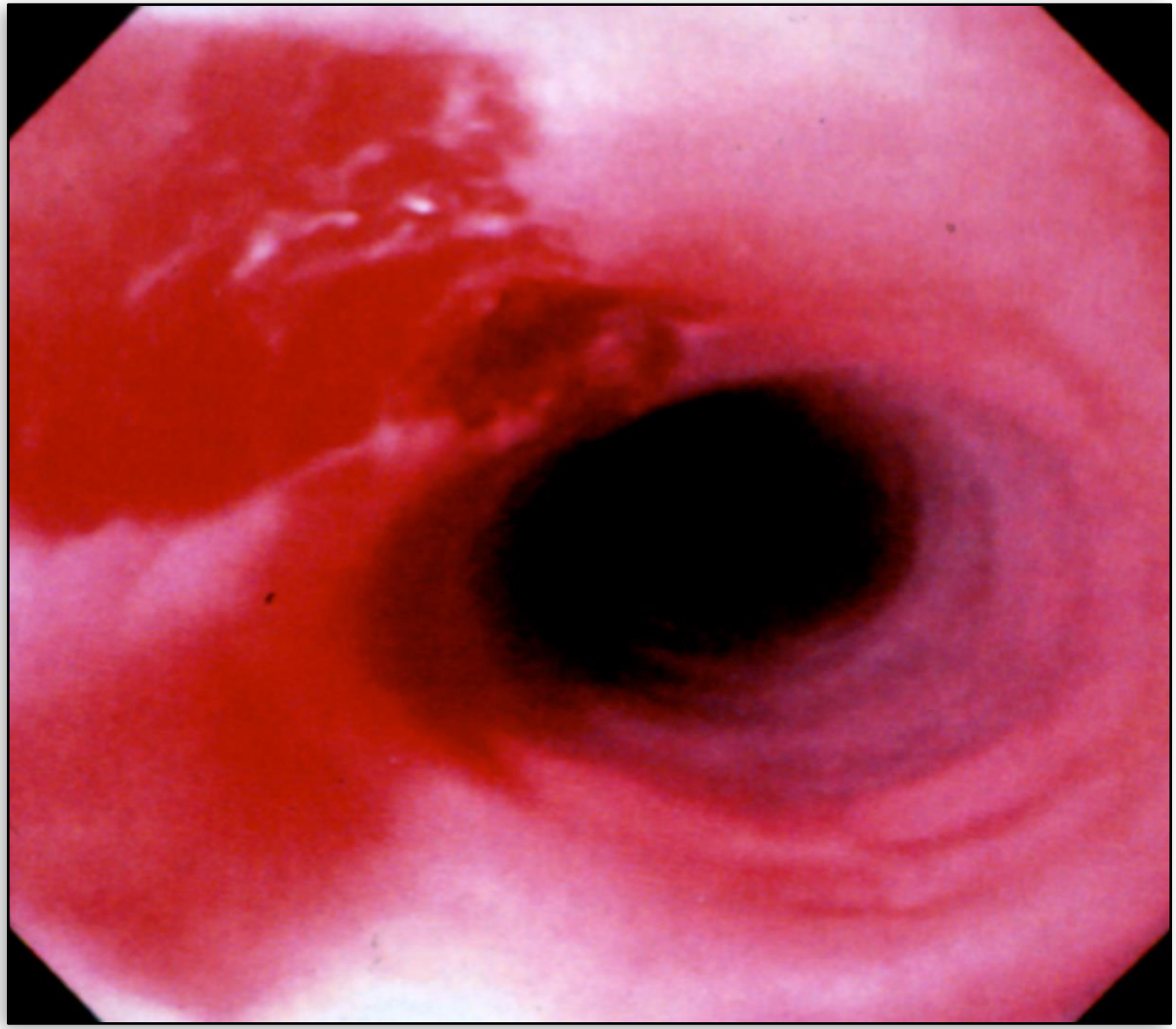


Sliding Hiatal Hernia

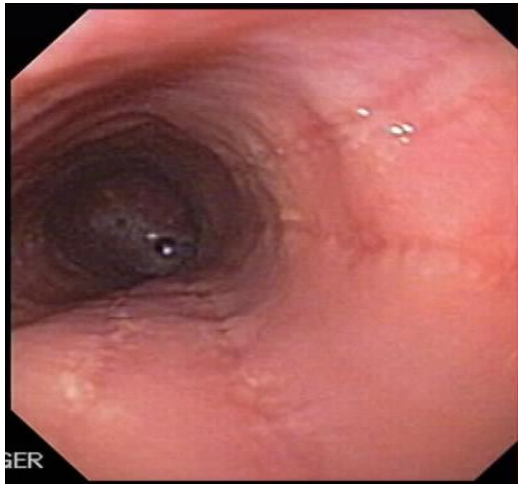




EGD Induced Laceration of Mucosa

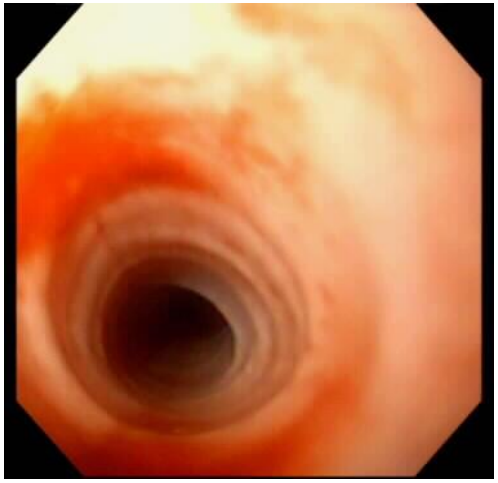


Endoscopic Progression in an Untreated EoE Patient

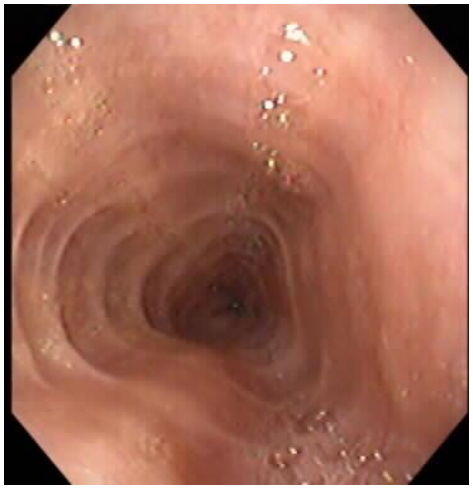


Initial presentation, age 7, with GER symptoms, refused therapy

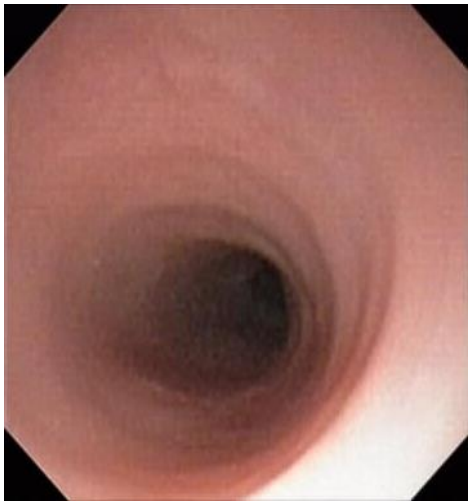
3 years later; intermittent dysphagia; refused therapy



1 week after treatment with solumedrol - symptoms and histology significantly improved



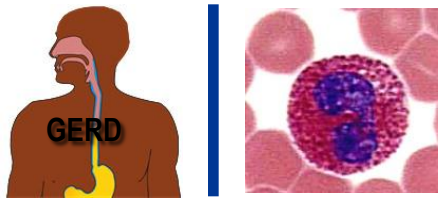
5 years after initial presentation; severe daily dysphagia – treated with systemic steroids

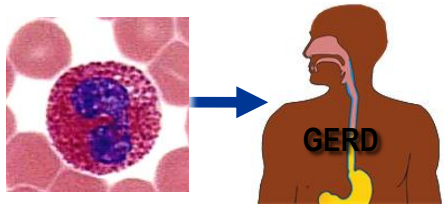


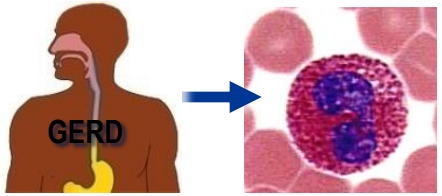
Treatment with PPIs

Rationale for PPI Therapy

- GERD causes eosinophilia
  - Usually less than 7 eosinophils/hpf but can be greater
- GERD and EoE co-exist but are unrelated
  - 20% to 40% of adults have GERD
- EoE contributes to or causes GERD
  - Eosinophil secretory products alter esophageal motility, permeability, and fibrosis causing secondary GERD
- GERD contributes to or causes EoE
  - Increased esophageal permeability results in exposure of deep epithelial layers to antigens
- A trial of proton pump inhibitors (PPI's), even when diagnosis of EoE appears clear-cut, is always recommended







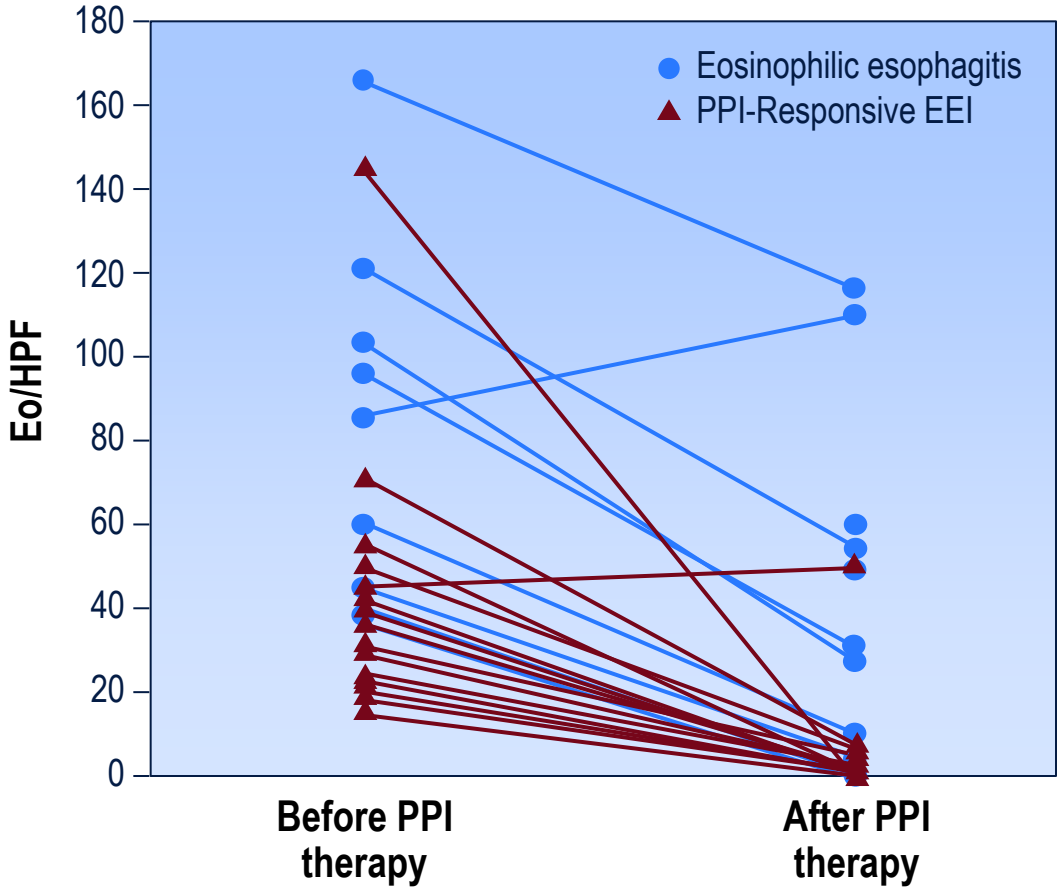
Spechler et al. *Am J Gastroenterol.* 2007; 102:1301-1306.

Eosinophils Respond to PPI's Adolescents/Young Adults

	Patient 1	Patient 2	Patient 3
Age (yr)/sex	14/M	25/M	13/F
Presentation	Pain	Food impaction	Dysphagia
Environmental Allergies	Yes	Yes	No
Treatment	Omeprazole 10 mg BID	Omeprazole 20 mg BID	Omeprazole 20 mg QD
Eosinophils/hpf			
Before treatment	37	21	59
After treatment	1	3	0

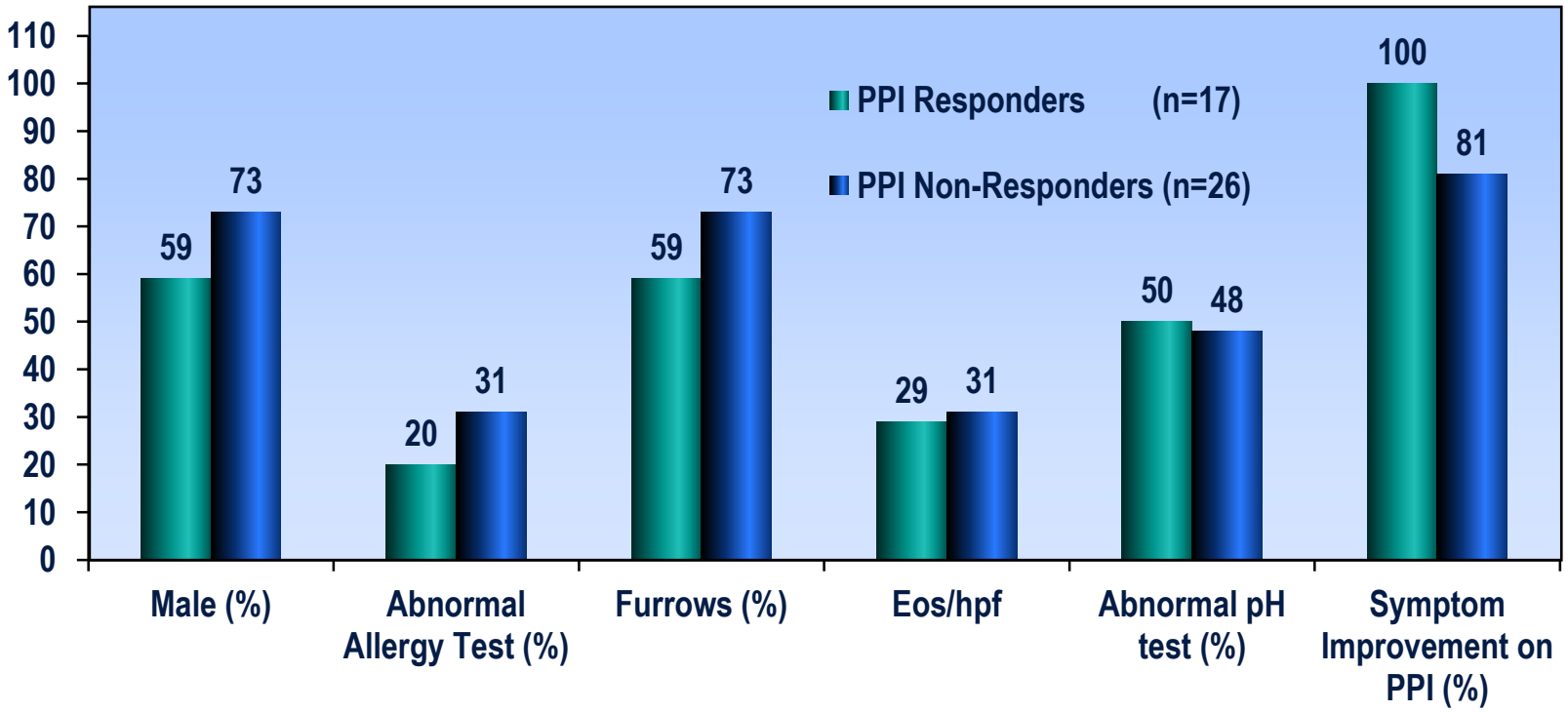
Ngo et al. *Am J Gastroenterol.* 2006; 101:1666-1670.

Eosinophils Respond to PPI's Adults



Molina-Infante et al. *Clin Gastroenterol Hep.* 2011;9:110-7.

Comparing PPI Responders and Non-Responders



Dranove et al. *J Peds. 2009;*154(1):96-100. Slide courtesy of Dr. Hirano.

Esophageal Eosinophils: EoE or GERD

- Retrospective review
  - 40 of 3,648 pts had more than 20 eosinophils/hpf
    - 8 (20%) had confirmed EoE
    - 28 (70%) had GERD
  - No significant difference in maximum number of eosinophils between GERD and EoE
  - No difference in eosinophilic abscesses, surface layering or basal zone hyperplasia

Rodrigo et al. *Am J Gastroenterol.* 2008;103:435.

PPI Therapy and EoE

- Acid suppression with PPI's
  - Important for making the diagnosis of EoE
  - Useful for treating symptoms associated with EoE that may be due to secondary GERD
  - Possible primary therapy for esophageal eosinophilia not related to acid suppression but instead to another, as yet identified, PPI related response
  - Proton pump inhibitor therapy alone, is insufficient for the treatment of EoE

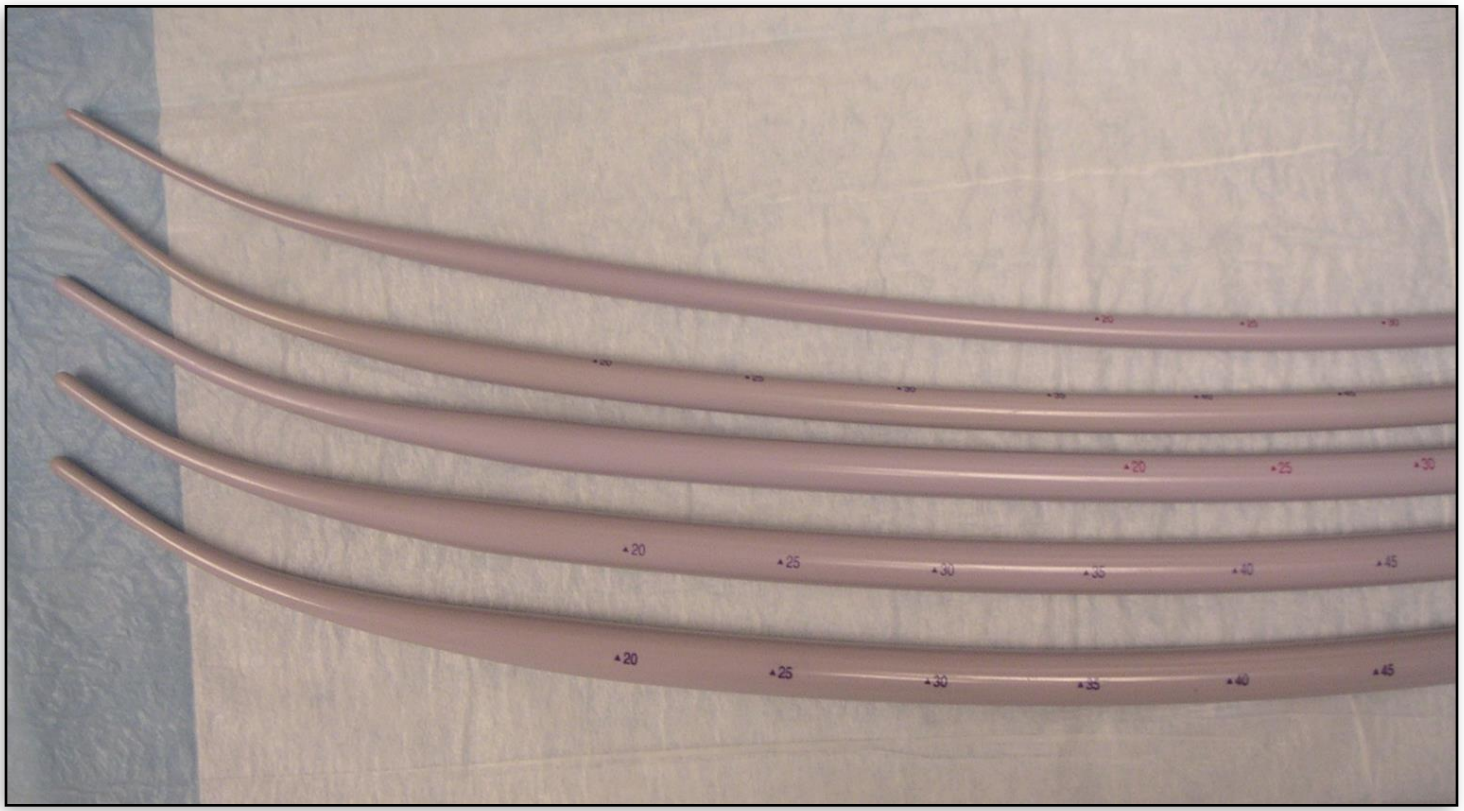
Comparison to GERD

Diagnostic Comparison of the Average Patient with either EoE or GERD

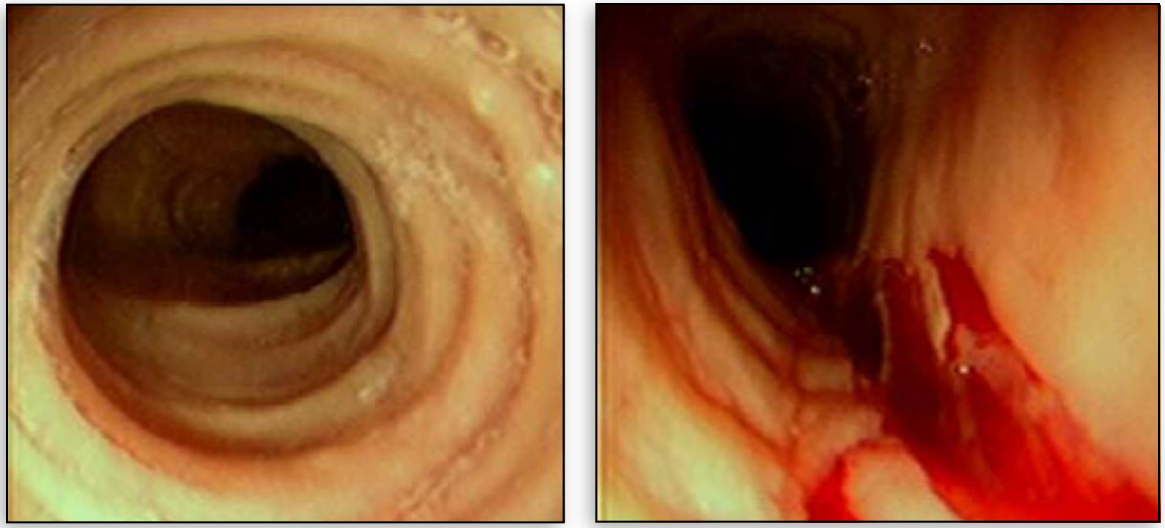
	EoE	GERD
Symptoms	Intermittent	Persistent
pH Probe	Normal	Abnormal
Acid blockade	Unresponsive	Responsive
Endoscopy	Often repeated needed	Typically none or once
Pathology	> 15 eos/hpf	1-5 eos/hpf

Dilation

Savary Esophageal Dilators



Laceration After Dilation in EoE



Hirano C. Foreign Bodies in the Esophagus. In: Shields, LoCicero, Feins, Reed, eds. *General Thoracic Surgery 7th Ed*. Lippincott Williams & Wilkins Publ. Chapter 145.

