

# Eosinophilic Esophagitis Diagnosis & Management

*2nd Edition*  
*Core Slide Set*

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# Presenter Disclosure

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# 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.



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# Background & Natural History



# 1995 Distribution of EoE



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# 2013 Distribution of EoE



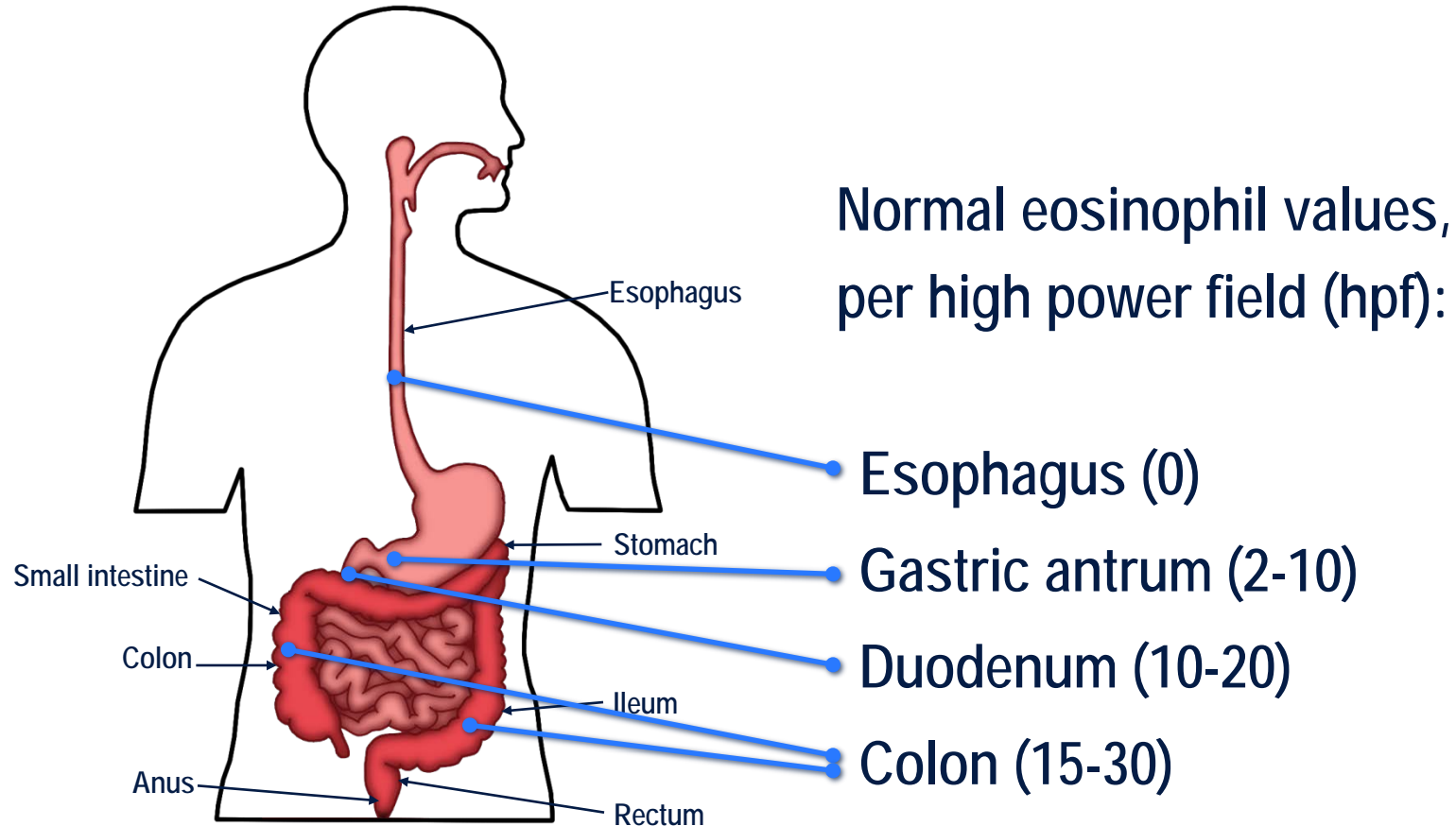


# Natural History Adults

- 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





# 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



# 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





# 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)

# PPI-Responsive Esophageal Eosinophilia

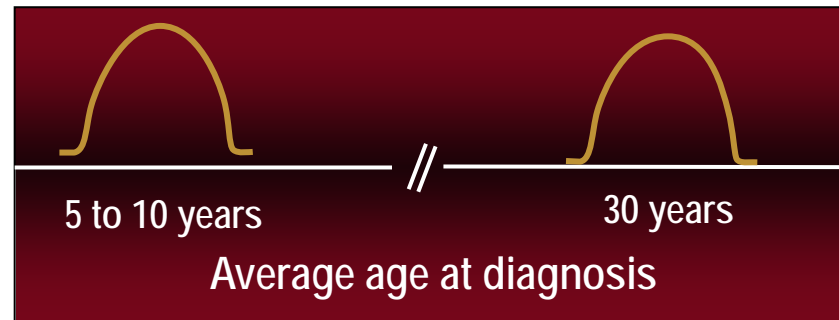


# PPI-Responsive Esophageal Eosinophilia

- 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

# 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.

# Frequency of EoE in a Single County<sup>‡</sup>

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

<sup>‡</sup> Hamilton County, OH

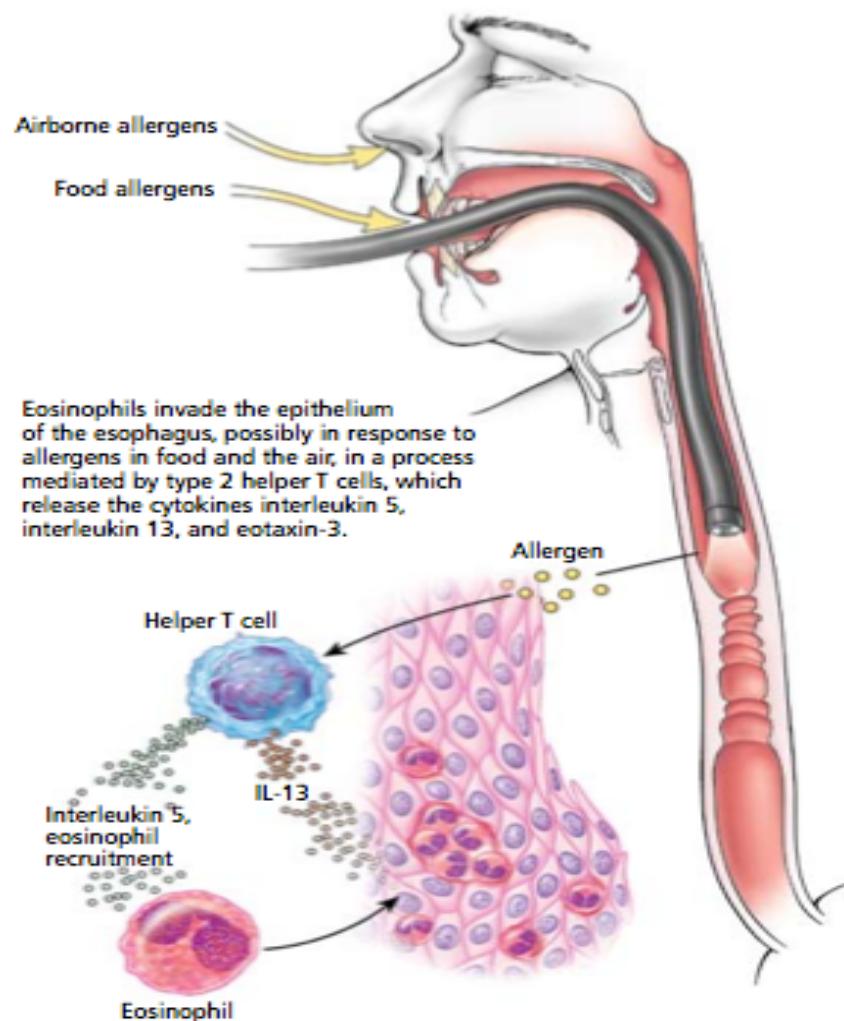
<sup>\*</sup> per 10,000 population age 0-19 years