Esophageal Dilation in EoE Prior to 2008

High Risk of Esophageal Complications

8 cases; 3 dilations
1 perforation with EGD

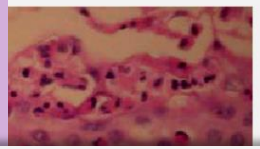
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2003;1:433–437

Endoscopy in Eosinophilic Esophagitis: "Feline" Esophagus and Perfo

MITCHEL
JOSEPH
*Section of
Chicago, Illi

CASE STUDIE

5 dilations
5 large lacerations
with EGD or dilation



Fragility of the esophageal mucosa:
A path
of prin

Alex Stra
MD, Pius
Beglinge

1 dilation
1 perforation

Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:1149–1153

6 dilations
3 perforations

pump inhibitor tr
gical diagnosis sh

ORIGINAL ARTICLES—ALIMENTAR

Competing intere

Endoscopy_UCTN_C
Endoscopy_UCTN_C

Unusual cases an

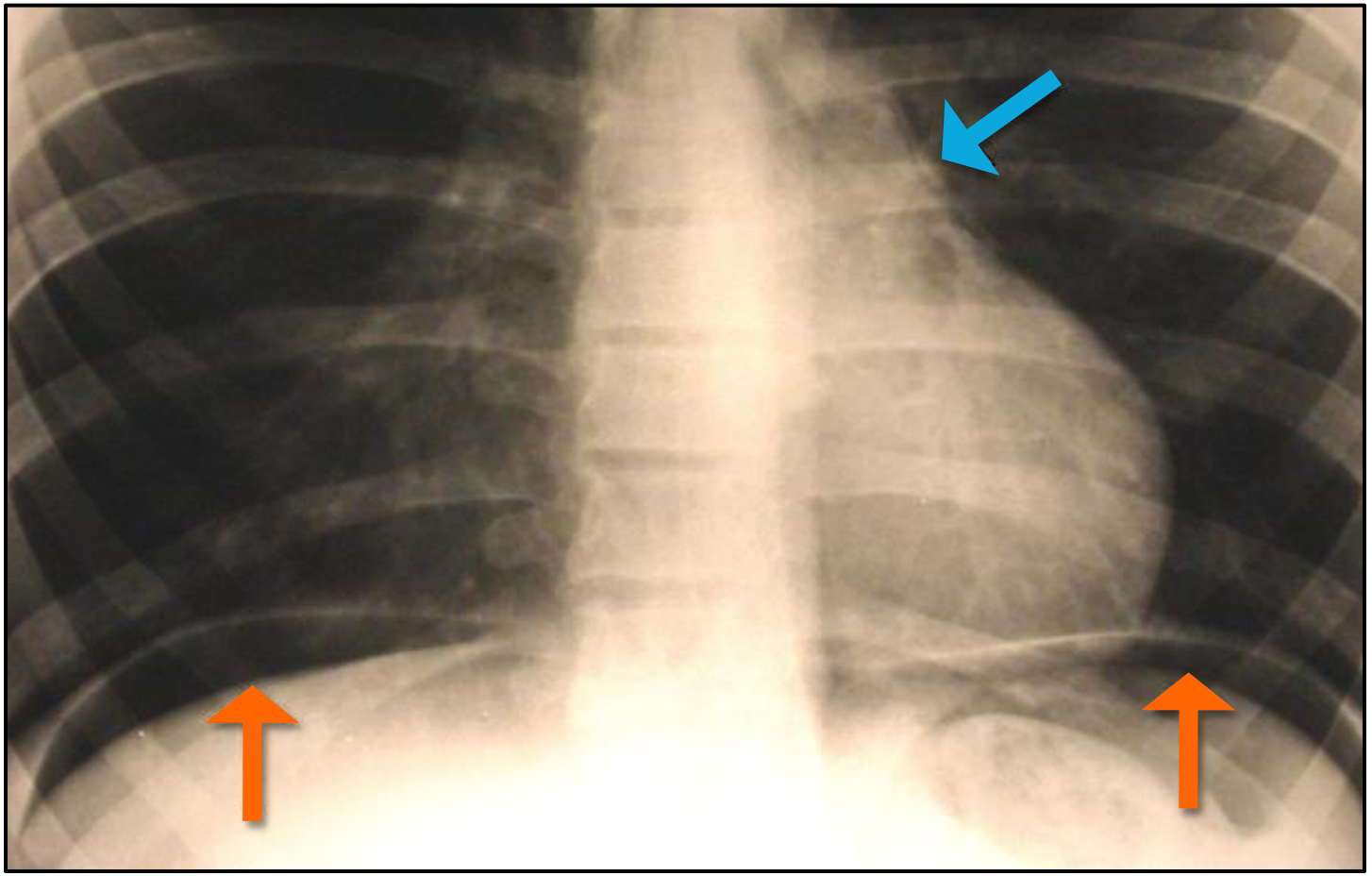
C. Eisenbach[1], U. I
P. Schirmacher[2], J
A. Stiehl[1], W. Stre
[1] Dept. of Gastroen

An Audit of Endoscopic Complications in Adult Eosinophilic Esophagitis

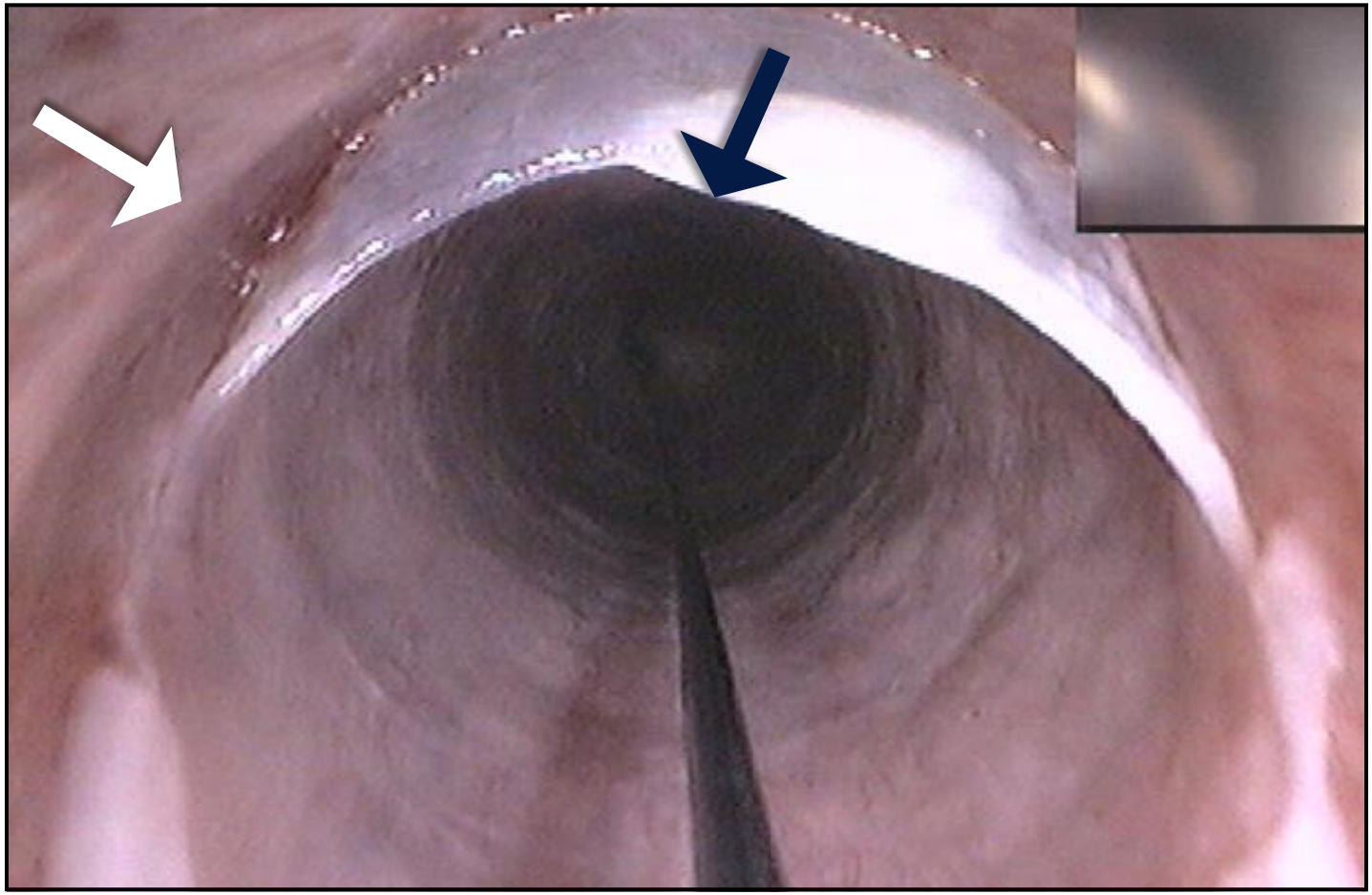
MATTHEW S. COHEN,* ADAM B. KAUFMAN,* JUAN P. PALAZZO,‡ DANIEL NEVIN,‡ ANTHONY J. DIMARINO JR* and SIDNEY COHEN*

*Division of Gastroenterology and Hepatology, and ‡Department of Pathology, Anatomy, and Cell Biology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

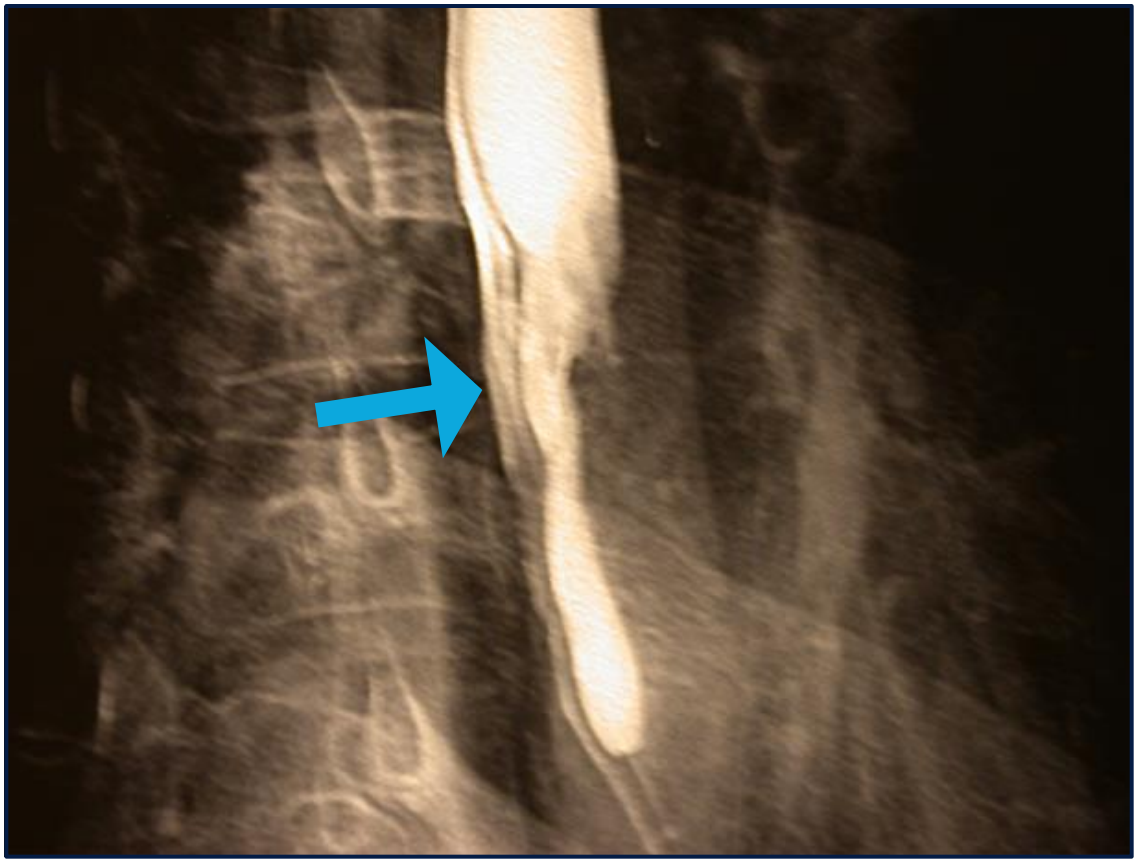
Complications after Dilation



Complications after Dilation

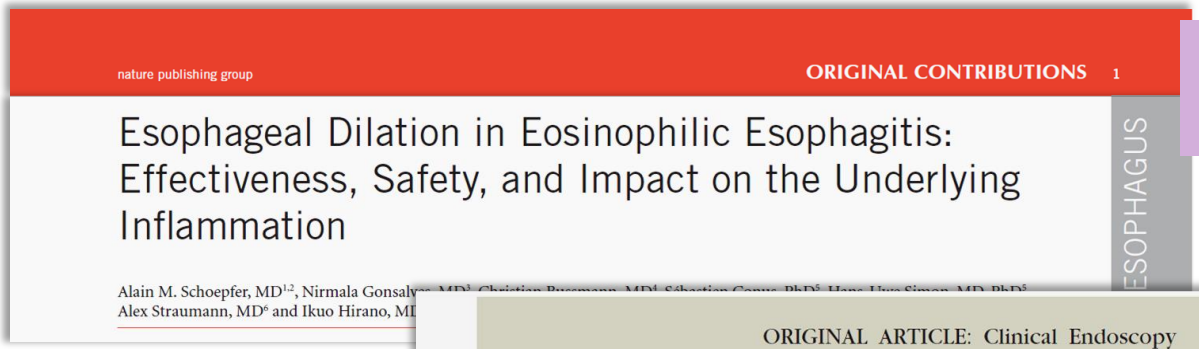


Complications after Dilation



Esophageal Dilation in EoE:

Low Risk of Esophageal Complications


nature publishing group

ORIGINAL CONTRIBUTIONS 1

Esophageal Dilation in Eosinophilic Esophagitis: Effectiveness, Safety, and Impact on the Underlying Inflammation

Alain M. Schoepfer, MD[1,2], Nirmala Gonsalves, MD[3], Christian Bussmann, MD[4], Sébastien Gonvers, PhD[5], Hans-Uwe Simon, MD, PhD[5], Alex Straumann, MD[6] and Ikuo Hirano, MD[7]

ESOPHAGUS

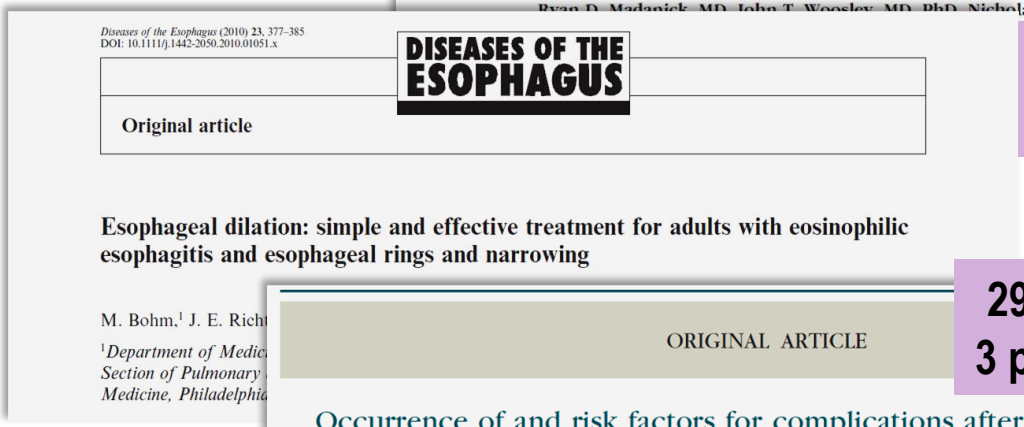
474 dilations
0 perforations


ORIGINAL ARTICLE: Clinical Endoscopy

Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications (CME)

Evan S. Dellon, MD, MPH, Wood B. Gibbs, MD, Tara C. Rubinas, MD, Karen J. Fritchie, MD, Ryan D. Madanick, MD, John T. Woosley, MD, PhD, Nicholas J. Shaheen, MD, MPH

70 dilations
0 perforations


Diseases of the Esophagus (2010) **23**, 377–385
DOI: 10.1111/j.1442-2050.2010.01051.x

DISEASES OF THE ESOPHAGUS

Original article

Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing

M. Bohm,[1] J. E. Richt

[1]*Department of Medic*
Section of Pulmonary
Medicine, Philadelphia

15 dilations
0 perforations


ORIGINAL ARTICLE

Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis

Kee Wook Jung, MD, Nancy Gundersen, MD, Jana Kopacova, Amindra S. Arora, MB, BChir, Yvonne Romero, MD, David Katzka, MD, Dawn Francis, MD, MHS, Julie Schreiber, Ross A. Dierkhising, MS, Nicholas J. Talley, MD, PhD, Thomas C. Smyrk, MD, SgPa, Jeffrey A. Alexander, MD

Rochester, Minnesota, USA; Seoul, South Korea

293 dilations
3 perforations

TIGER THE INTERNATIONAL GASTROINTESTINAL EOSINOPHIL RESEARCHERS

NASPGHAN FOUNDATION For Children's Digestive Health & Nutrition

Esophageal Dilation in EoE:

Effectiveness, Safety and Impact on Underlying Inflammation

- Retrospective study of 474 dilations in 207 adults
- 63 patients treated with dilation alone
  - 93% of patients reported slight or no dysphagia after dilation
- Esophageal diameter increased from 11 mm pre to 16 mm post dilation
- 3 mm incremental dilation per session; median 2 sessions per patient (range 1-13)
- No perforations; post procedure pain 74%

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

Dilation Summary

Esophageal Dilation in EoE

- Dilation does not address the underlying disease process
- Relapse is common after dilation although prolonged remission can occur
- Significant risk of long mucosal lacerations and pain
- Esophageal perforation risk is low but consequences can be substantial
- Pharmacologic and dietary therapy is effective at relieving symptoms and treating strictures
- *Whenever possible, pharmacologic or dietary therapy should be attempted prior to esophageal dilation*

Furuta et al. *Gastroenterology.* 2007; 133:1342-63.
Liacouras et al. *J Allergy Clin Immunol.* 2011; 128:3–20.

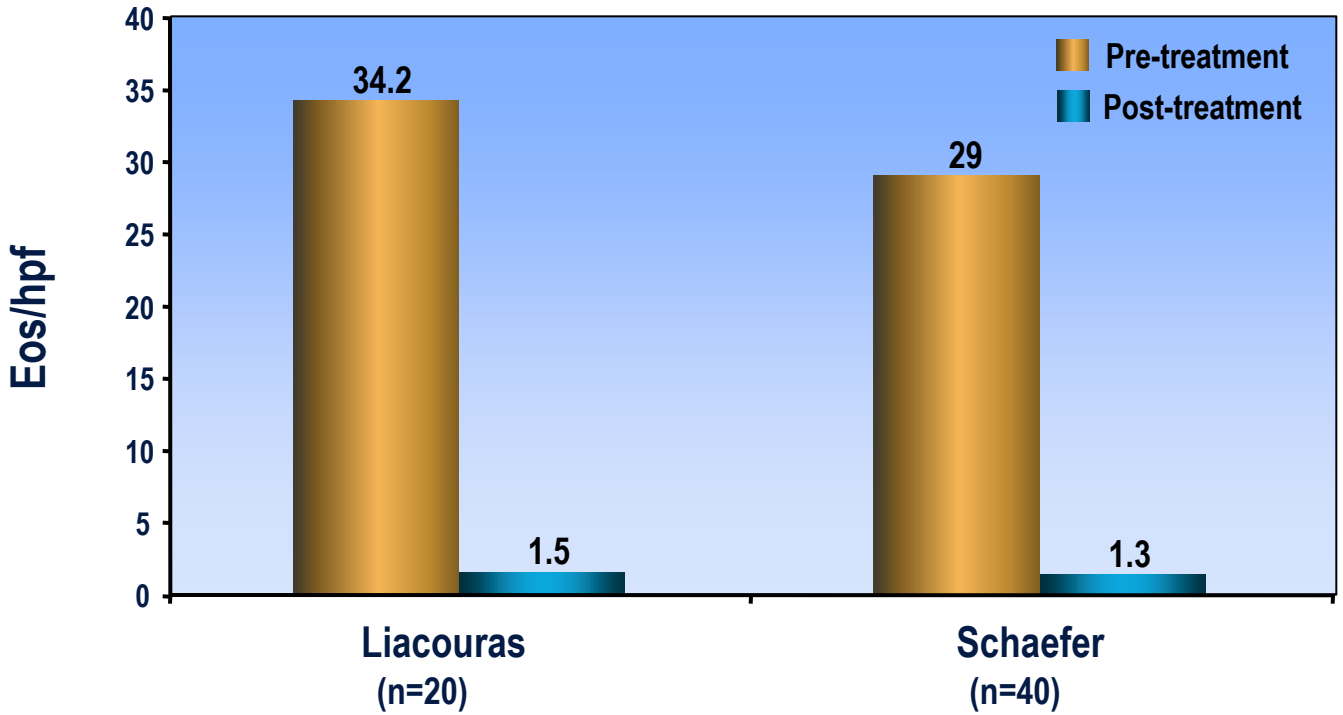
Steroid Treatment in Pediatrics

Systemic Corticosteroids

- Initial report in 1998 (Liacouras)
- 20 patients treated with methylprednisolone
  - 1.5 mg/kg/day for 4 weeks, weaned over next 6 weeks
- Clinical and histological resolution noted in majority
  - 34.2 eos/hpf to 1.5 eos/hpf at Week 4
- Considerations: Side effects, unclear incidence of relapse and duration to relapse

Liacouras et al. *J Pediatr Gastroenterol Nutr.* 1998; 27:90-93.