<sup>†</sup> Chi-square test for trend NS

# 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







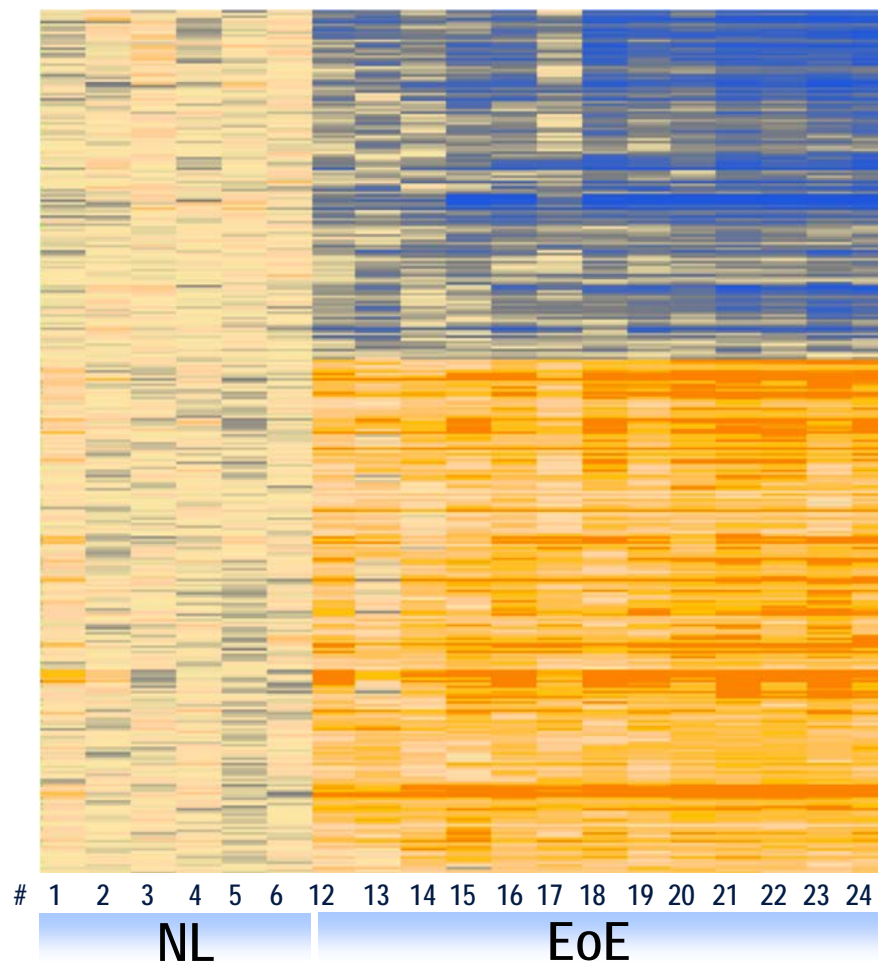
# Cells Related to EoE

- 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

# Genetics



# Gene Expression Profile of EoE



230 Genes  
Downregulated

344 Genes  
Upregulated

EoE patients have a unique gene expression profile



# EoE - Genetics

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

# 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.

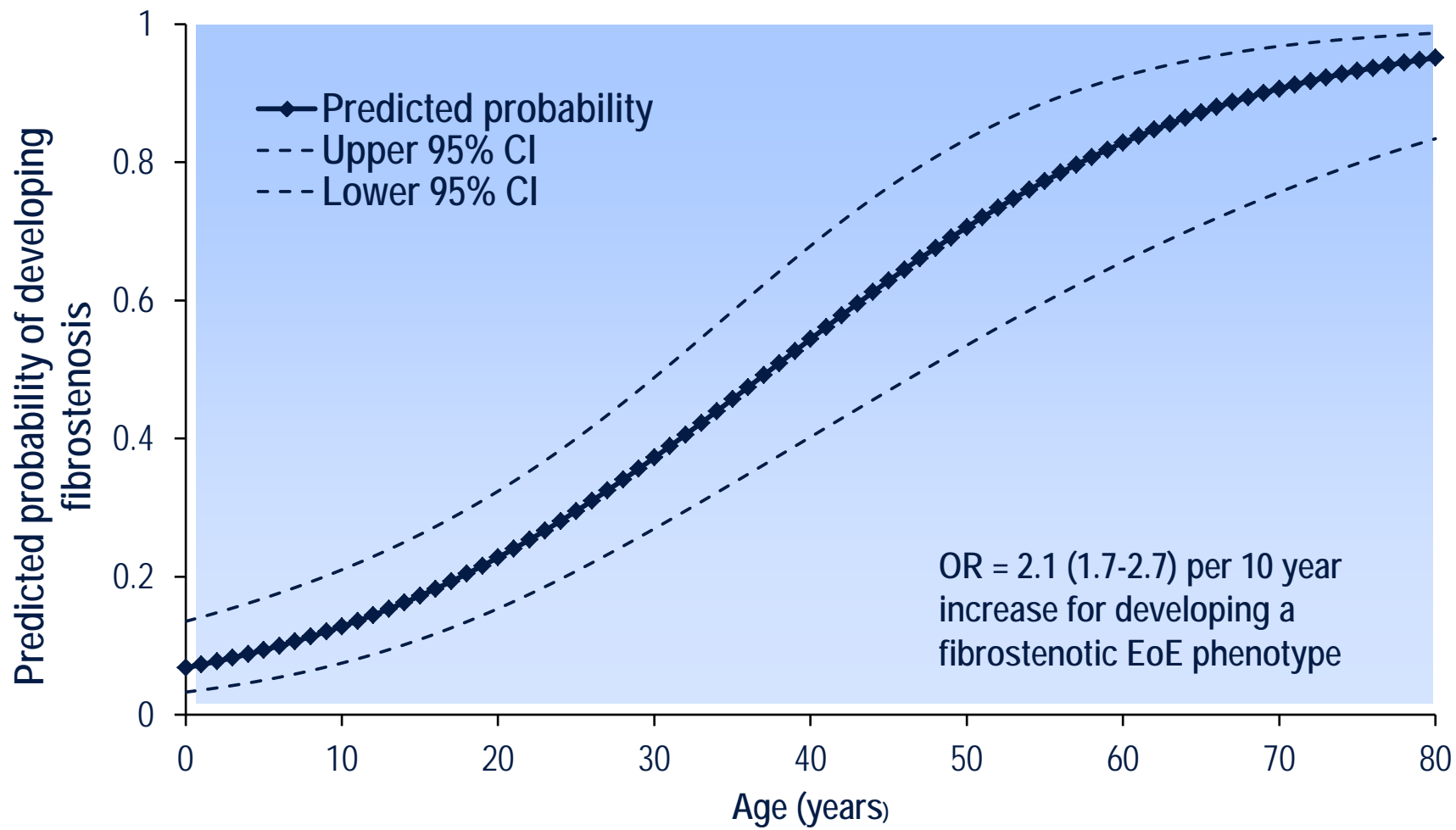
Chehade et al, *J Pediatr Gastroenterol Nutr.* 2007; 45(3):354-357.

Aceves et al. *J Allergy Clin Immunol.* 2007; 119(1):206-2012.