Oral Steroid Studies



1 mg/kg BID; max 30 mg BID

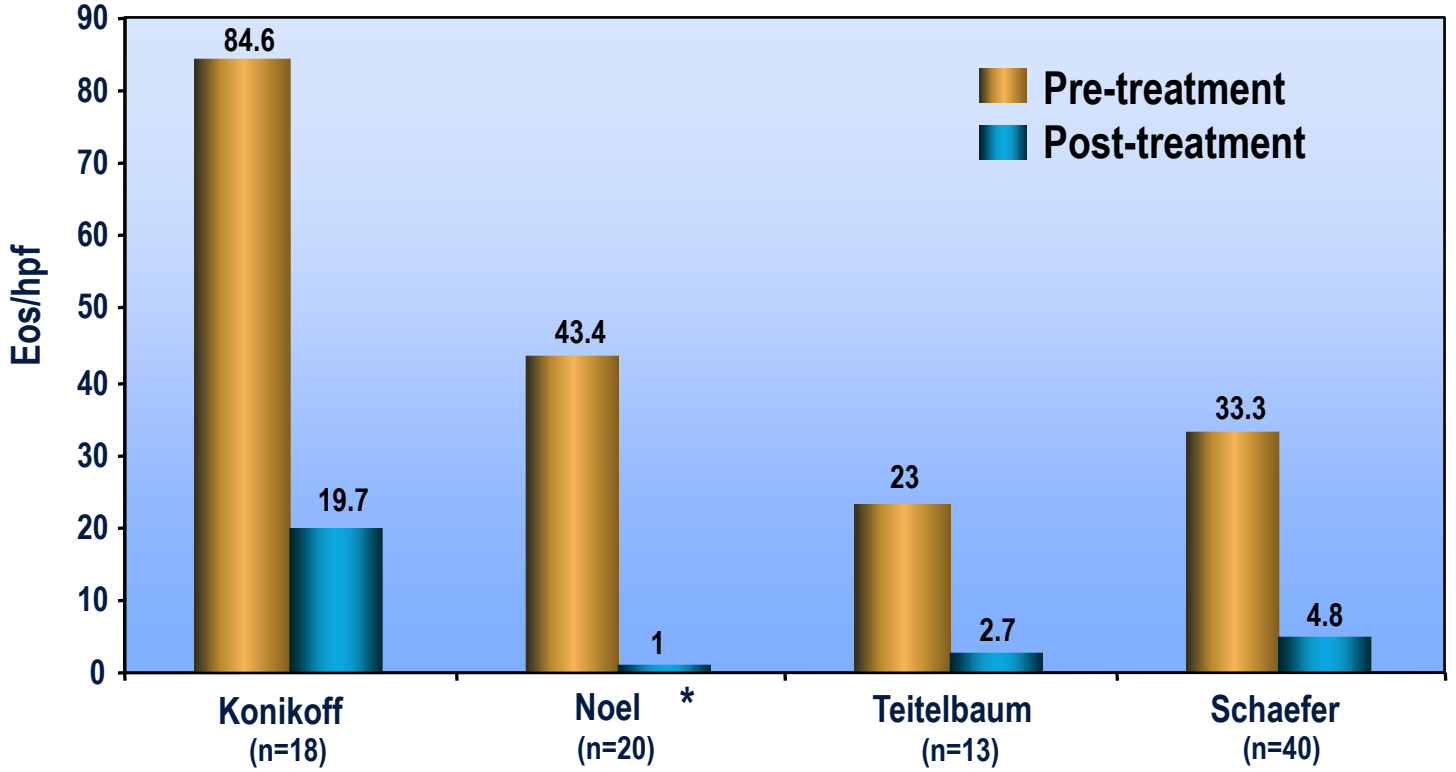
Liacouras et al. *J Pediatr Gastroenterol Nutr.* 1998; 27:90-93.
Schaefer et al. *Clin Gastroenterol Hepatol.* 2008; 6:621-629.

Topical Corticosteroids

- Initial report by Faubion et al, in 1998, in 4 children
- Fluticasone now a common therapy
- Demonstrated improved symptoms and histology
- Side effects not common, and often mild (*Candidiasis* can be seen)

Faubion et al. *J Pediatr Gastroenterol Nutr.* 1998; 27:90.

Topical Steroids *(Swallowed Fluticasone)*



	Konikoff	Noel	Teitelbaum	Schaefer
Design:	RCT	Retrosp	Prosp	RCT
Max Dose:	880 mcg/day	1320 mcg/day	880 mcg/day	1760 mcg/day

*Post treatment data on 16 patients.

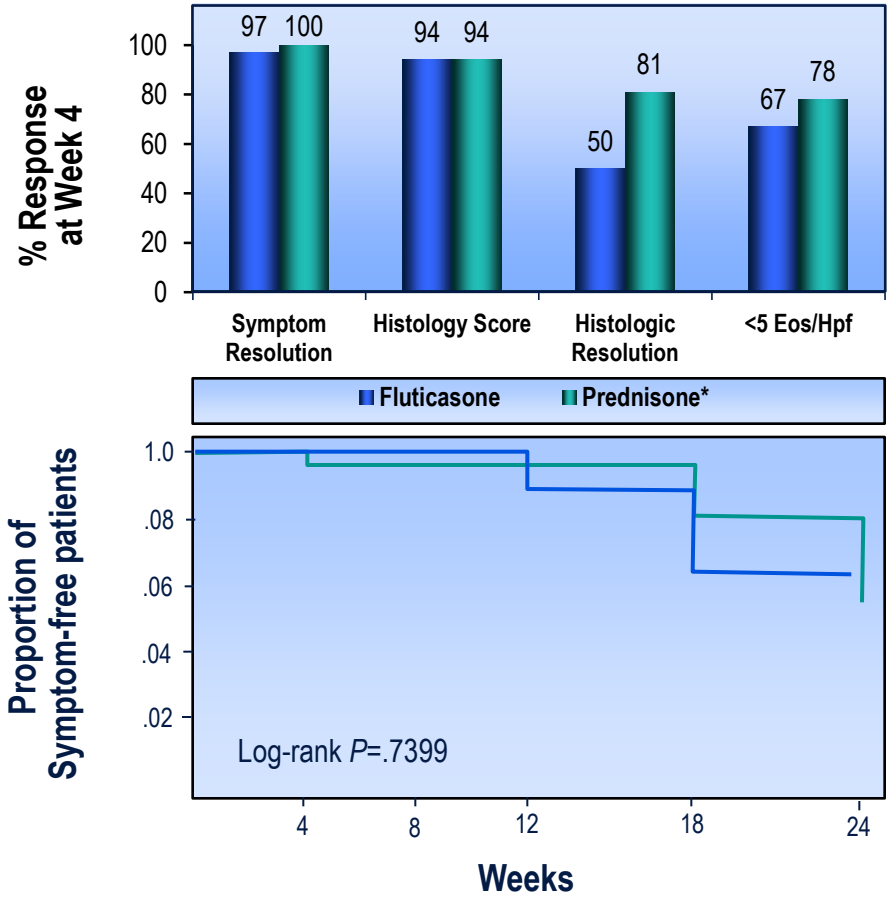
Konikoff et al. *Gastroenterology.* 2006; 131:1381-1391.
Noel et al. *Clin Gastroenterol Hepatol.* 2004; 2(7):523-530.
Teilbauam et al. *Gastroenterology.* 2002; 122:1216.
Schaefer et al. *Clin Gastroenterol Hepatol.* 2008; 6:621-629.

Issues with Swallowed Fluticasone

- Variable dosing regimens in studies:
  - Strength (44, 100, 220 mcg/actuation)
  - Frequency (2-4 puffs bid to qid)
  - Duration
  - Weaning schedule, etc
- 2 puffs qid x4 wks, tid x3 wks, bid x3 wks, qd x2 wks, stop
  - 1-10 year old: 110 mcg/actuation
  - ≥ 11 year old: 220 mcg/actuation
- Side effects uncommon; *Candidal* overgrowth encountered
- Long-term safety and pK not rigorously studied

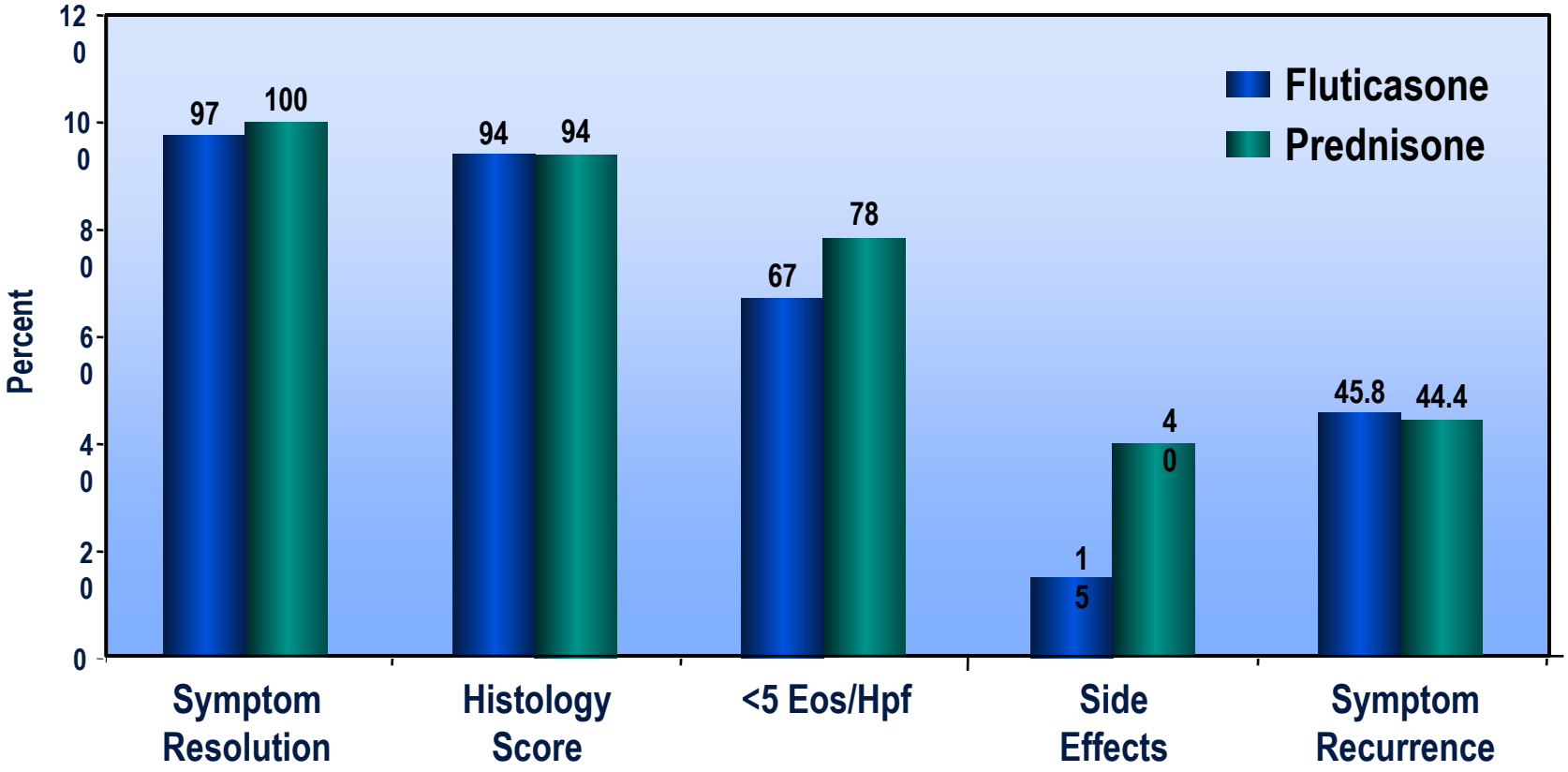
Faubion et al. *J Pediatr Gastroenterol Nutr.* 1998; 27:90.

Randomized Trial of Fluticasone vs Prednisone in Pediatric EoE (n=80)



Schaefer et al. *Clin Gastroenterol Hepatol*. 2008;6(2):165-73. 2008.
(Slide courtesy Dr Hirano)

Comparing Types of Corticosteroids



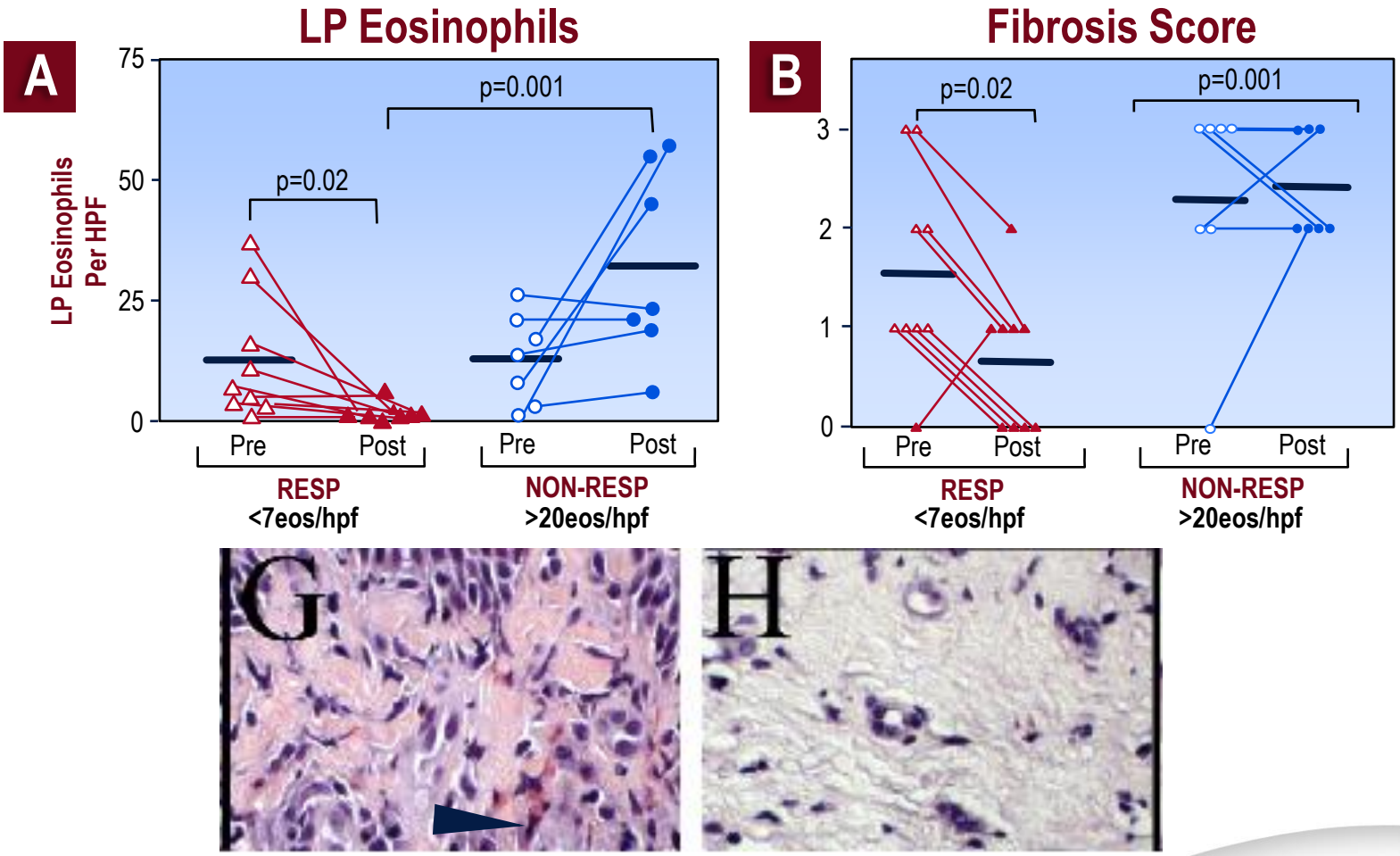
Schaefer et al. Clin Gastroenterol Hepatol. 2008; 6:621-629.

Liquid Budesonide

- 20 children with EoE (baseline: 87 eos/hpf)
- Prescribed liquid budesonide (1-2 mg once daily) mixed with a sucralose (Splenda®) paste
  - 16 responders (< 8 eos/hpf);
  - 3 partial responders (8-23 eos/hpf);
  - 1 non-responder (no change in eos) after 3-4 months of treatment;
  - No significant adverse effects; esophageal *Candidiasis* in one patient

Aceves et al. *Am J Gastroenterol*. 2007; 102:2271-2279.

Topical Budesonide Resolves LP Eosinophilia and Fibrosis



Aceves et al. *Allergy.* 2010;65(1);109-116.

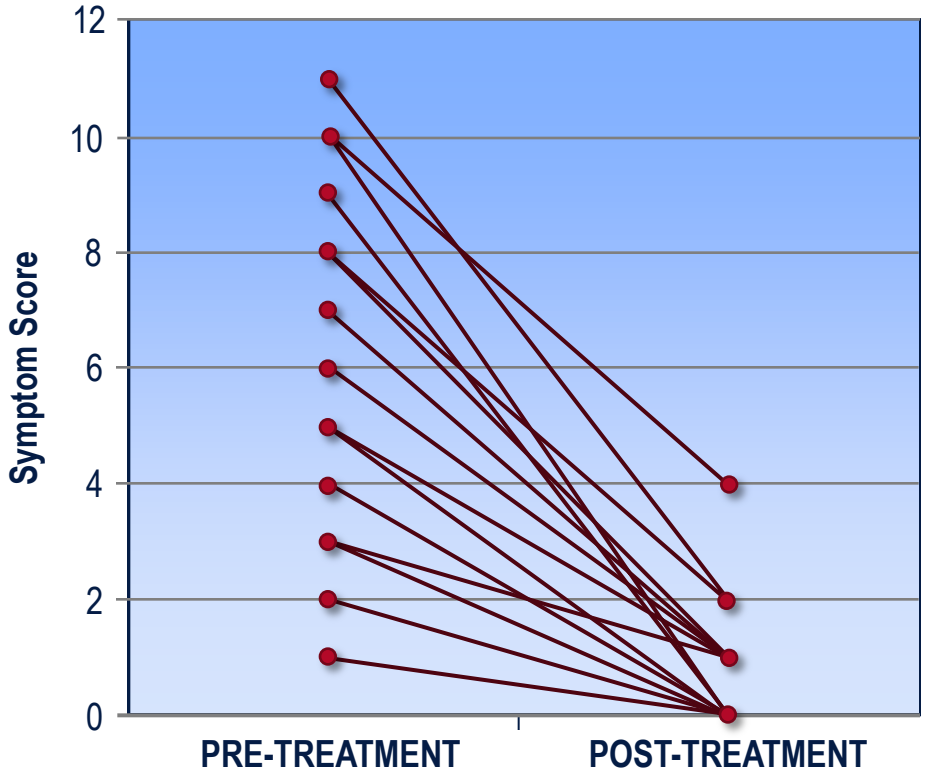
Steroid Treatment in Adults

Fluticasone in Adults

- Retrospective study
  - 21 adult patients with EoE, mean age 40
  - Treatment with fluticasone swallowed twice daily for 6 wks
  - All patients with complete resolution of solid food dysphagia
- Side effects
  - Transient xerostomia
  - No cases of oral Candidiasis

Arora et al. *Mayo Clinic Proc.* 2003; 78:830-835.