# EoE as a Progressive Disease



# Pediatric Clinical Symptoms



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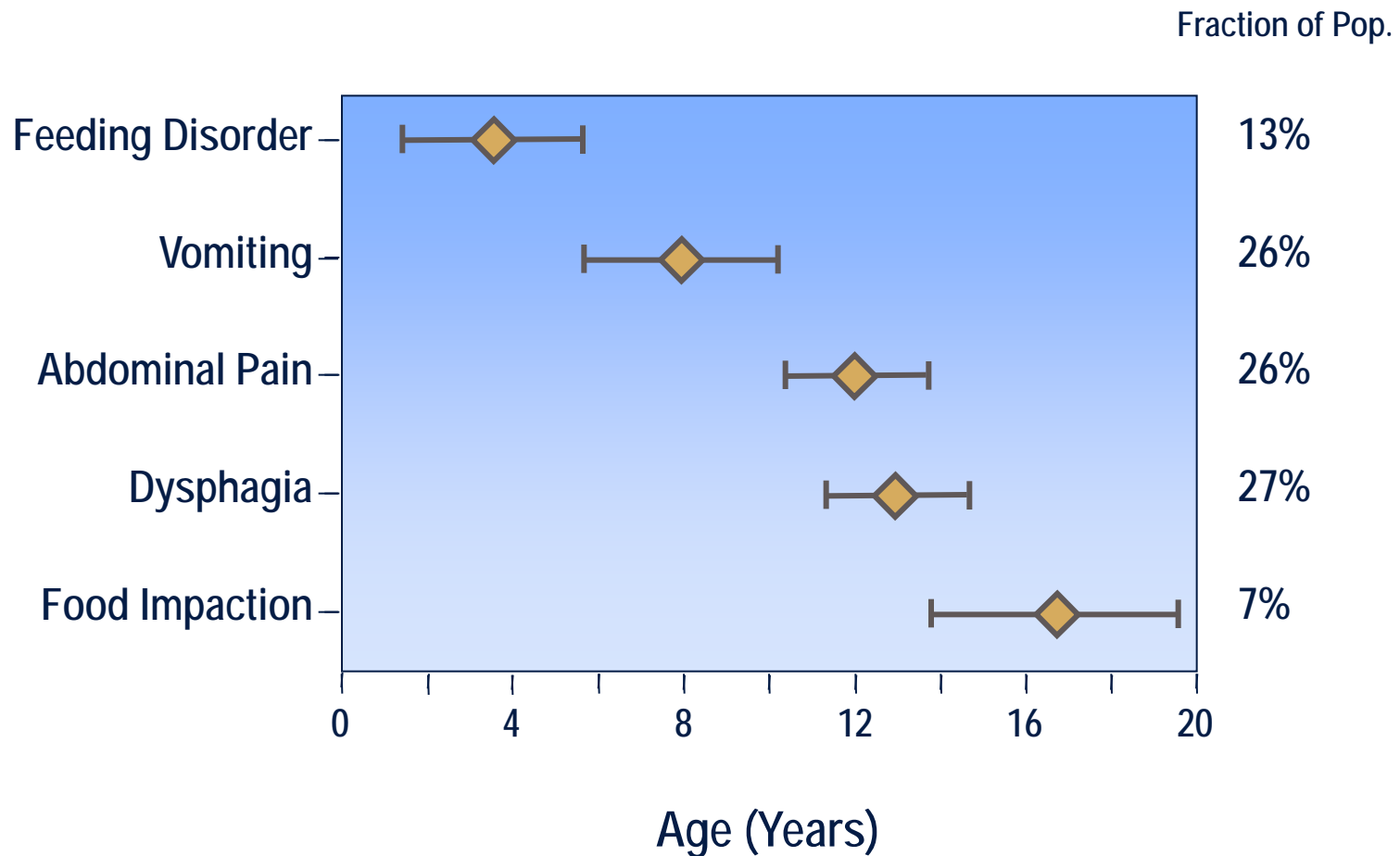


# Clinical Features

- 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



# EoE Presentation by Age





# 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



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# 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

# 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

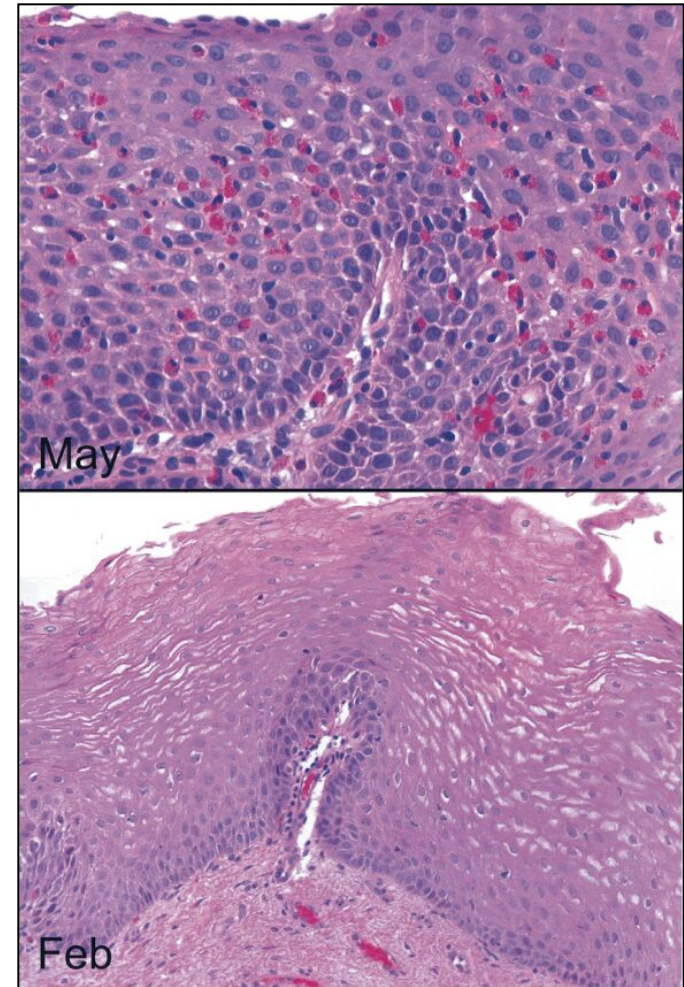
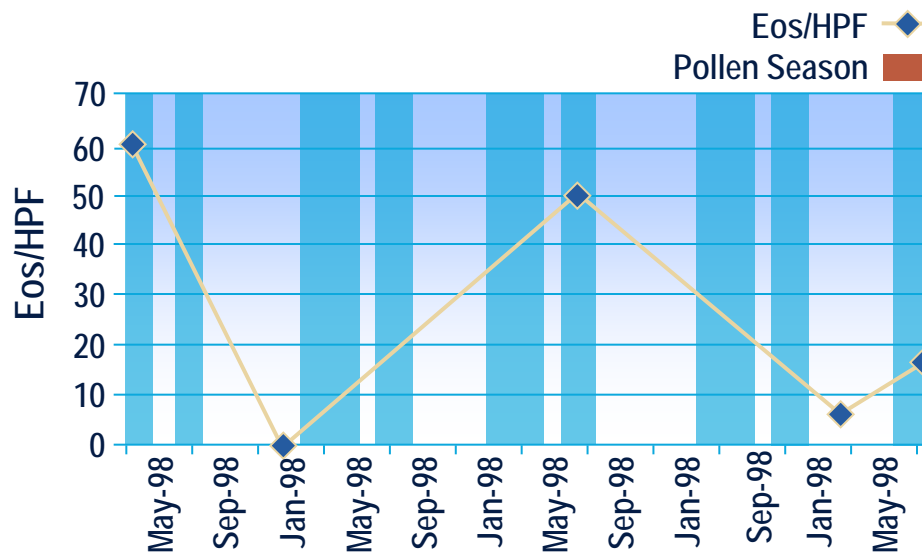
\* H/O positive skin-prick, RAST, or clinical response