Fluticasone Decreases Symptoms in Adults

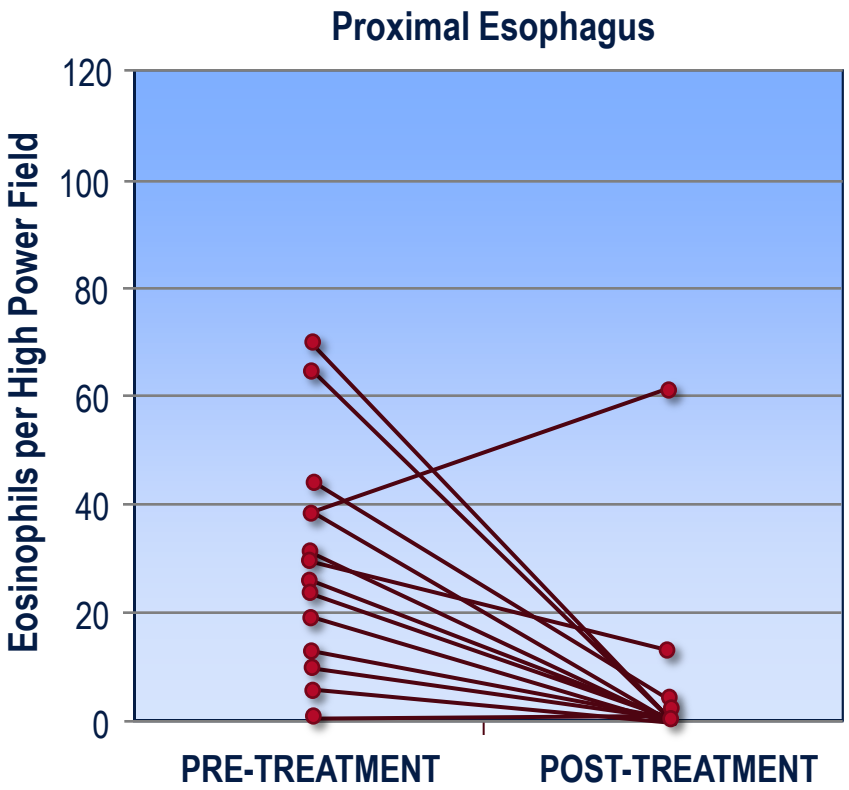


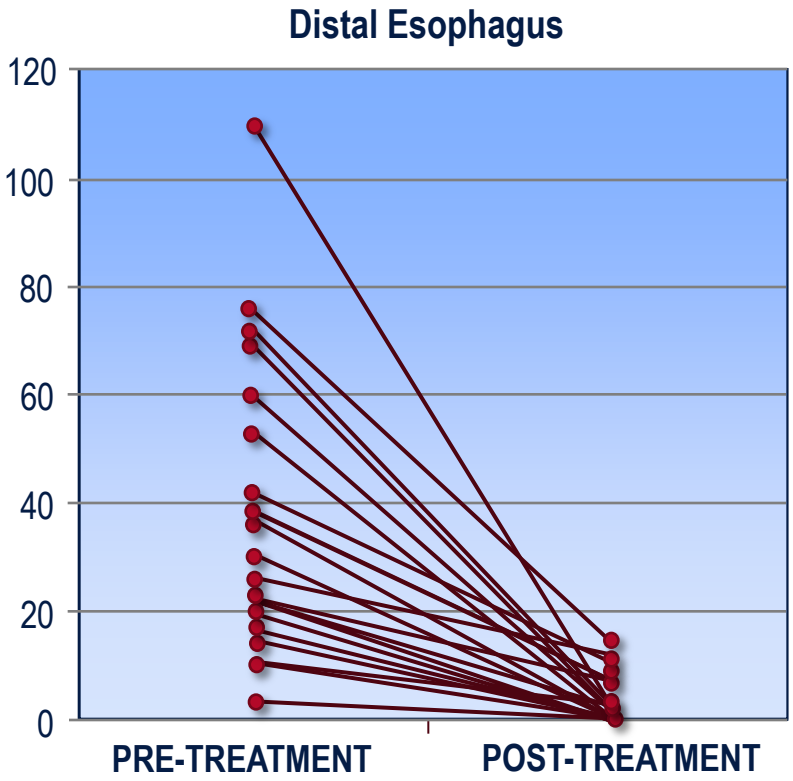
Symptoms include: dysphagia, chest pain, heartburn, regurgitation, vomiting, abdominal pain

(p<0.001)

Remedios et al. *Gastrointest Endosc.* 2006; 63:3-12.

Fluticasone Lowers Esophageal Eos in Adults





Remedios et al. *Gastrointest Endosc.* 2006; 63:3-12.

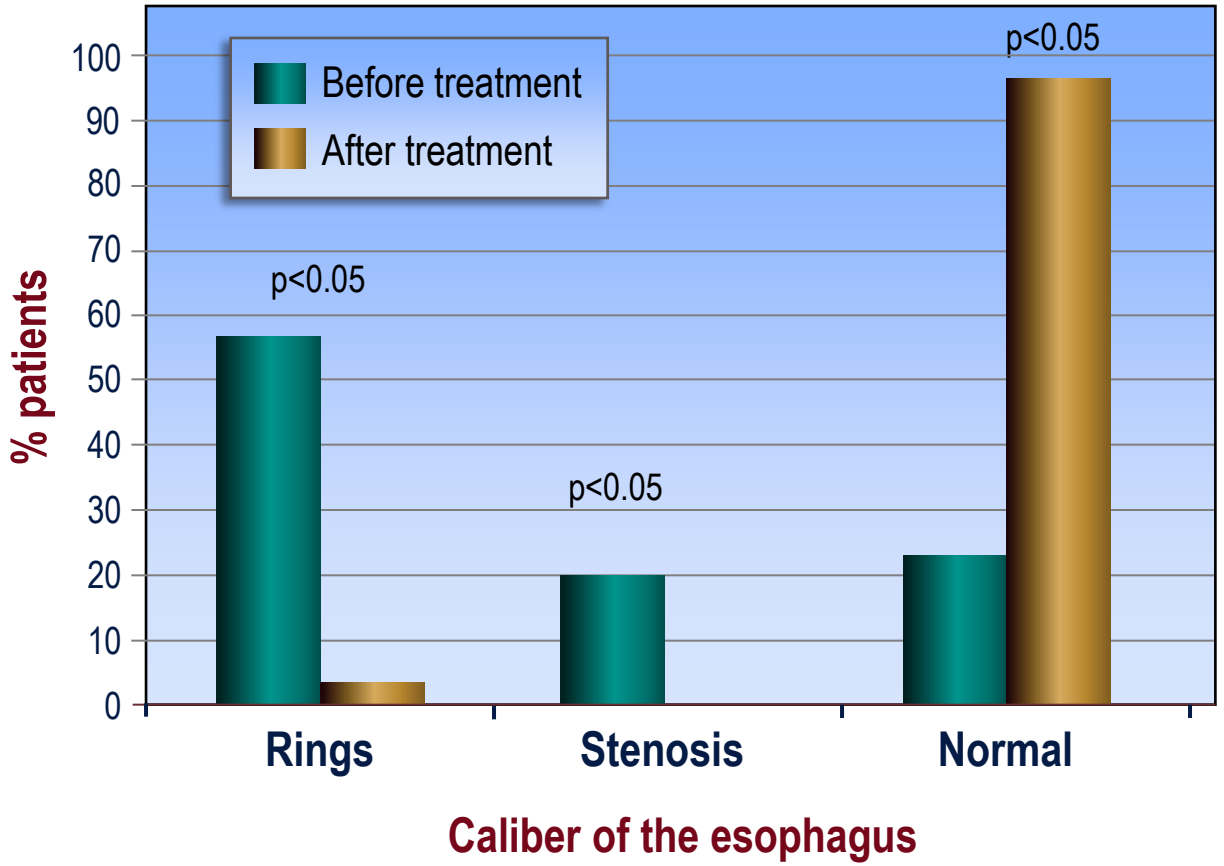
Randomized Controlled Trial of Topical Fluticasone in Adult EoE

- 42 pts with EoE treated with fluticasone 880 mcg BID or placebo x 6 weeks; 34 completed trial
- Significant histologic response (defined by < 15 eos/hpf)
  - 71% of fluticasone vs 10% of placebo (p<.01) by ITT analysis
  - 79% fluticasone vs 13% placebo (p<.01) by PP analysis
- Symptom response was similar between groups
  - 71% fluticasone vs. 48% placebo by ITT analysis
  - 68% fluticasone vs. 74% placebo by PP analysis

Alexander et al. *Clinical Gastro Hepatology.* 2012;10(7):742-749.

Fluticasone Effect on Esophagus

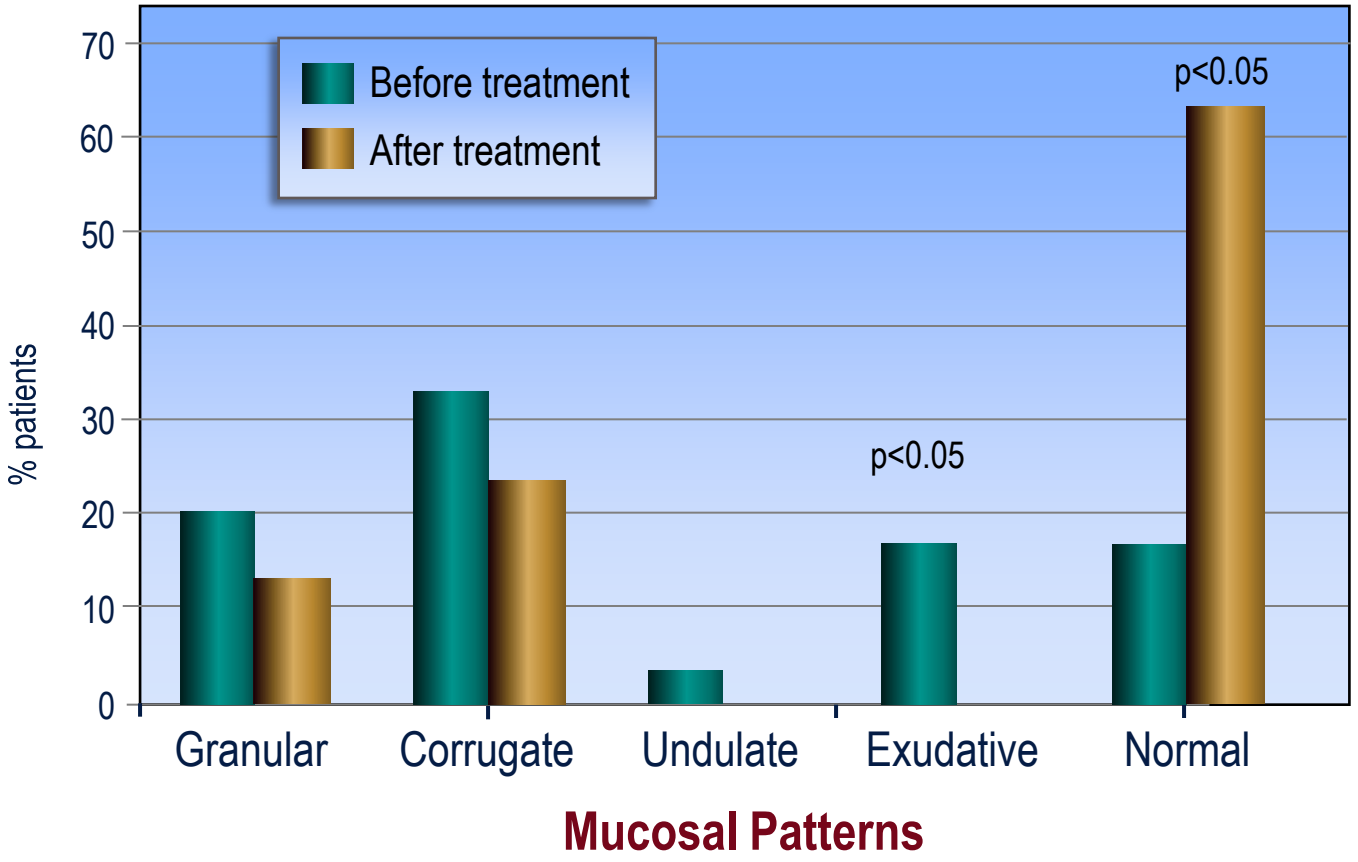
Prospective, n=30 Adults, Fluticasone x 3 mos



Lucendo et al. *Endoscopy. 2007; 55(12):1739-1745.*

Fluticasone Effect on Esophagus in EoE

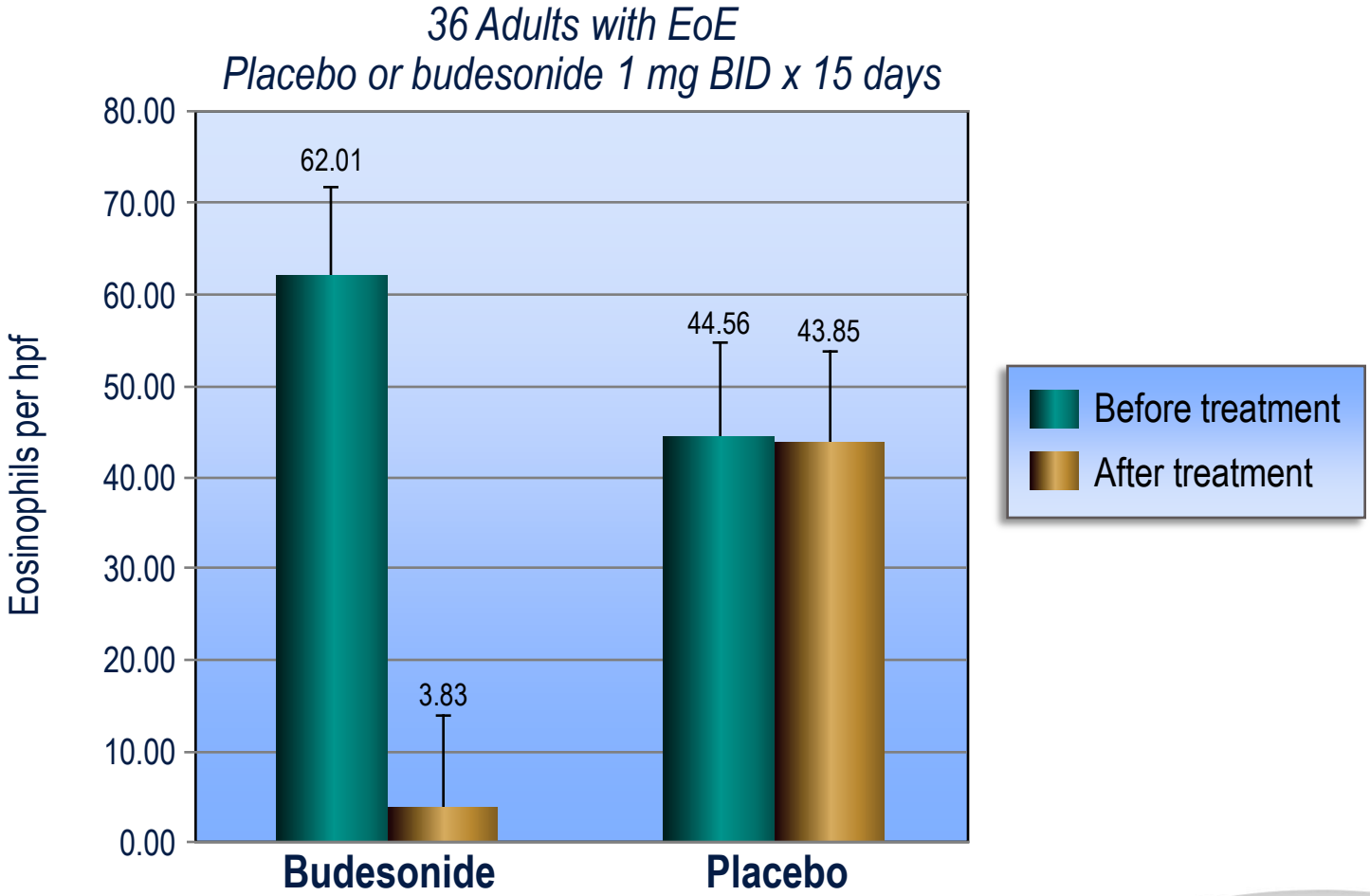
Prospective, n=30 Adults, Fluticasone x 3 mos



Lucendo et al. *Endoscopy. 2007; 55(12):1739-1745.*

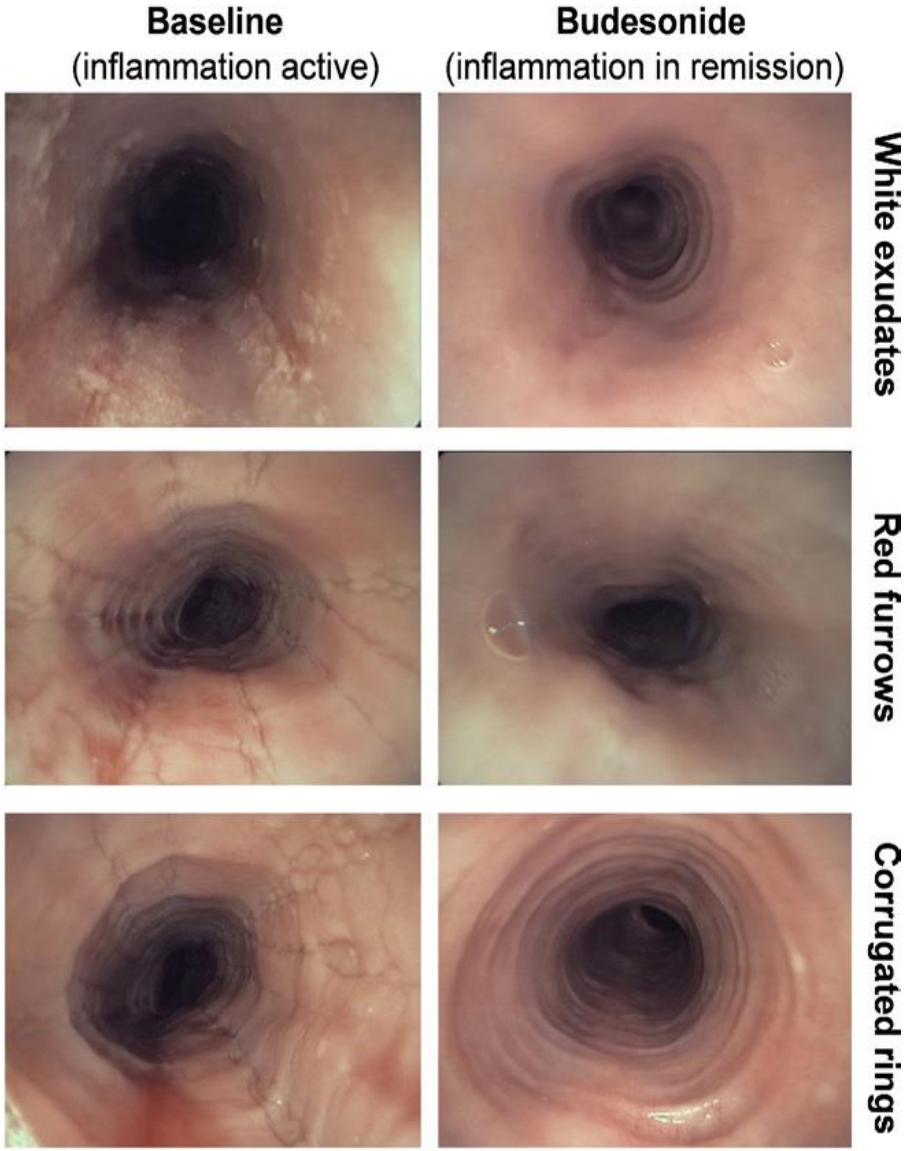
Liquid Budesonide

Randomized, Double-Blind Placebo Controlled Trial Budesonide (BEE Trial)



Straumann et al. *Gastroenterology*. 2008; 134(Suppl):A104.

Topical Steroid: Endoscopic Improvement



Straumann et al. *Clinical Gastro Hepatology.* 2011;9(5):400-409.

Corticosteroid Summary

Guidelines for Corticosteroids in EoE

- Systemic and topical corticosteroids effectively resolve the acute clinico-pathological features of EoE.
- When discontinued, the disease generally recurs.
- Systemic corticosteroids may be utilized in emergent cases such as dysphagia requiring hospitalization, dehydration due to swallowing difficulties and weight loss, etc.
  - Because of the potential for significant toxicity their long-term use is not recommended.
- Topical corticosteroids are effective in inducing a remission of EoE when utilized in high doses (pediatrics & adults).
  - The incidence of long term side effects with this form of administration has not been formally studied but currently it is well tolerated (fungal infections).
- Topical corticosteroids are used for maintenance of EoE but have not been well studied.

Furuta et al. *Gastroenterology.* 2007; 133:1342-63.
Liacouras et al. *J Allergy Clin Immunol.* 2011; 128:3–20.

Dietary Treatment in Pediatrics

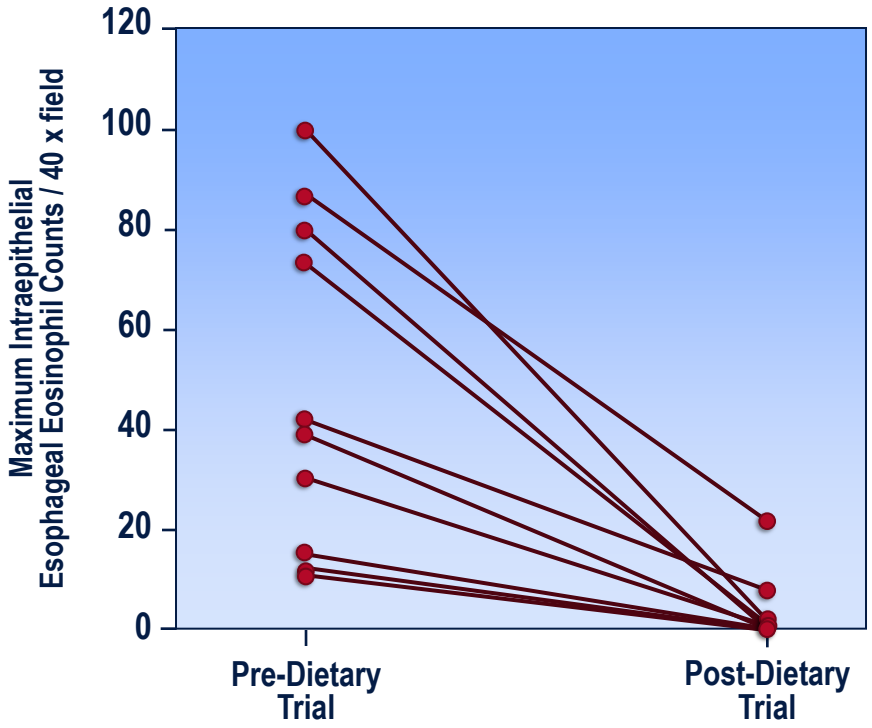
History of Diet and EoE

- In 1995: “Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula”
  - 10 patients with refractory reflux symptoms
  - 6 had received anti-reflux surgery without resolution
  - All with markedly elevated esophageal eosinophils
- Patients given a trial of an “elemental diet”
  - Amino acid based formula
  - Minimized any risk of food allergy

Kelly et al. *Gastroenterology.* 1995; 109:1503-1512.