# Association with Environmental Allergies

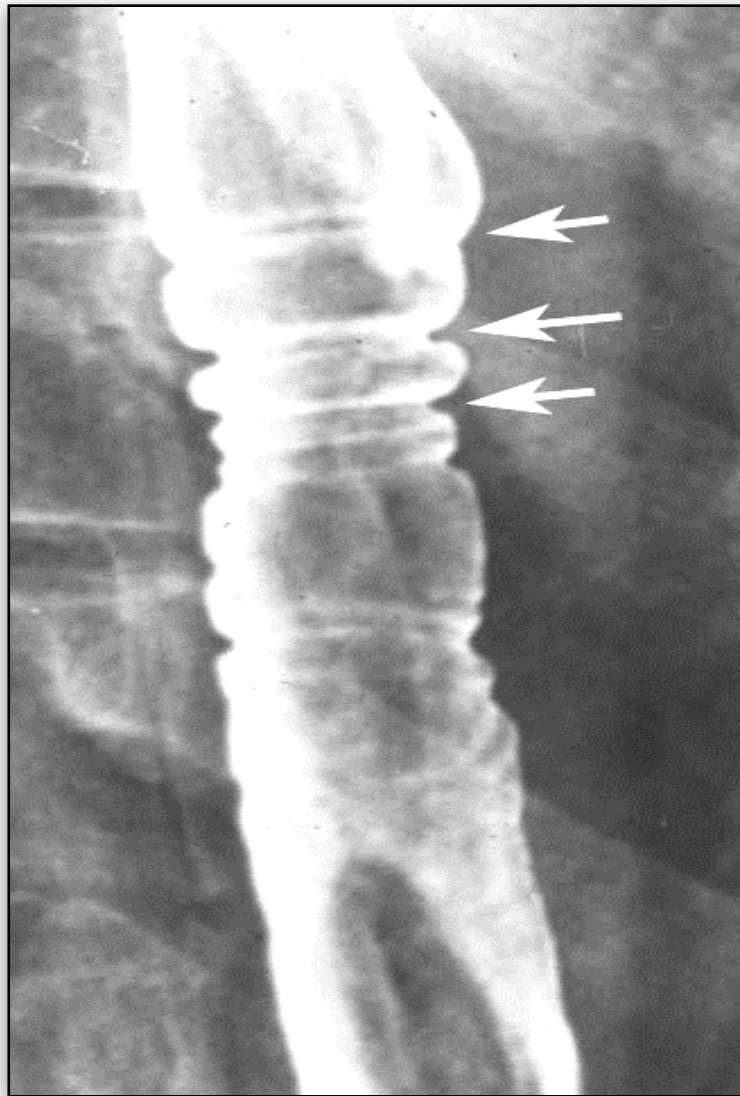
# Seasonal Variation in EoE

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

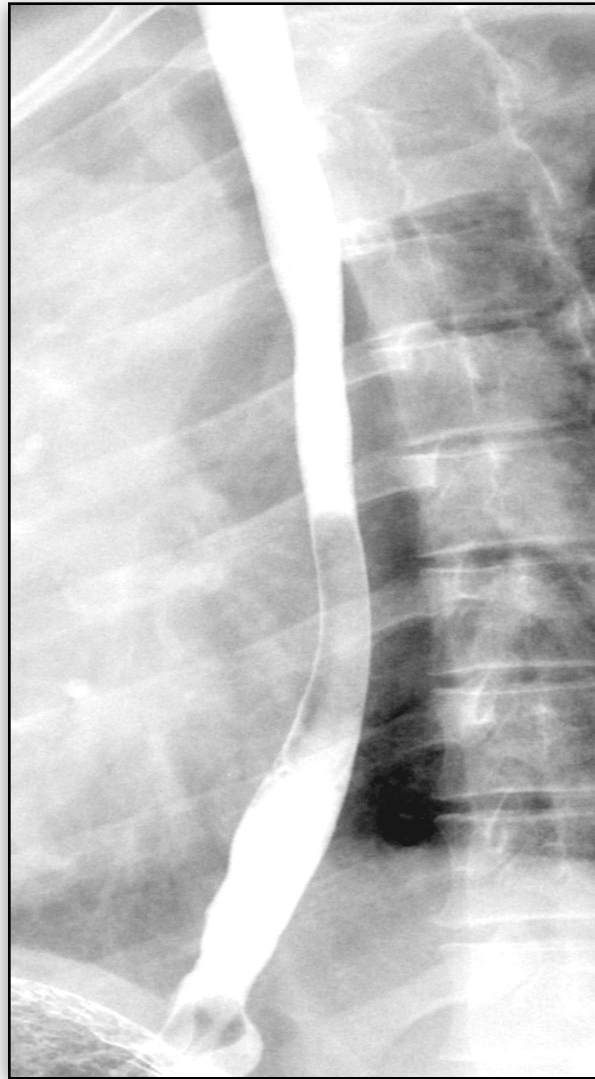


# Radiologic Findings

# Esophageal Rings

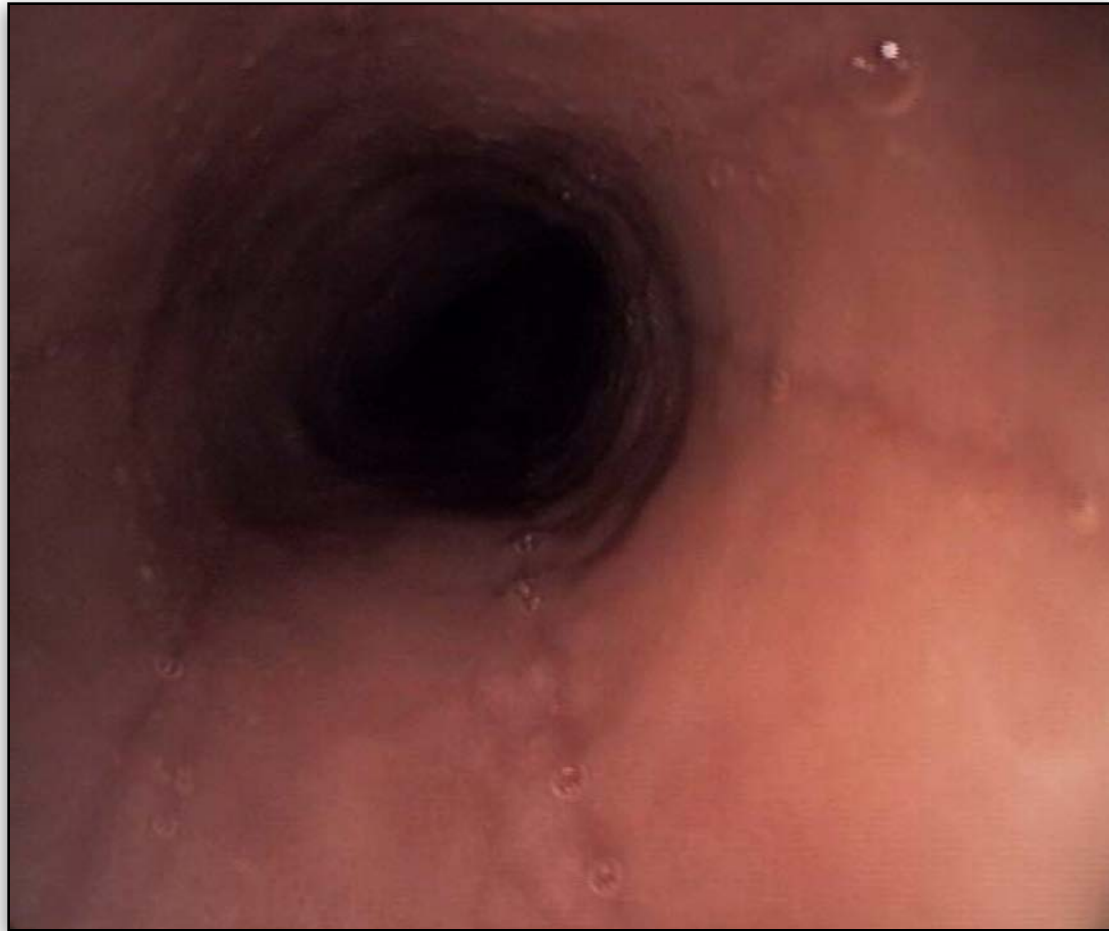


# Small Caliber Esophagus



# Endoscopic Findings

# Esophageal Furrowing