Diet and Eosinophilic Esophagitis

- After elemental diet:
  - Symptom resolution in 8 patients, improvement in 2
  - Improvement occurred within 3 weeks
  - Biopsies improved as well
- Symptoms returned after food was reintroduced
- Conclusions:
  - EoE is an allergic phenomenon
  - EoE improves with food elimination



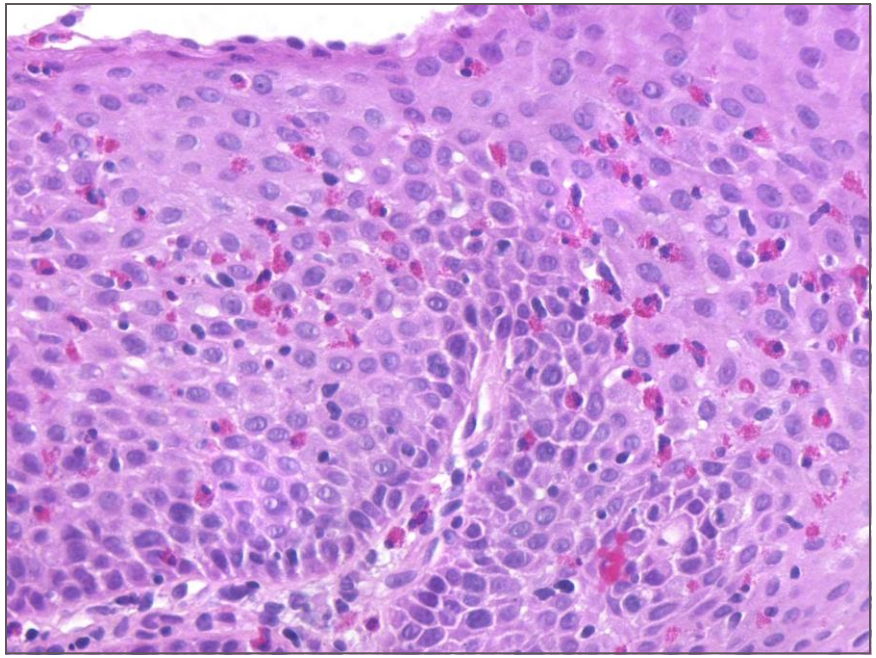
Dietary Management
Amino Acid–Based Formula

- 172 Patients (128 nasogastric tube, 32 oral, 4 failed, 8 noncompliant)
  - 160 patients completed therapy
- Patients evaluated 4-6 weeks after instituting diet

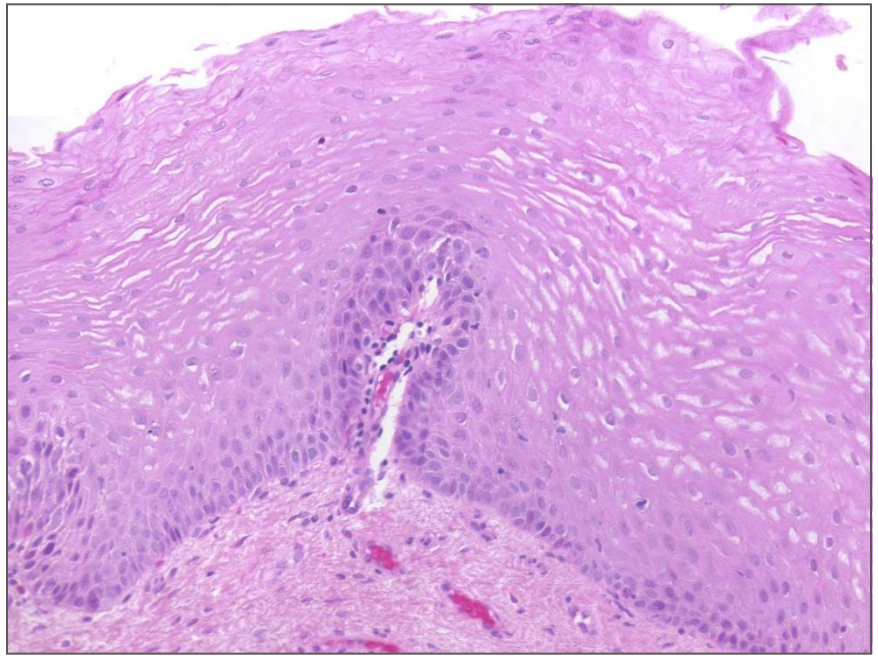
160 Patients	Pre-diet	Post-diet	*P* Value
Eosinophils per hpf	38.7 ± 10.3	1.1 ± 0.6	<.001
Dysphagia	30	1	<.01
GERD symptoms	134	3	<.01

Liacouras et al. *Clin Gastroenterol Hepatol.* 2005; 3:1198-1206.

EoE – Elemental Diet



Before



After

Types of Dietary Therapy for EoE

- Total Elimination Diet
  - Amino-Acid based formula
- Selective Diet
  - Empiric Diet
  - Directed (Targeted) Diet

Advantages of Elemental Diet

- When administered correctly:
  - > 95% demonstrate clinical and histologic response
  - Allows systematic re-introduction of foods
- Can lead to prolonged remission clinically and histologically without the need for medications
- Causative foods may be able to be reintroduced successfully later (tolerance)

Obstacles to Elemental Diet

- Elemental formula is unpalatable
- Commonly needs nasogastric or gastrostomy tube to administer
- Nutritional status must be monitored closely
- Elemental formulas are expensive
  - Variable insurance coverage
  - Usually significant out of pocket expense
- Quality of Life issues

Selective Elimination Diet

- Removal of a limited number of foods
- 2 types of dietary restriction
  - Empiric (based on history of the most likely foods)
    - "The usual suspects"
    - Milk, soy, egg, peanut, wheat, fish, meats
  - Directed (based on allergy testing or clinical symptoms)
    - Clinical history
    - Allergy testing (skin prick tests, atopy patch tests)

Empiric Elimination Diet

- Six food elimination diet (SFED)
- 60 EoE patients – retrospective review
  - 35 given diet without milk, soy, wheat, egg, peanut, nut and fish
  - 25 given amino acid formula
- Biopsies done at start compared with 6 weeks of diet therapy
- Improvement in restricted group 75% while amino acid group 90%

Kagalwalla et al. *Clin Gastro Hepatol.* 2006; 117(2Suppl):S470.

SFED Follow-up

- Single Food Reintroduction in 36 children
- Specific food sensitivities
  - 74% to milk
  - 26% to wheat
  - 17% to egg
  - 10% to soy
  - 6% to peanut
- Single food in 72%, 2 foods in 8% and 3 foods in 8%

Kagalwalla et al. *J Pediatr Gastroenterol Nutr.* 2011 Aug;53(2):145-9.

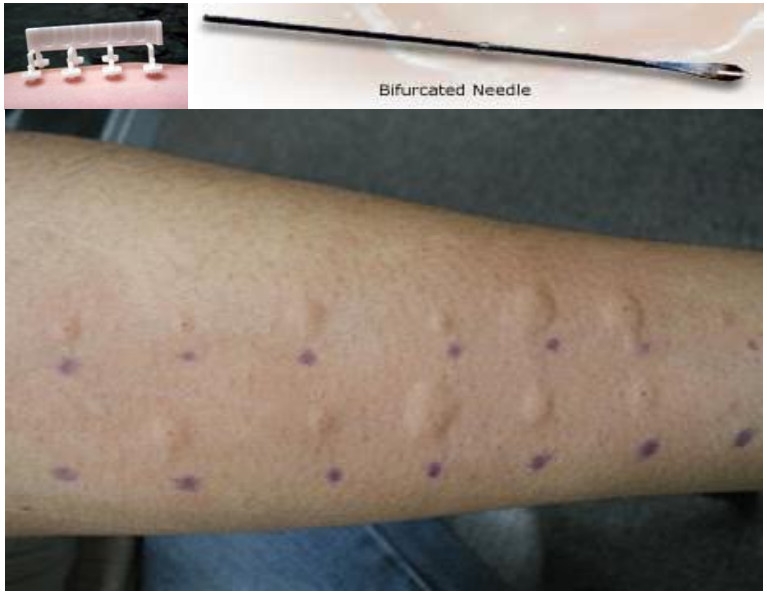
Empiric Diet Elimination

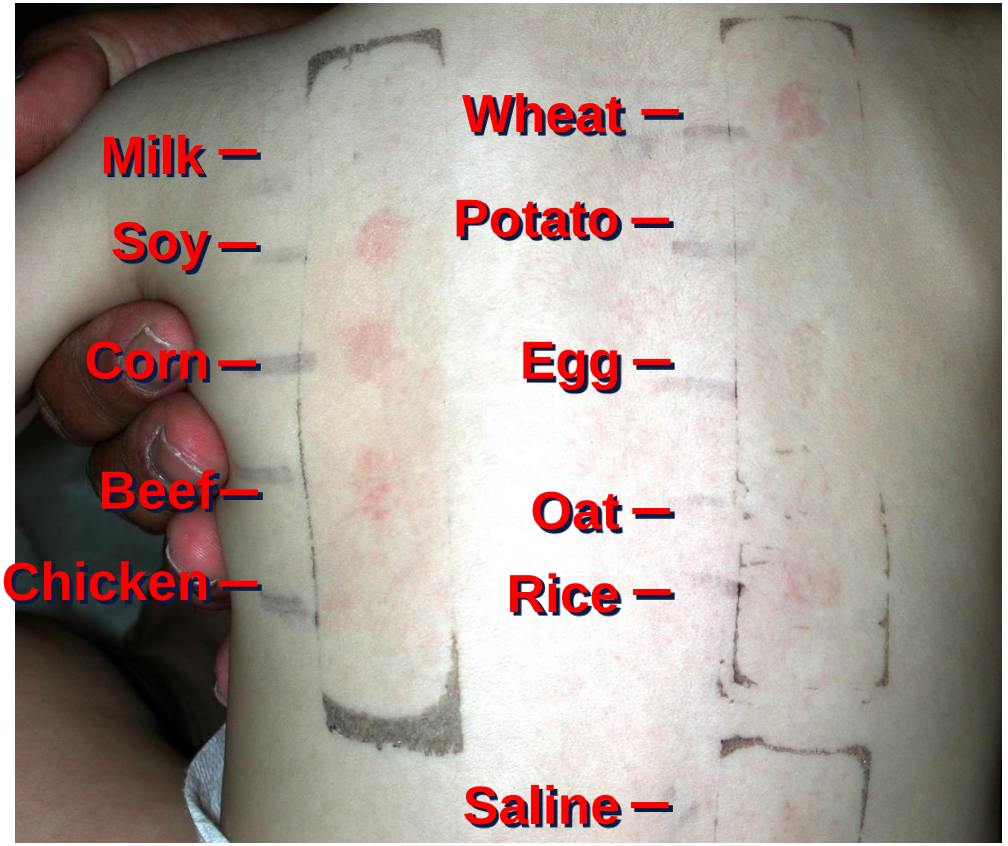
- Easy, do not need testing
- Few studies in the literature
- May not eliminate all foods necessary to induce remission
- May eliminate foods that are not necessary to be eliminated
- May prolong the process of food elimination and re-introduction

Directed Diet Elimination

- Elimination by history/symptoms (or guessing) is challenging
  - Reactions may be delayed several days after exposure
  - Reactions may persist several days after exposure
  - More than one food may be causing reaction
- Elimination based on diagnostic testing is inaccurate

Methods of Direct Allergy Testing for EoE





Food Testing in EoE

- 74% patients were atopic (asthma, ARC, or AD)
- 1/3 have negative skin prick tests
- Most common foods were
  - Egg, soy, milk, peanuts, beef, chicken, wheat, corn, peas, and potato
- 1/4 have negative atopy patch tests

  -1/8 have both negative skin prick tests and atopy patch tests

  - Wheat, corn, soy, milk, beef, rice, chicken, egg, rye, oat, and potato

Spergel et al. *J Allergy Clin Immunol.* 2012 Aug;130(2):461-467.

Predictive Values: Combination of Skin Prick Test and Atopy Patch Test

TABLE III. Comparison of food prick skin testing and atopy patch testing precision in patients with eosinophilic esophagitis

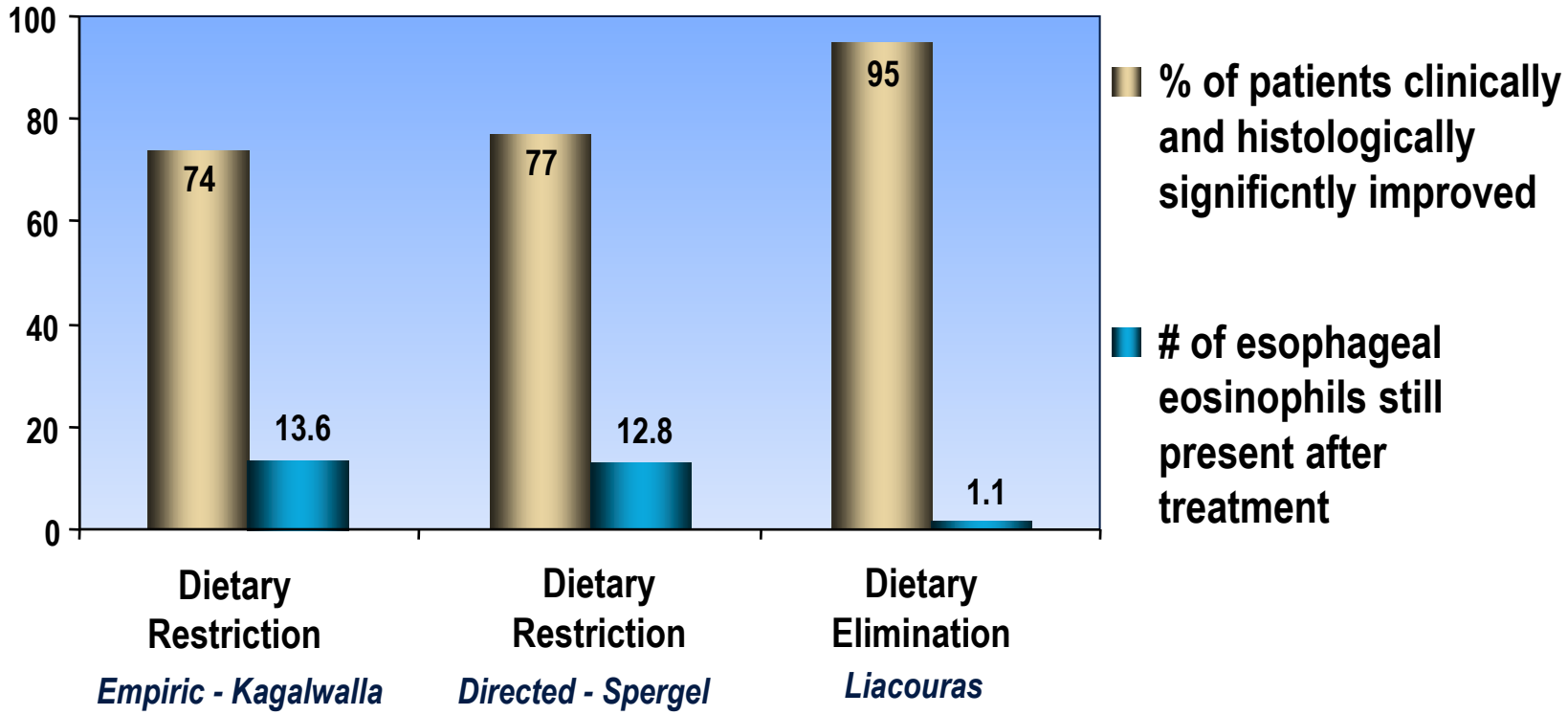
	Prick skin test precision				Atopy patch testing precision			
Food	**Sensitivity**	**Specificity**	**NLR***	**PLR***	**Sensitivity**	**Specificity**	**NLR***	**PLR***
Milk	**26.6**	**87.8**	**0.84**	**2.18**	**29.9**	**87.0**	**0.81**	**2.30**
Egg	**70.0**	**85.8**	**0.35**	**4.92**	**48.8**	**91.4**	**0.56**	**5.70**
Soy	**40.4**	**82.1**	**0.73**	**2.25**	**52.5**	**86.7**	**0.55**	**3.95**
Wheat	**18.1**	**87.4**	**0.94**	**1.44**	**57.1**	**81.8**	**0.52**	**3.14**
Peanut	**88.2**	**88.4**	**0.13**	**7.61**	**60.0**	**92.6**	**0.43**	**8.15**
Corn	**30.6**	**91.5**	**0.76**	**3.60**	**92.1**	**86.7**	**0.09**	**6.91**
Beef	**45.7**	**92.3**	**0.59**	**5.90**	**55.6**	**89.1**	**0.50**	**5.11**
Chicken	**55.9**	**89.5**	**0.49**	**5.31**	**68.0**	**88.0**	**0.36**	**5.67**
Rice	**13.3**	**97.5**	**0.89**	**5.32**	**86.7**	**87.5**	**0.15**	**6.93**
Potato	**42.1**	**97.0**	**0.60**	**14.00**	**69.2**	**91.3**	**0.34**	**7.93**
Pork	**29.4**	**95.4**	**0.74**	**6.34**	**47.1**	**89.6**	**0.59**	**4.51**

NLR, Negative likelihood ratio; PLR, positive likelihood ratio.

**Values in bold type represent a NLR of <0.20 or less or a PLR > 5.00, which, when applied to the pretest probability of having the disease can estimate the posttest probability of the disease. All values in the table are from reference 51 except rice, which are from reference 48; these data are exclusively from a pediatric population, and these values may not be applicable in adult populations.*

Spergel et al. ***J Allergy Clin Immunol.*** **2012 Aug;130(2):461-467.**

Response of 3 Types of Dietary Restriction



Kagalwalla et al. *Clin Gastroenterol Hepatol.* 2006; 117(2Suppl):S470.
Liacouras, et al. *Clin Gastroenterol Hepatol.* 2005; 3:1198-1206.
Spergel et al. *Ann Allergy Asthma Immunol.* 2005; 95(4):336-343.

Diet Choice

TABLE V. Comparison of food prick skin testing and atopy patch testing precision in patients with eosinophilic esophagitis

Approach	Definition	Pros	Cons
Elemental	Diet exclusively consisting of amino acid–based formula	• Hypoallergenic • Nutritionally comprehensive • Reduces symptoms and eosinophil counts	• Taste (may require feeding tube) • Expense • Age appropriateness • Excludes all food • May have adverse impact on quality of life
Empiric diet	Diet that eliminates the major food allergens from the diet (typically milk, egg, wheat, soy, peanut/tree nut, and fish/shellfish, though variants exist)	• Allergy testing not required • Studied across all ages • Reduces symptoms and eosinophil counts	• Some avoidance may be unnecessary • Only four foods may be necessary • Expense • May be nutritionally incomplete
Targeted diet	Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)	• Most specific therapy • Can preserve diet • Established sensitivity, specificity, and NLR/PLR to assist with add-back • Reduces symptoms and eosinophil counts	• Testing precision and technique is inconsistent across centers • Milk testing precision very poor when negative • Empiric milk elimination as an addition greatly improves response • Some avoidance may be unnecessary (sensitization without clinical allergy)

Greenhawt et al. *J Allergy Clin Immunol.* In Practice 2013;1(6):602-607.

Foods Causing EoE

- Foods found in single elimination or reintroduction with positive biopsies
  - Milk > Egg, Soy > Corn, Wheat, Beef > Chicken > Peanuts, Rice, Potato > Oat, Barley, Turkey, and Pea
- Most EoE patients, average 4 to 5 foods
- Up to 25% have severe food allergies - unable to tolerate ANY food without symptoms and histologic changes

Food Reintroduction

After Normal Biopsy

Reintroduction Strategy	Pediatric	Adult
Suggested order	Fish/shellfish	Fish/shellfish
	Peanut/tree nut	Egg
	Soy	Peanut/tree nut
	Wheat	Soy
	Egg	Milk
	Milk	Wheat

Food

TABLE IV. Comparison of identification of dietary triggers and successful food reintroduction

			Foods*						
Study	N	Age (y)	Milk, %	Egg, %	Soy, %	Wheat, %	Peanut/tree nut, %	Fish/Shellfish, %	Legumes, %
Gonsalves	20	22-55	50	5	10	60	10		
Kagalwalla	36	3-18	74	17	10	26	6		
Lucendo	42	17-57	62	26.2	14.3	28.6	16.7	19	23.8
Henderson	26	0.9-22	65	40	38	37			
Spergel	319	1-18	66.1	24.5	16.3	22.6	5.0	0	
Total†	442		64.0	22.2	15.4	24.9	5.9	1.8	

*Foods that cause changes in esophageal eosinophil counts on reintroduction; multiple foods were reintroduced in the same patient.
†Total percentages represent an average of all 5 studies.

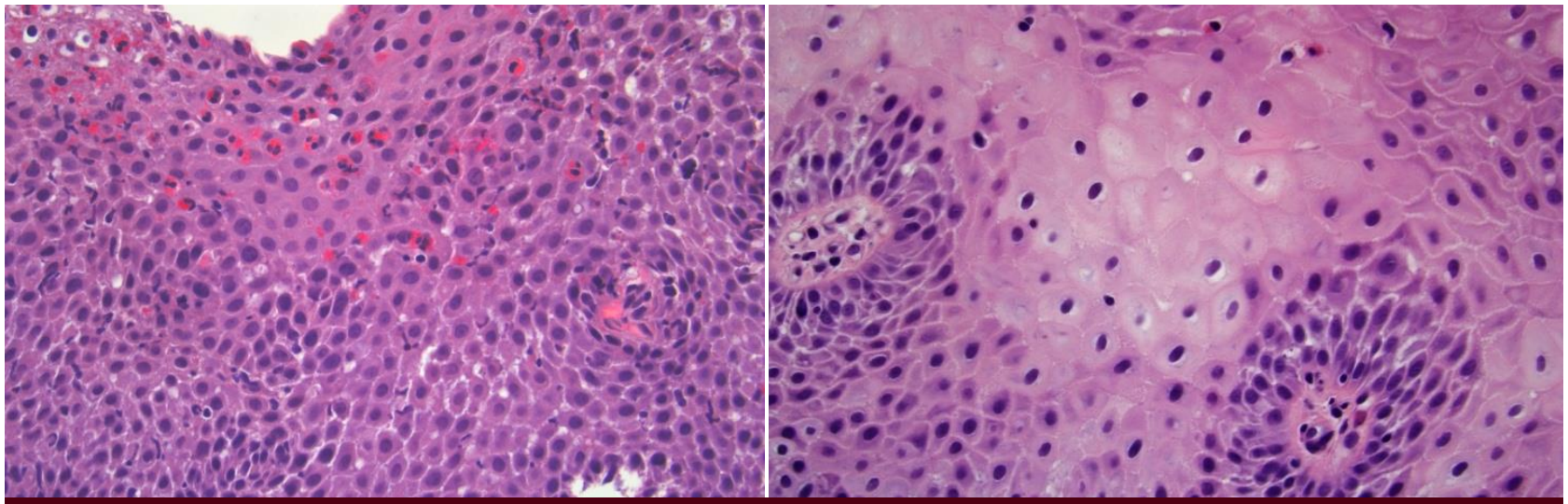
Greenhawt et al. *J Allergy Clin Immunol.* In Practice 2013;1(6):602-607.

Dietary Treatment in Adults

Dietary Therapy in Adults

Six Food Elimination Diet is highly effective at reducing symptoms, histology & endoscopic changes in adult EoE

Prospective Study in Adults (n=50)
6 wk elimination (milk, wheat, soy, egg, nuts, seafood)

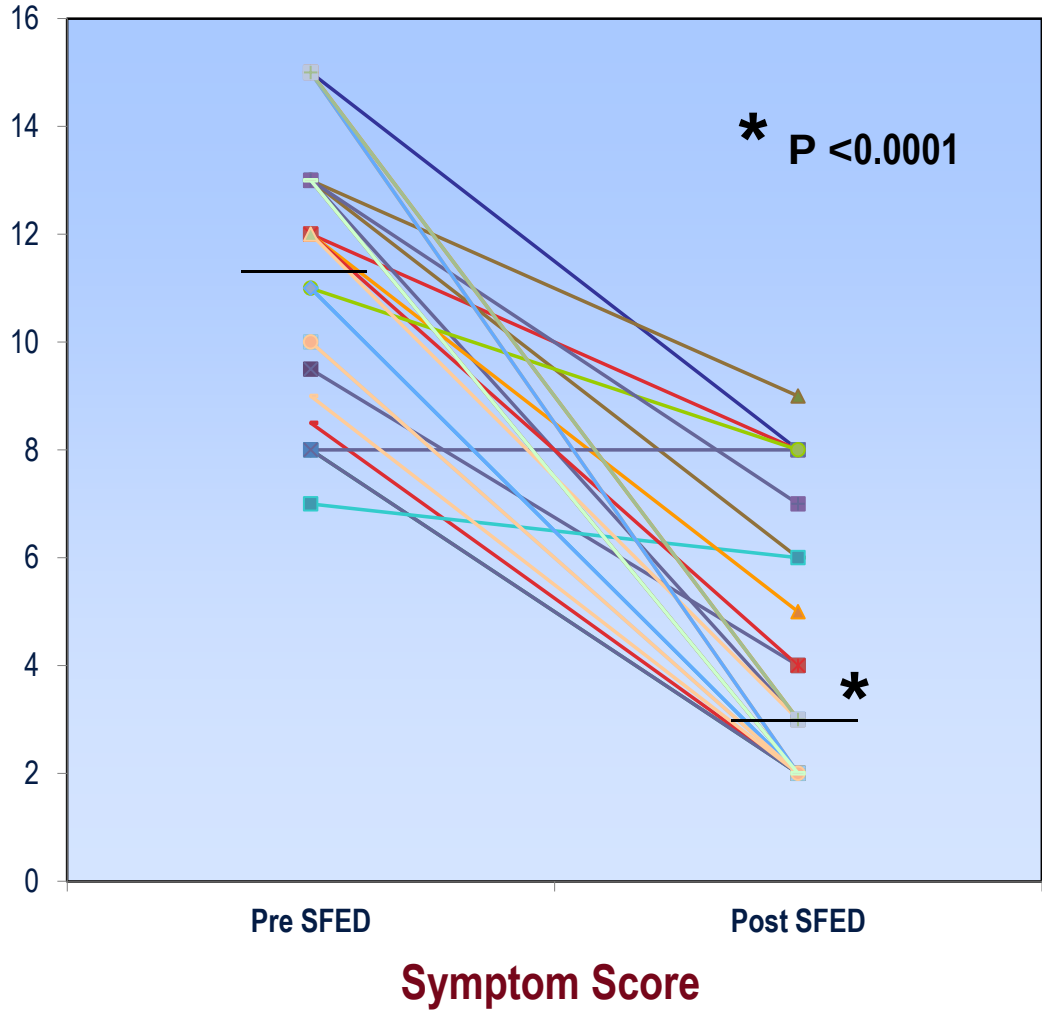


70% had peak eos <10/hpf

Before Diet	After Diet

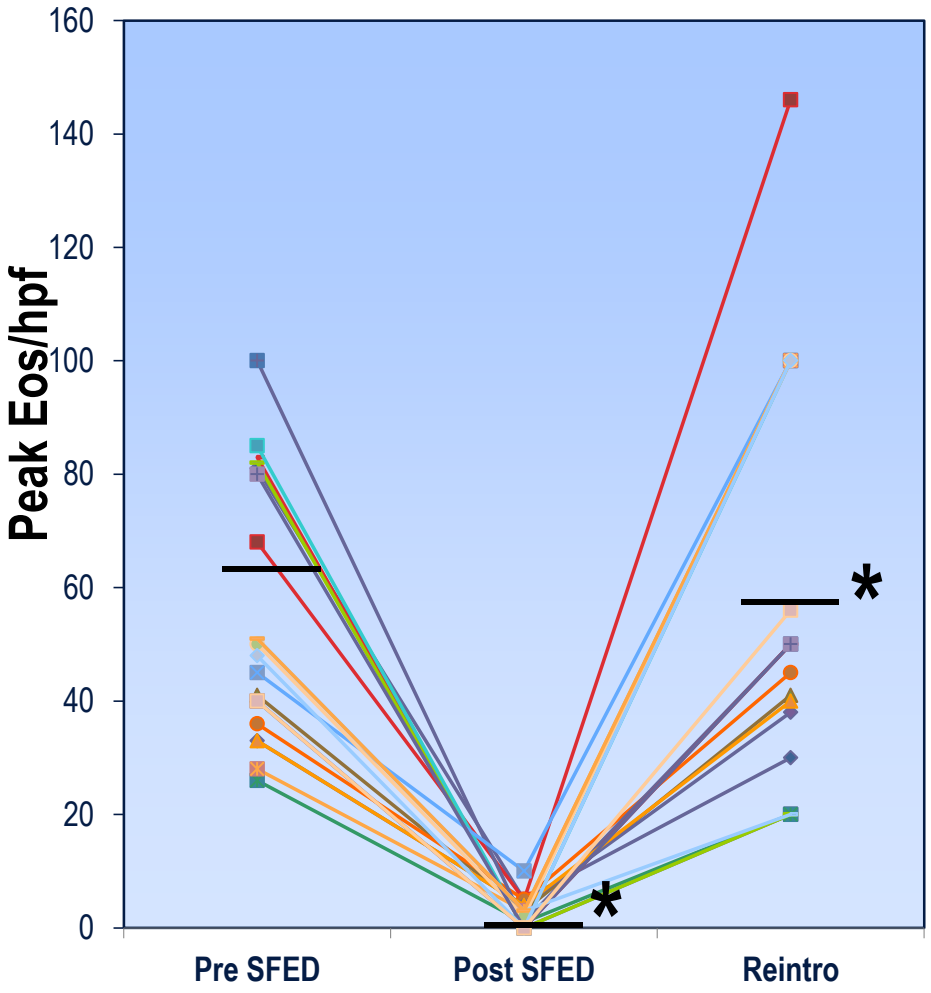
Gonsalves et al. *Gastroenterol.* 2012;142:1451–59.

94% Had Decrease in Symptom Score



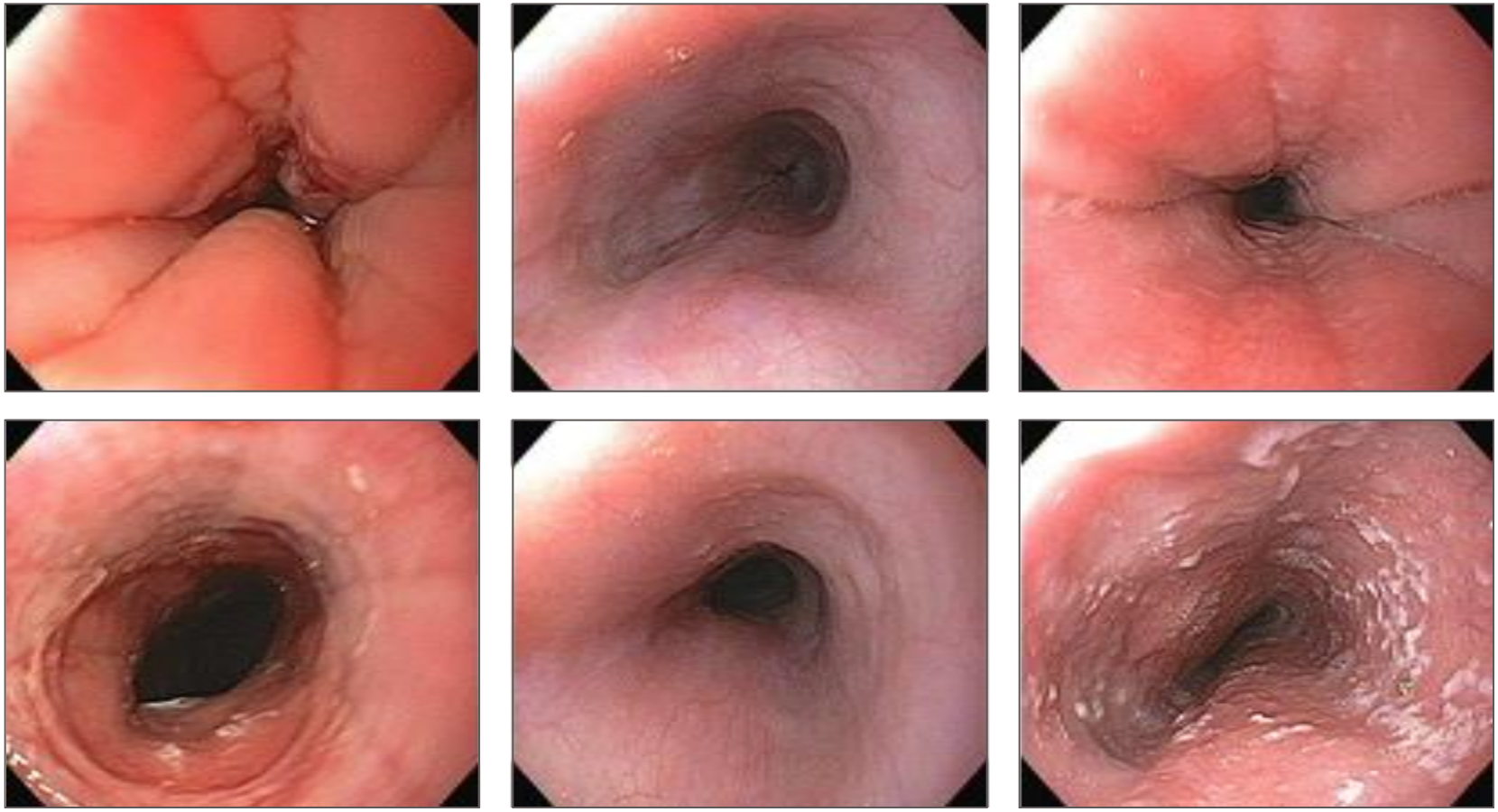
Gonsalves et al. *Gastroenterol.* 2012;142:1451–59.

Effect of Food Reintroduction on Esophageal Eosinophilia



* p<0.0001

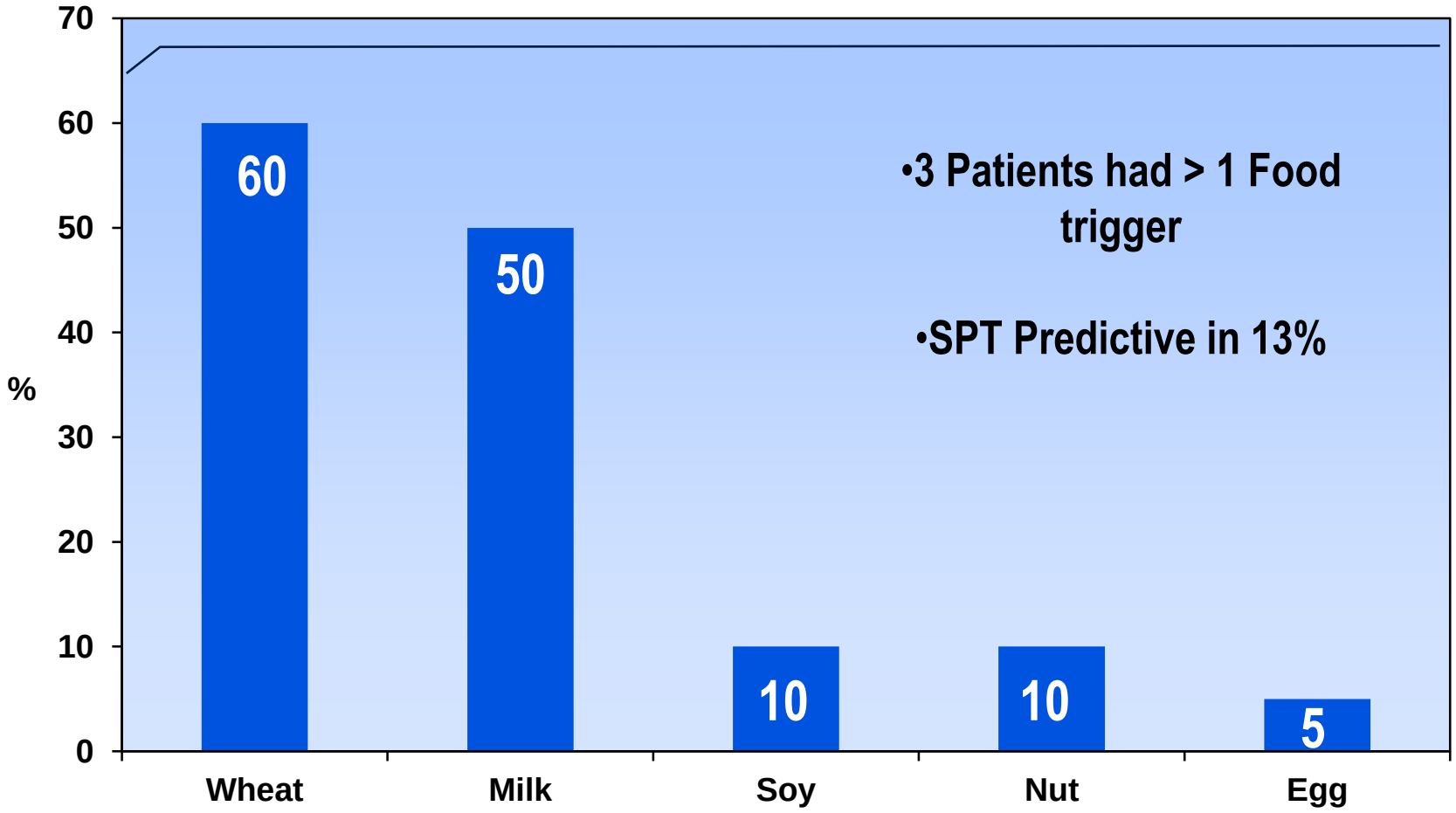
Endoscopic Improvement



Pre Diet | Post Diet | Reintroduction of Wheat

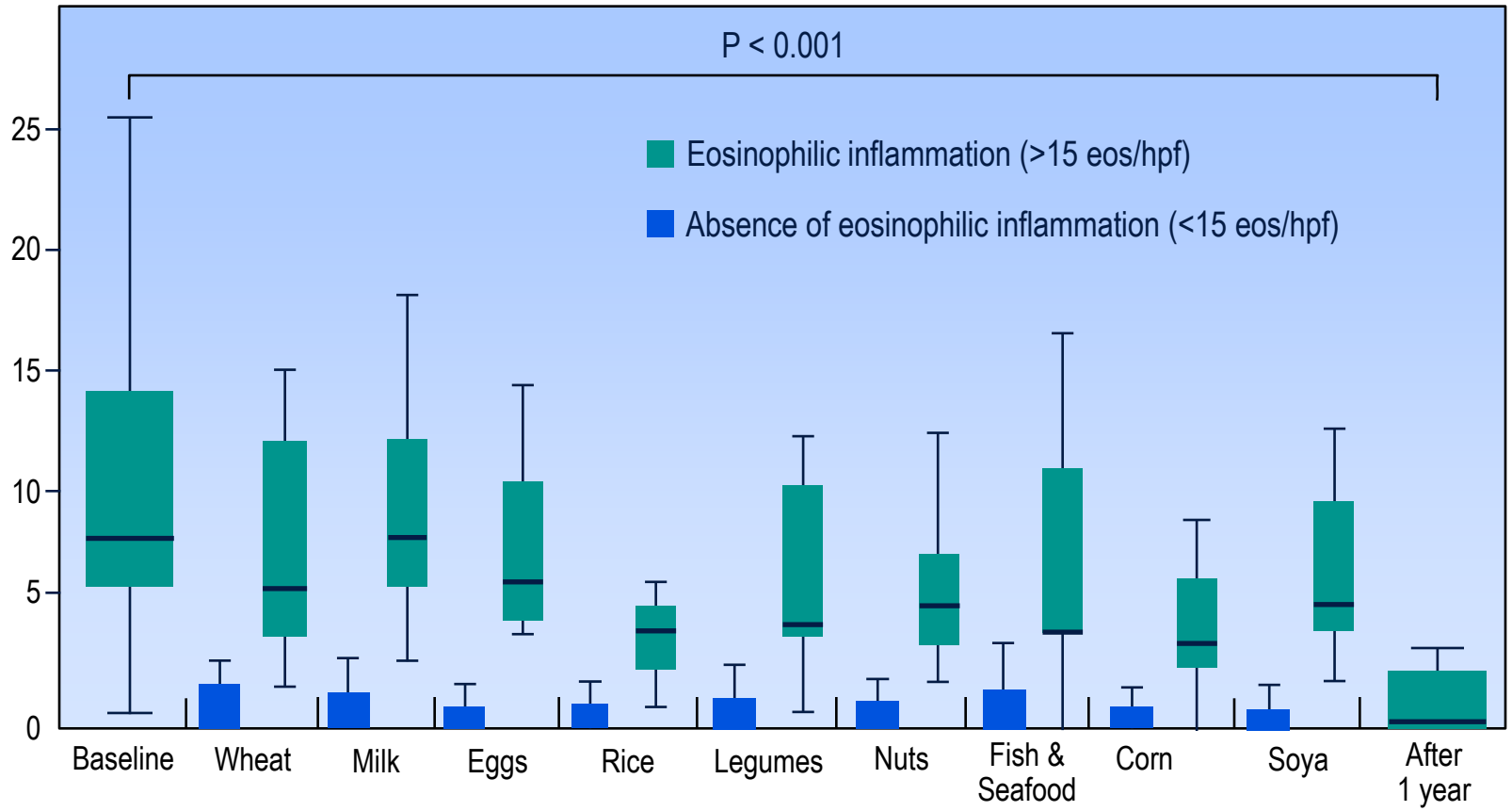
Gonsalves et al. *Gastroenterology.* 2008; 134(Suppl):A104.

Causative Foods in Adult EoE in the US



Gonsalves et al. *Gastroenterol.* 2012;142:1451–59.

SFED in Adults



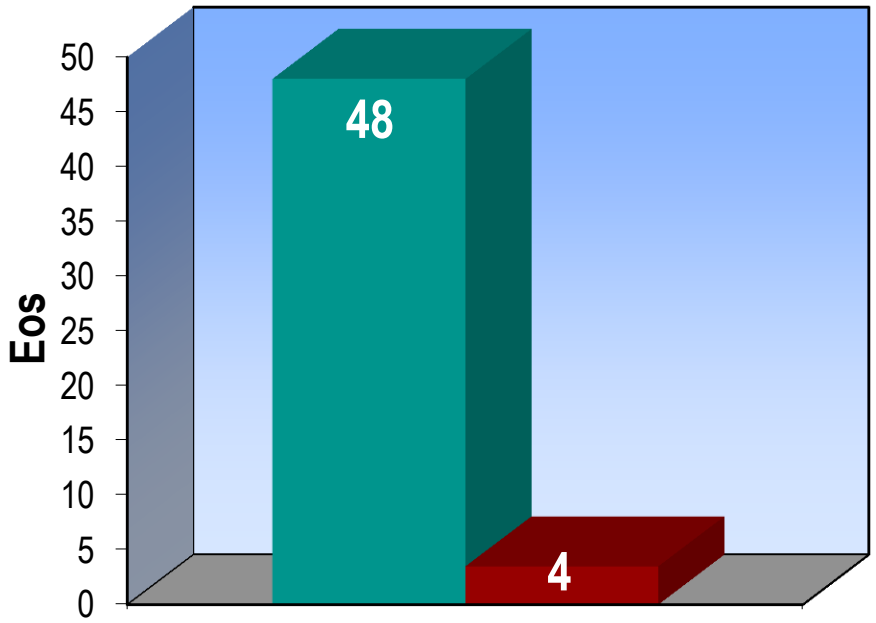
Lucendo et.al. *J Clin All Immunol*. 2013;131:797-804.

Dietary Therapy in Adults in Spain

Empiric elimination of wheat, rice, corn, milk, eggs, soy, peanuts, legumes, fish, shellfish

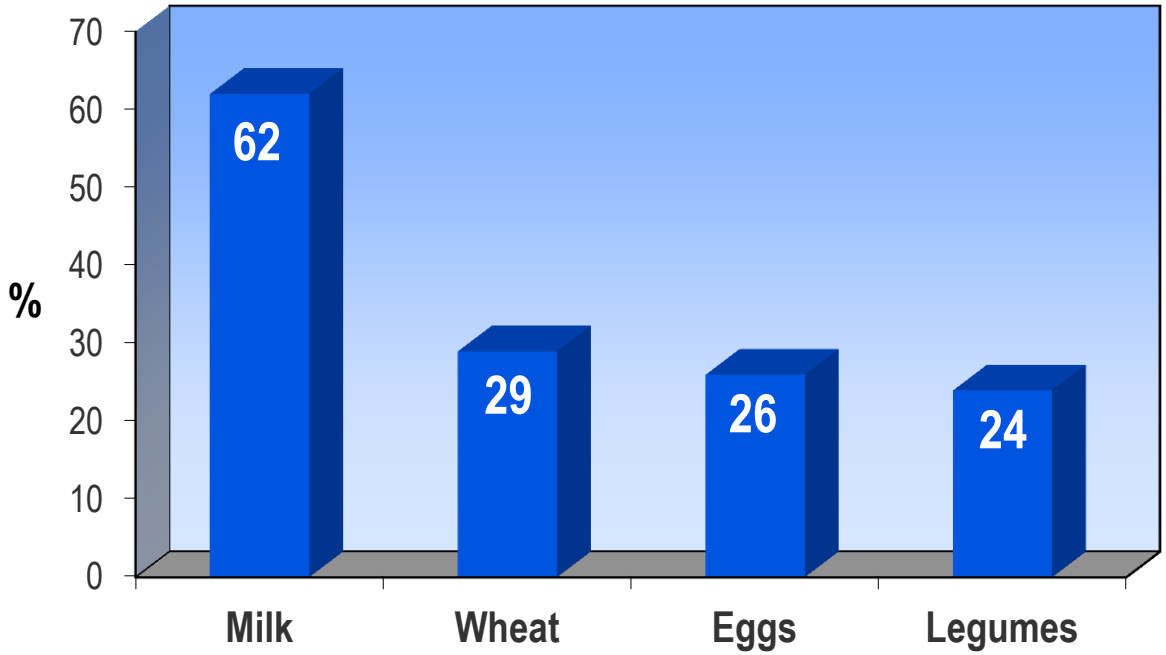
Prospective Study in Adults (n=67)

73% had eos <15/hpf after treatment



Lucendo et al. *J Allergy Clin Immunol.* 2013;131:797-804.

Causative Foods in Adult EoE in Spain



Food Triggers

- ***36% had 1***
- ***31% had 2***
- ***33% >3***

Allergy testing not predictive

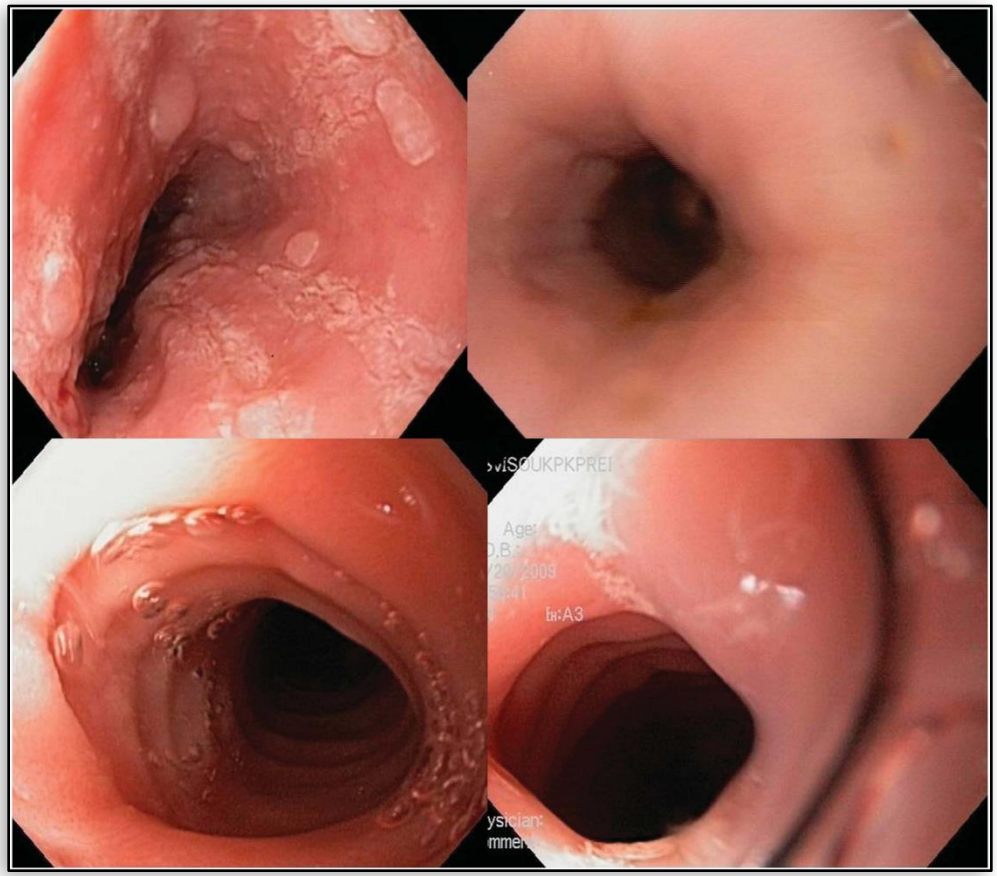
Lucendo et al. *J Allergy Clin Immunol.* 2013;131:797-804.

SFED Diet

- SFED significantly improves symptoms, endoscopic features and histopathology in adults with EoE with 52% achieving <10 eos/hpf
- Skin prick testing was predictive in only 21% of patients therefore dietary elimination based solely on skin prick testing may not be effective in adults

Straumann et al. *Curr Allergy Asthma Rep.* 2006; 6:65.
Gonsalves et al. *Gastroenterology.* 2008; 134 (Suppl):A104.

Elemental Diet in Adults with EoE



- *18 adults*
- *72% with eos <10 after ED for 6 wks*
- *Improvement in endoscopic features and histology, not symptoms*

Peterson et al. *Am J Gastroenterol.* 2013; 108:759–766.

Dietary Summary

Guidelines for Dietary Therapy in EoE

- Dietary therapy (AA formula, SFED, directed diet) should be considered and discussed in all patients with a diagnosis of EoE
- The use of dietary therapy may lead to a complete or near-complete resolution of both the clinical and histologic abnormalities.
- Dietary therapy may reverse esophageal fibrosis.
- Consultation with a registered dietician is strongly recommended to ensure proper calories and micronutrients.

Furuta et al. *Gastroenterology.* 2007; 133:1342-63.
Liacouras et al. *J Allergy Clin Immunol.* 2011; 128:3–20.

Nutrition in EoE

Role of Dietician in EoE

- Assessment of nutritional status
- Determination of dietary adequacy
- Working within dietary restrictions to provide balanced, acceptable diet
- Education of patient & family
- Identification /assessment of barriers to effective nutritional therapy

Role of Dietician in EoE

- Meeting nutritional requirements despite diet restrictions
- Providing ongoing education and support to enhance adherence to restrictions
- Managing problematic feeding behaviors
- Facilitating thorough communication among clinicians and families

Components of Nutrition Assessment

- Accurate anthropometric data
- Detailed diet & symptom history
- Evaluation of dietary adequacy
- Identification of feeding difficulties/food refusal behaviors
- Biochemical

Diet History—Know Where You're Starting

- Types of food/beverages, volume consumed, brand names, ingredients of homemade foods
- Multi-vitamin infusion, herbals, supplemental formulas
- Product labels, school menus
- Review of meal & snack structure (time, location)
- Multiple caregivers involved

Diet History—Established Patient

- Review current list of allergens (determine if and how confirmed)
- Are additional foods avoided? If so, why?
- Assess adherence to diet & confidence in allergen-avoidance

Nutritional Considerations: Dietary Adequacy

- Single-food hypersensitivity managed well with appropriate food choices/substitutions
- Risk of dietary inadequacy increases with multiple allergens
- Micronutrient supplementation often necessary
- Dietary fiber supplementation may be needed
  - Alternate grains tend to be low in fiber
  - No/little fiber in elemental formulas
  - Increase fruits & vegetables as able; some commercial fiber supplements can be used

Elimination Diets

Essentials

- Careful identification of allergens
- Education of patient, family, other caregivers
- Assessment and monitoring to ensure adequate intake, preservation/improvement of nutritional status
- Supplementation with elemental formula may be needed

Food Allergen Labeling and Consumer Protection Act (FALCPA)

- Requires foods manufactured on or after 1/1/06 to include declaration of presence of a “major food allergen”:

Milk	Egg	Wheat
Peanut	Tree nut*	Soybean
Fish*	Crustacean shellfish*	

- *Specific type will be used (e.g., almond/walnut, flounder/cod, crab/shrimp, etc.)
- All packaged food sold in U.S.(domestic/imported)

Elimination Diets: Keys to Success

- Reading food labels crucial to successful avoidance
  - Should be read each time patient/family shops
  - Contacting manufacturer only way to clarify presence of “minor” allergen
  - Avoid food if any doubts or if ingredient list not available.
  - Educate family re: FALCPA
- Education on cross-contamination (home/restaurants)
- Acquainting families with resources to assist with food shopping/prep, restaurant eating, etc.
- Emphasizing what CAN be eaten vs. what cannot

Elemental Diet

- 100% amino-acid based formula as sole source of nutrition (Neocate, Elecare, etc.)
- Can use in combination with elemental semi-solid (Neocate Nutra)
- Usually no solid food. Water OK. Certain fruit juices /Gatorade/candy (Dum-Dums/Smarties) may be permitted
- Typically 4-6 weeks, then repeat endoscopy
- Tube feeding if volume goals cannot be met by mouth

Elemental Formulas: Enhancing Acceptance

- Flavoring formulas sometimes helpful
  - Flavor packets from manufacturer
  - Chocolate/strawberry syrup (allergen-free)
  - Sugar-based drink mixes (Kool-Aid, Crystal Light)
- Serve chilled; smoothies/popsicles
- Closed cup (with/without straw) sometimes helpful

Practical Considerations

- Cost
- Food refusal behaviors
  - May persist after allergens are removed or biopsies normalize (in EoE); refer to feeding specialist sooner vs. later
- Access to allergen-free products remains limited in some areas
  - May require modification of plan (if able)

Family Support

- Work with schools to educate staff and minimize risk of allergen exposure (FARE program)
  - Provide safe, non-perishable foods for snack time, parties
  - Emergency kit /Epi must be available
  - Other FARE resources (restaurants, camps, etc.)
- Thorough, updated, easily understood education materials
- Team communication (Allergy/GI/Nutrition)
- Provide information to empower patients families and encourage self-education. Practice the “art” of delivering the science.

Family Support

- Depression
  - Kids (perceived deprivation; hard being “different”)
  - Parents can have significant fears (food safety/cross-contamination, tube feedings, letting others care for their children, question ability to safely feed their own children)
- Address concerns when they arise and refer directly or work with PCP to encourage families to seek support when needed

Allergy Testing

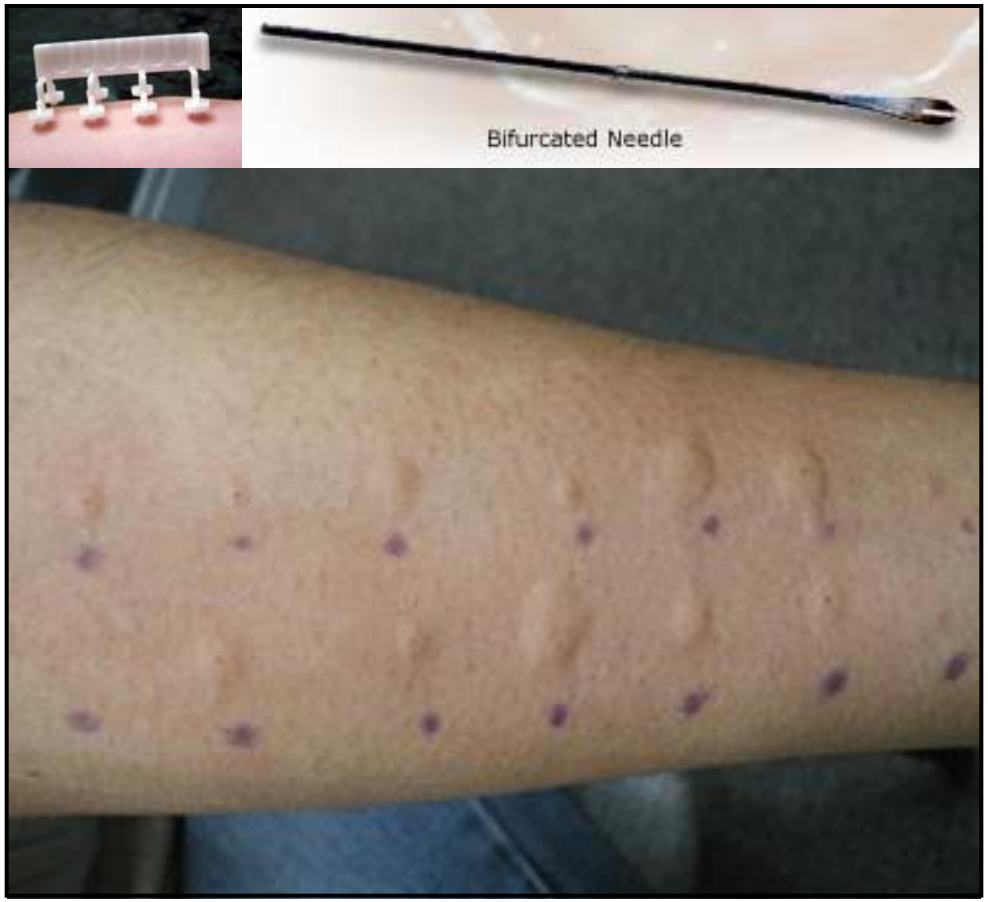
Types of Allergy Testing

- Prick Skin
- Specific IgE
- Atopy Patch
- Others
  - Provocation/neutralization, cytotoxic tests, applied kinesiology (muscle response testing), hair analysis, electrodermal testing, food-specific IgG or IgG4 (IgG "RAST")

Prick Skin Test

- Test for specific IgE to food
- Tests for immediate reactions
  - Hives, respiratory symptoms, anaphylaxis
  - Food reactions are reproducible
- Size of reaction does not indicate severity of reaction
- Predictive values vary for each food, test and by age

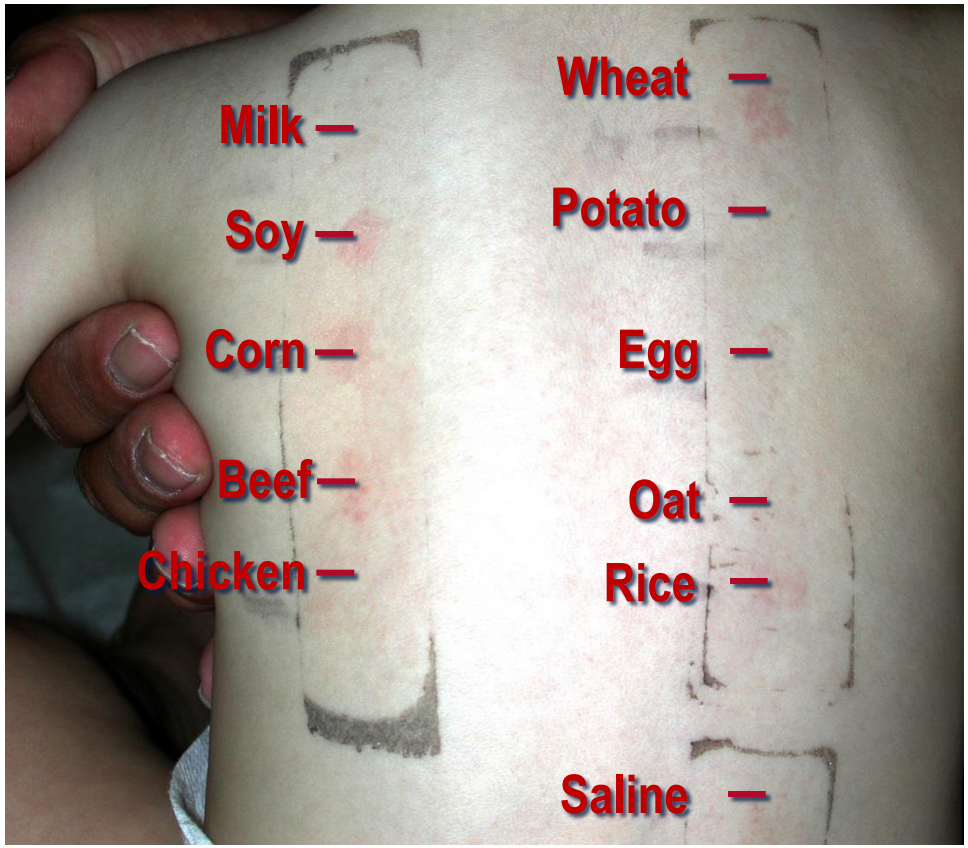
Skin Test Devices/Reactions



Atopy Patch Test

- For non-IgE mediated reaction
- First developed for contact dermatitis in 1890s
- Developed for foods in 1990s
- Used in atopic dermatitis and EGIDs
- Reagents are not standardized

Atopy Patch Testing



Other Treatments for EoE

Other Treatments for EoE

- In addition to the more accepted treatments for EoE, there are a few treatments that have been reported in small patient samples
  - Mast-cell stabilizers
  - Leukotriene receptor antagonists
  - Anti-tumor necrosis alpha antibodies

Mast Cell Stabilizers

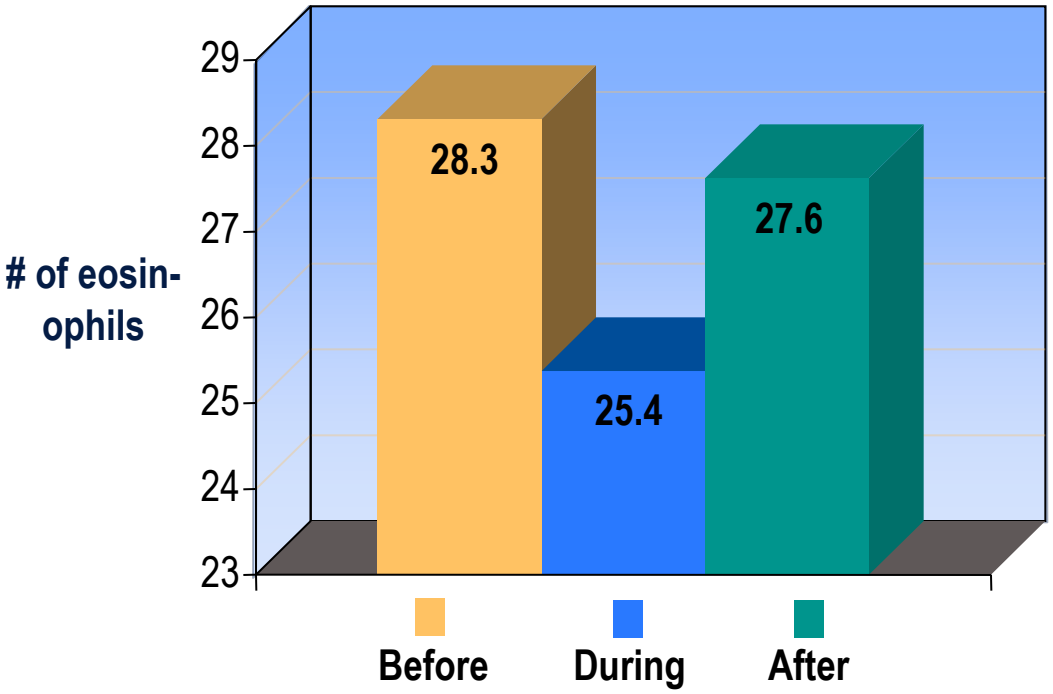
- Agents
  - Cromolyn sodium (Gastrocrom®)
  - Ketotifen fumarate
- Actions
  - Block IgE-mediated calcium channels on the mast cell membrane
  - Prevents the release of mast cell granules that contain histamine and leukotrienes

Mast Cell Stabilizers

- Long history of use in asthma and allergic conjunctivitis
- Numerous anecdotal reports in eosinophilic gastrointestinal disorders
- Potential benefits
  - Excellent safety profile
  - Minimal side effects
  - Ease of administration

Response of EoE to Cromolyn Sodium

- 14 patients
- GER symptoms
  - 0/13 improved
- Dysphagia
  - 0/1 improved



Liacouras et al. *Clin Gastroenterol Hepatol.* 2005; 3:1198-1206.

Ketotifen Fumarate

- Mast cell stabilizer with anti-histamine activity
- May have direct inhibitory effects on eosinophils
- No reported trials for EoE
  - Several reports of improvement in patients with eosinophilic gastroenteritis
- Available in the United States as an ophthalmic preparation and in Europe as an oral form

Leukotriene Receptor Antagonists

- Montelukast (Singulair®)
  - Blocks the action of leukotriene D4 at CysLT1
  - CysLT1 found in eosinophils, among other places

- Trial of 8 EoE patients
  - 7 of 8 patients with dysphagia had resolution of symptoms
  - 5 patients remained in clinical remission for 14 months
  - Patients relapsed within 3 weeks of stopping the medication
  - No histologic changes occurred

Attwood et al. *Gut.* 2003; 52(2):181-185.

Biologic Treatment

Interleukin 5 (IL-5)

- Cytokine that regulates eosinophil function
  - Proliferation and release from bone marrow
  - Maturation
  - Survival
  - Activation
- Overproduction of IL5 in transgenic mice leads to eosinophilic esophagitis

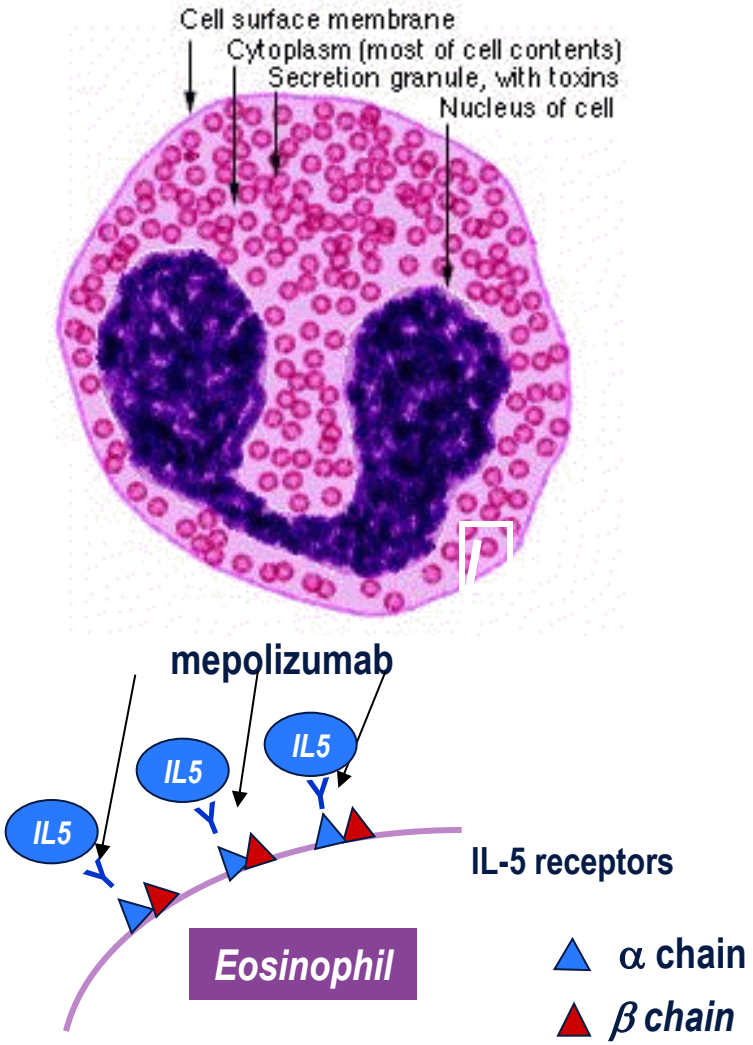
Mishra et al. *J Immunol.* 2002; 168:2464-2469.
Stein et al. J *Allergy Clin Immunol.* 2006; 118:1312-1319.

Anti-IL5

- Investigational monoclonal antibody - direct antagonist of IL-5
- Effective for hypereosinophilic syndrome
- Effective in a small series of adults with EoE (n = 4), with dramatic reduction in esophageal eosinophilia
- Pediatric trials in progress

Rothenberg et al. *N Engl J Med.* 2008; 358(12); 1215-1228.
Stein et al. *J Allergy Clin Immunol.* 2006; 118:1312-1319.

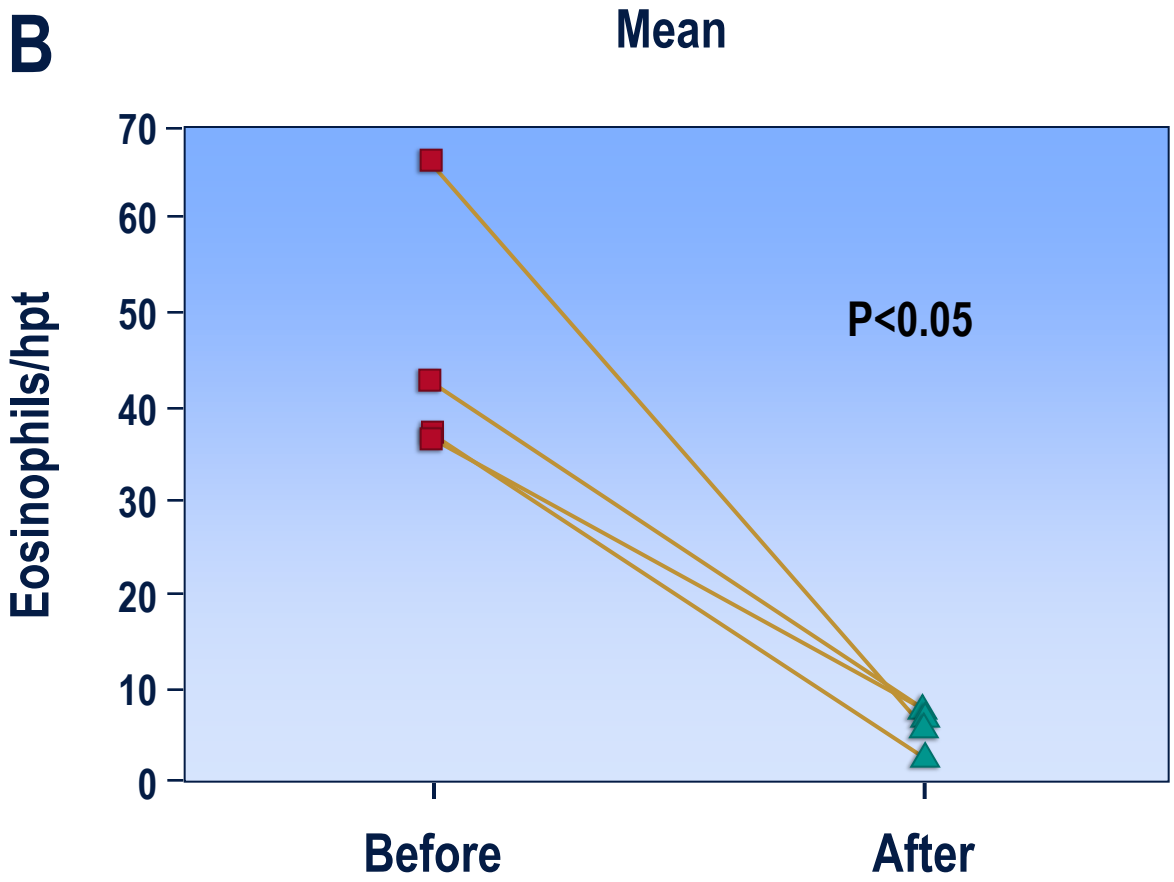
Anti-Interleukin 5



- IL-5 is the predominant cytokine mediating eosinophil function; eosinophil lifeline
- Pediatric and Adult trials –
- Eos counts reduced in most; complete histologic resolution in only a small #. No change in symptoms in adults.

Straumann et al. *Gut.* 2010;59:21–30.

Anti-IL5 on Esophageal Eosinophils



Stein et al. *J Allergy Clin Immunol.* 2006: 118:1312.

Anti-IL5 - Current Studies

- Mepolizumab
  - Utilized 3 different doses of anti-IL5 via 4 week infusions
  - Significantly reduced esophageal eosinophilic inflammation
  - Symptom improvement difficult to assess
- Reslizumab
  - Placebo controlled trial
  - Anti-IL5 significantly reduced esophageal eosinophils
  - Symptom improvement similar between placebo and anti-IL5

Assa'ad et.al. *Gastroenterol*. 2011;141:1593-1604
Spergel et.al. *J All Clin Immunol.* 2012;129:456-63

Overall Treatment Approaches

Treatment

- EoE has become a significant component of most practices in both pediatric and adult gastroenterology
- Centers for the care of patients with EoE have been developed to coordinate multiple health care providers including allergy/immunology, gastroenterology, and nutrition

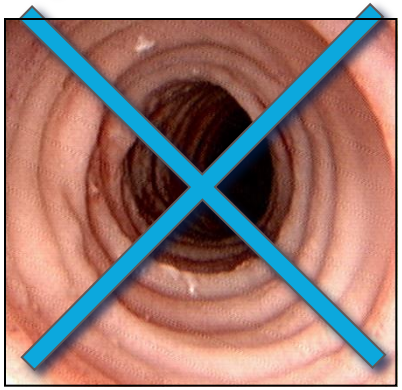
A trial of PPI therapy is required for patients with presumed eosinophilic esophagitis, even if the diagnosis seems clear-cut.

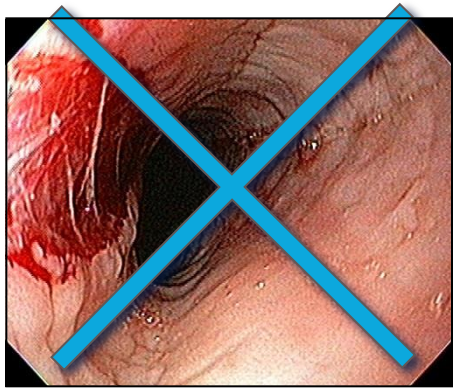
Spechler et al. *Am J Gastroenterol.* 2007;102(6):1301.

Treatment Goals of EoE

- Eliminate symptoms
  - Dysphagia
  - Heartburn

- Prevent complications
  - Esophageal stenoses
  - Esophageal fragility

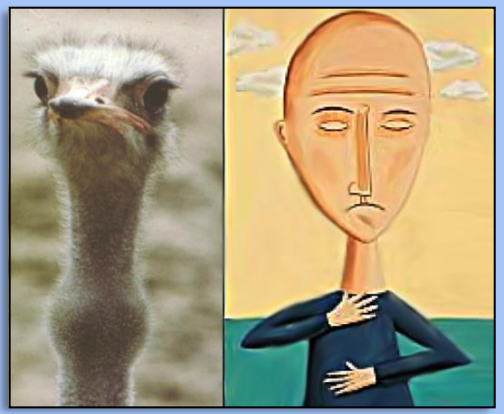




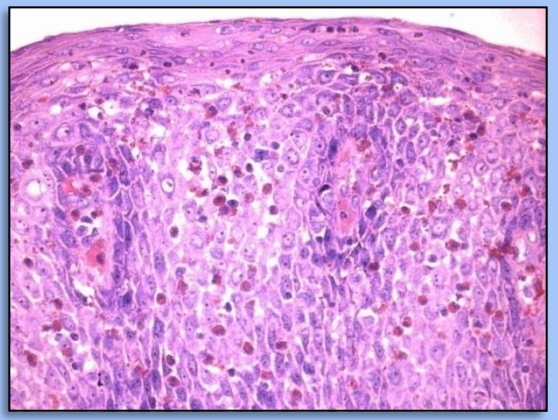
Endoscopic photos from Dr. Ikuo Hirano

Proposed Endpoints for Treatment of Eosinophilic Esophagitis

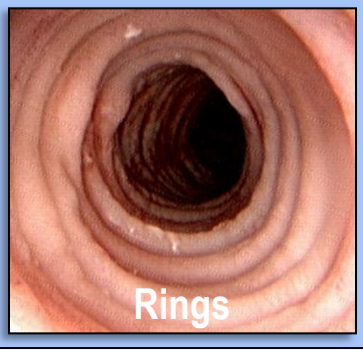
Symptomatic Remission

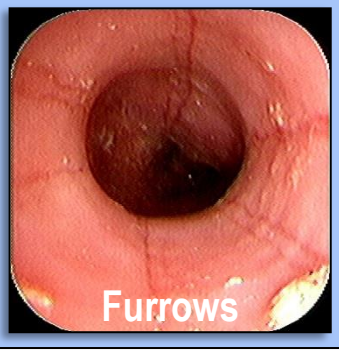


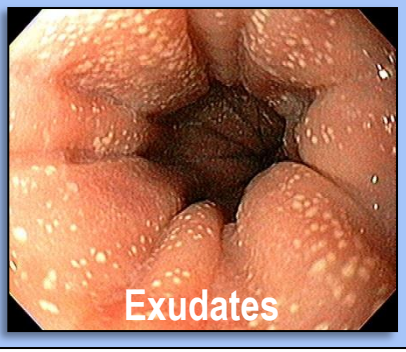
Histological Remission



Endoscopic Remission







Endoscopic photos from Dr. Ikuo Hirano

Is Symptomatic Remission Sufficient?

For Requiring Histological Remission

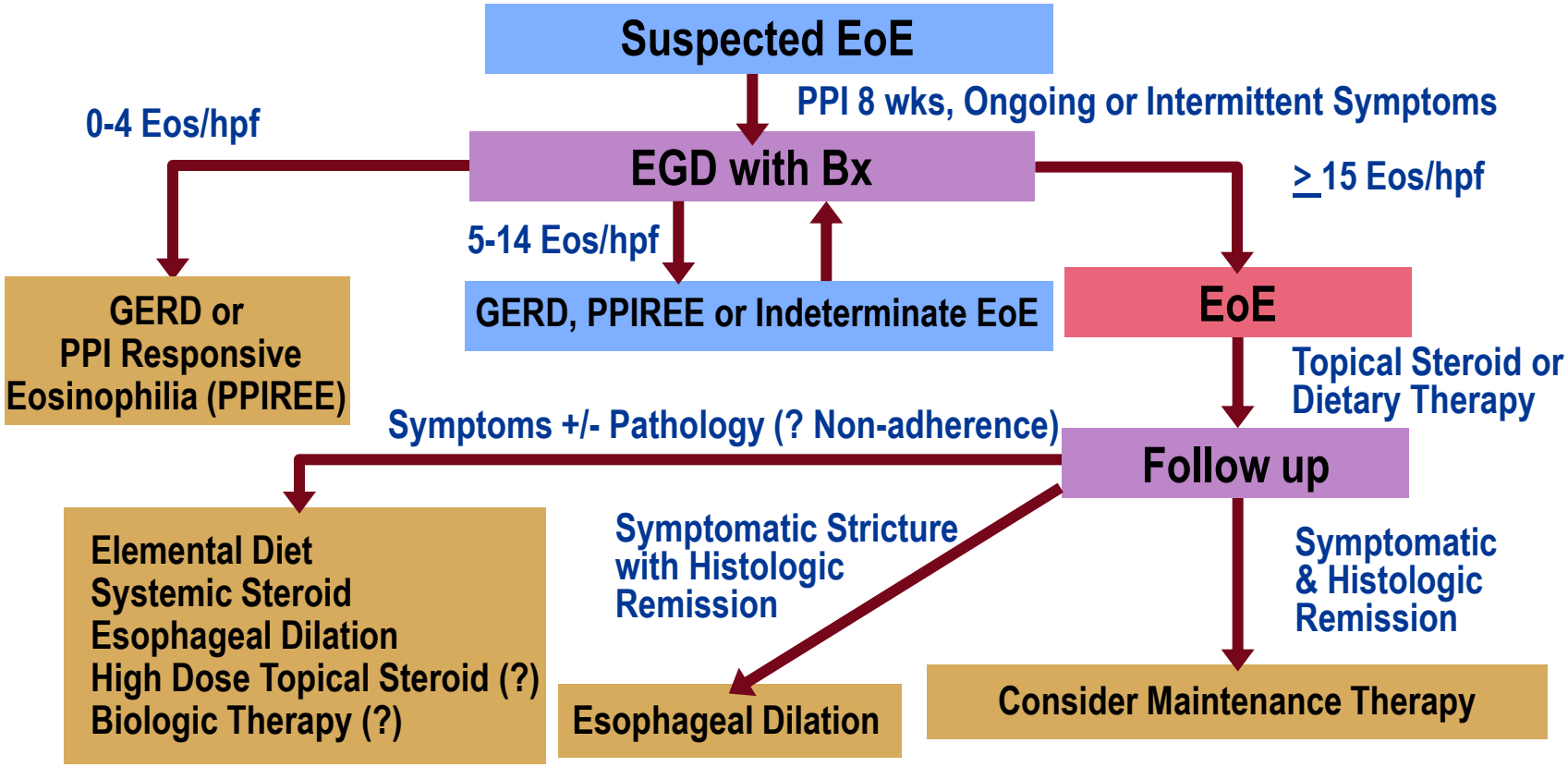
- Experimental and clinical evidence that eosinophils cause tissue remodeling (e.g. collagen deposition)[1]
- Therefore, elimination of esophageal eosinophils should prevent complications

Against Requiring Histological Remission

- Requires endoscopy (expense, inconvenience, risk)
- Might need higher doses and additional meds (expense, inconvenience, risk)
- No proof of efficacy in preventing complications

Mishra et al. *Gastroenterology.* 2008; 134:204.

Suggested Algorithm for Management of Eosinophilic Esophagitis



Hirano, I. *Eosinophilic Esophagitis.* 2012. Ed C. Liacouras. 2011.

Future

The Next Frontiers

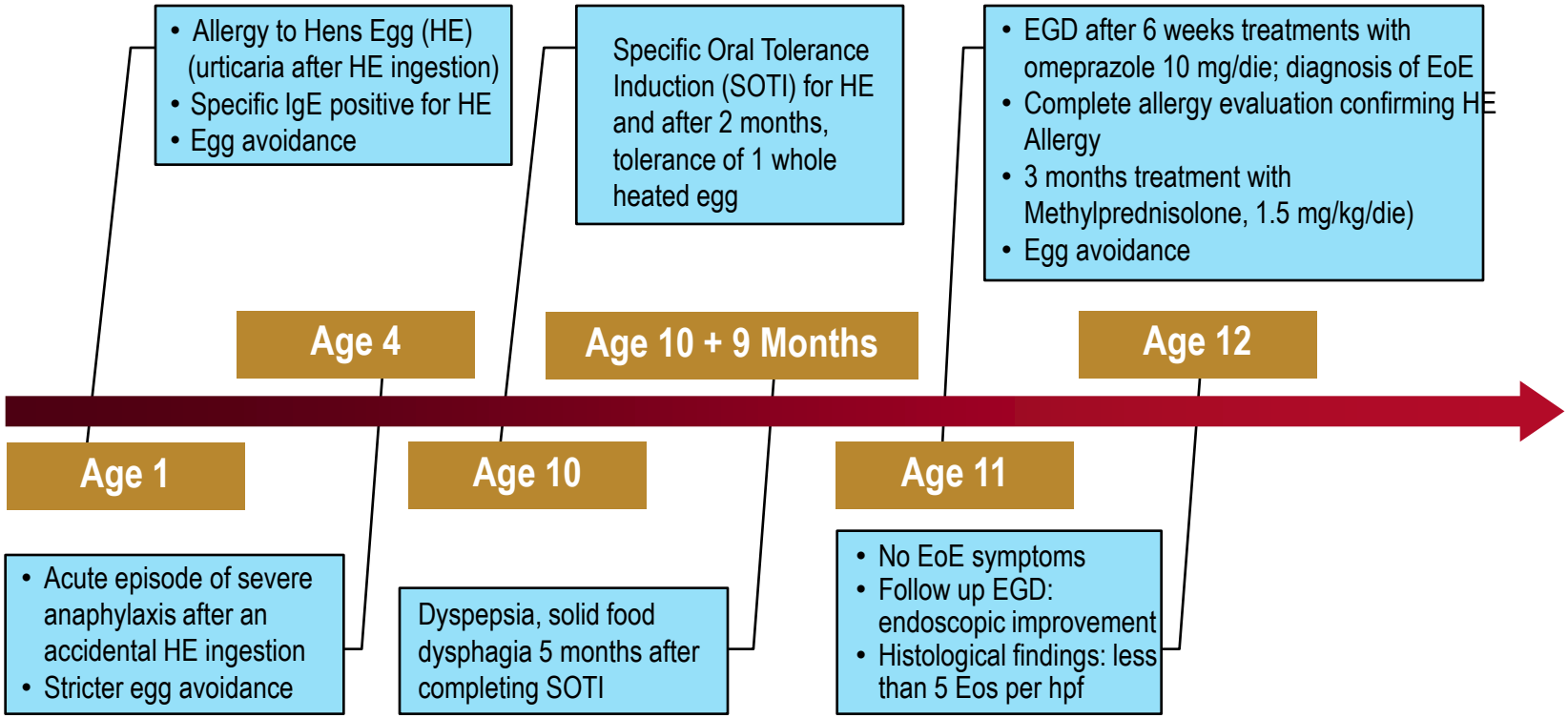
- Steroid formulations with greater viscosity and/or esophageal tissue adherence; other delivery methods
- Antibodies targeting IL-13 and eotaxin
- Prostaglandin D2 inhibitor – 'CRTH2'
- ? co-therapy with PPI – augment CRTH2; block eotaxin-3 release
- Other mechanisms of PPI effects
- FDA approval of drugs currently used or under study

EoE - Future Testing Methods

- Esophageal biomarkers
- Serum biomarkers
- Esophageal String Test
  - Capsule filled with a 90 cm string, swallowed with string to remain in place (taped to face) for a period of time
  - String removed and proximal secretions evaluated for biomarkers of disease

Furuta et.al. *Gut*. 2013;62:1395-1405.
Bhardway N et al. *Ann All Asthma Immunol*. 2012;109:155-9

Oral Immunotherapy Induces EoE



- Seen after egg, milk and peanut oral immunotherapy
- Incidence about 5-20%
- Indicates foods causes EoE and it is not TH_2 mechanism

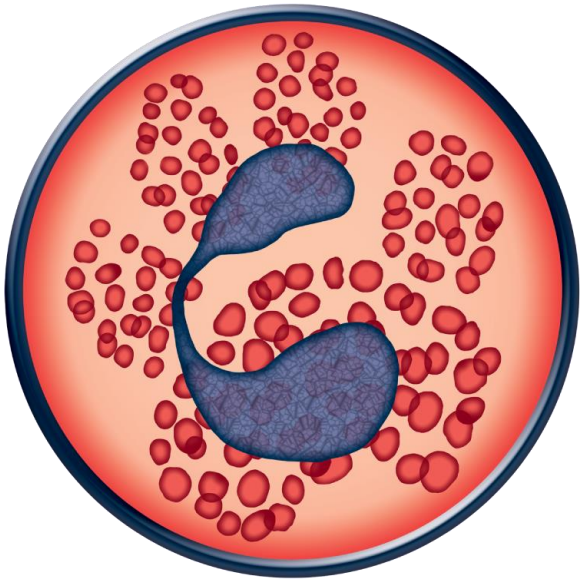
Ridolo et al. *Ann Allergy Asthma Immunol.* 2011 Jan; 106(1):73-74.
Cepeda et al *J. Allergy Clin Immunol.* 2012 129:1416-1468.

Advocacy Groups

Advocacy Groups

- American Partnership for Eosinophilic Disorders
  - www.apfed.org
- Campaign Urging Research for Eosinophilic Disorders
  - www.curedfoundation.org
- Food Allergy Network
  - www.foodallergy.org

TIGER



TIGER

THE INTERNATIONAL GASTROINTESTINAL EOSINOPHIL RESEARCHERS

Conclusions

- EoE is a clinico-pathologic disorder diagnosed by clinicians
- EoE can occur “at any age”
- Pediatric and Adult EoE are likely the same disease
- Incidence and prevalence continue to increase
- Important that you make the distinction between
  - Eosinophilic Esophagitis
  - Esophageal Eosinophila
  - “PPI-responsive” esophageal eosinophilia
- “Stay tuned”
  - Expect changes to occur within the guidelines as therapy, research and interest continues