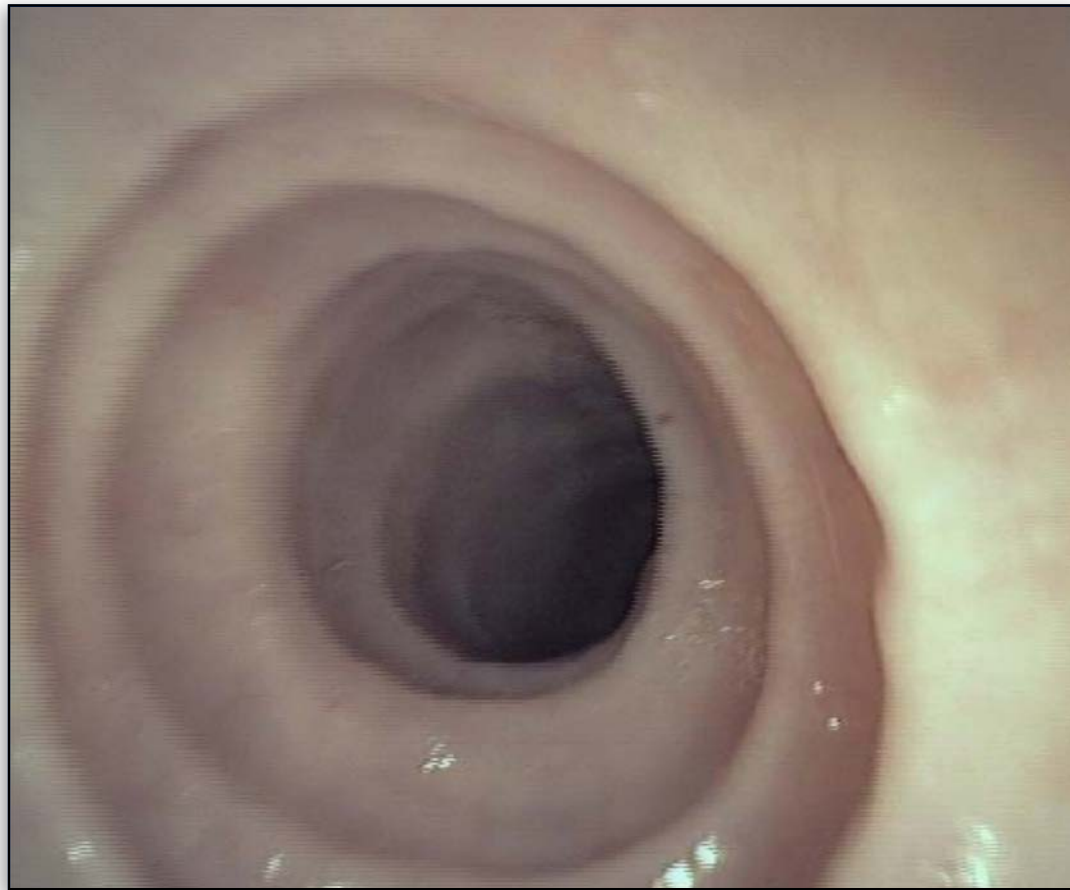
# White Plaques





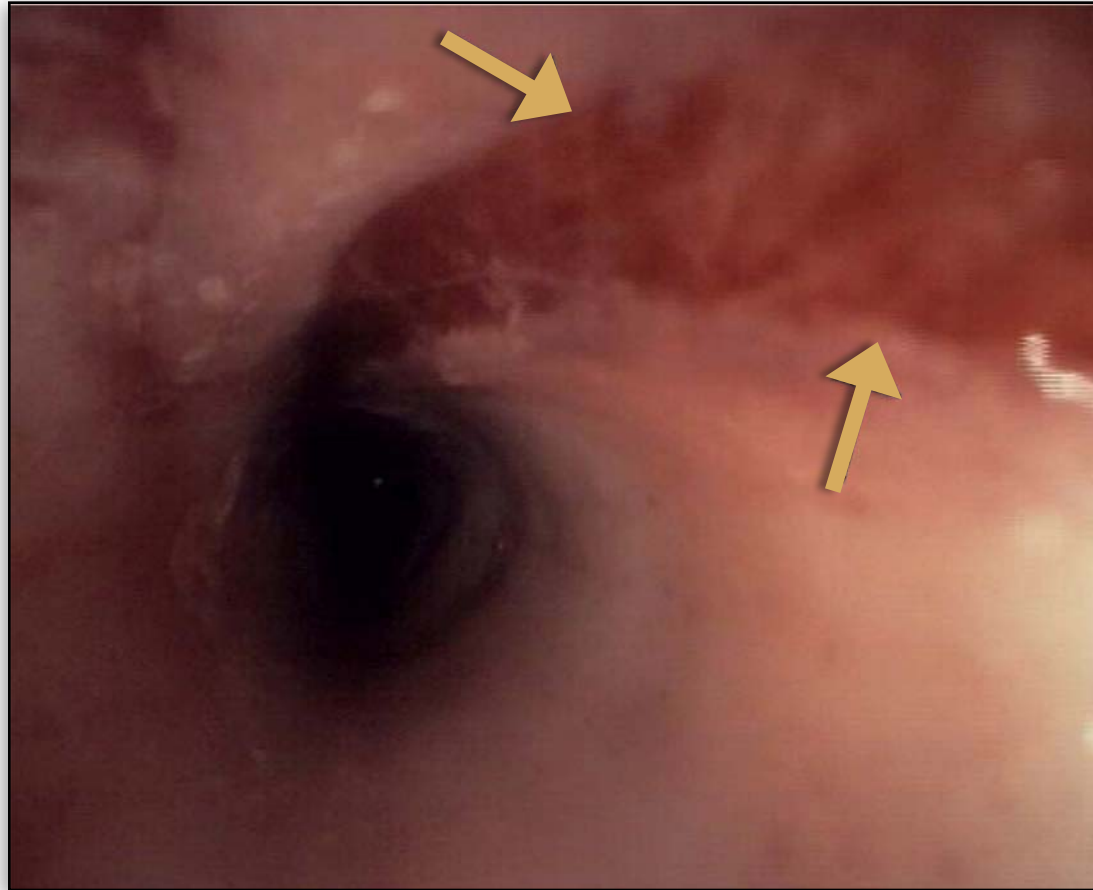


# Esophageal Rings



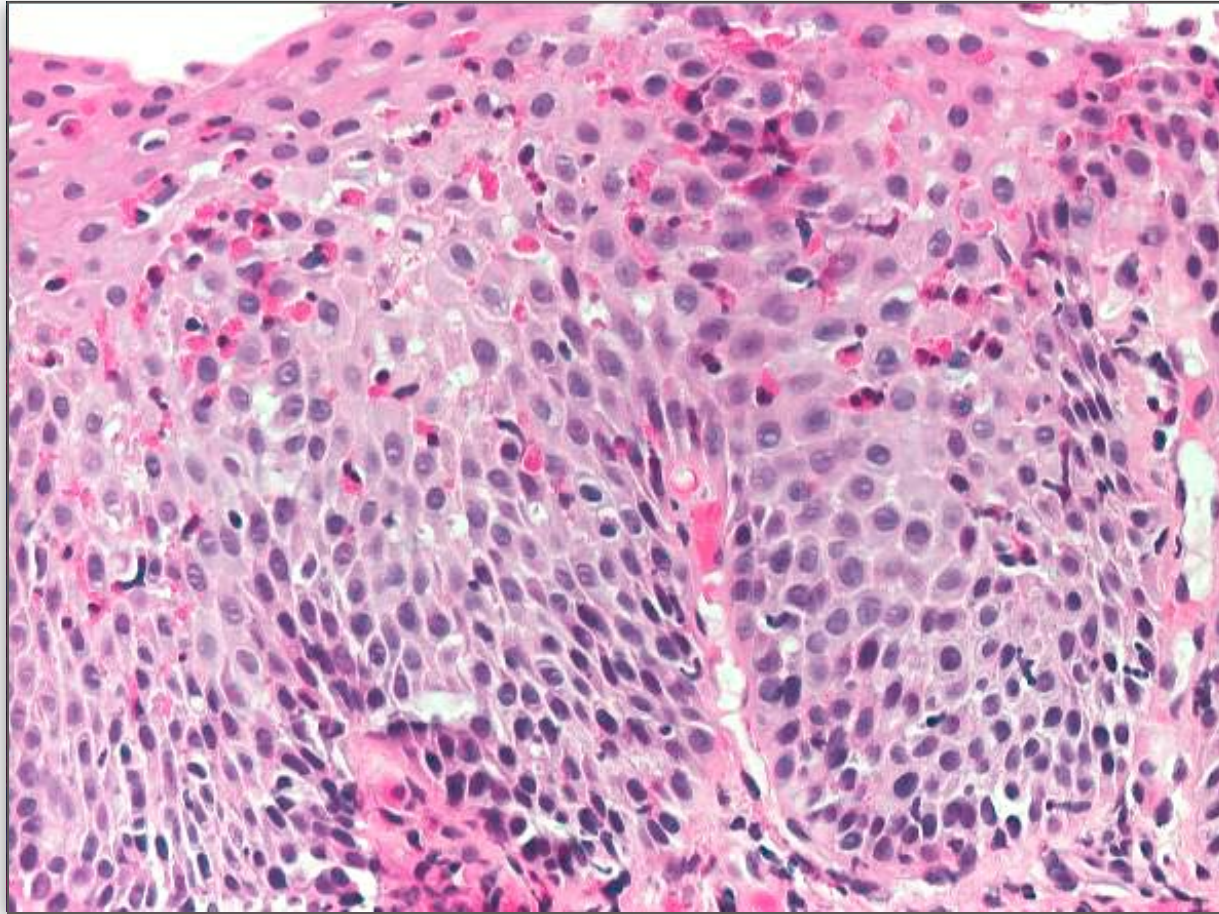


# Esophageal Fragility



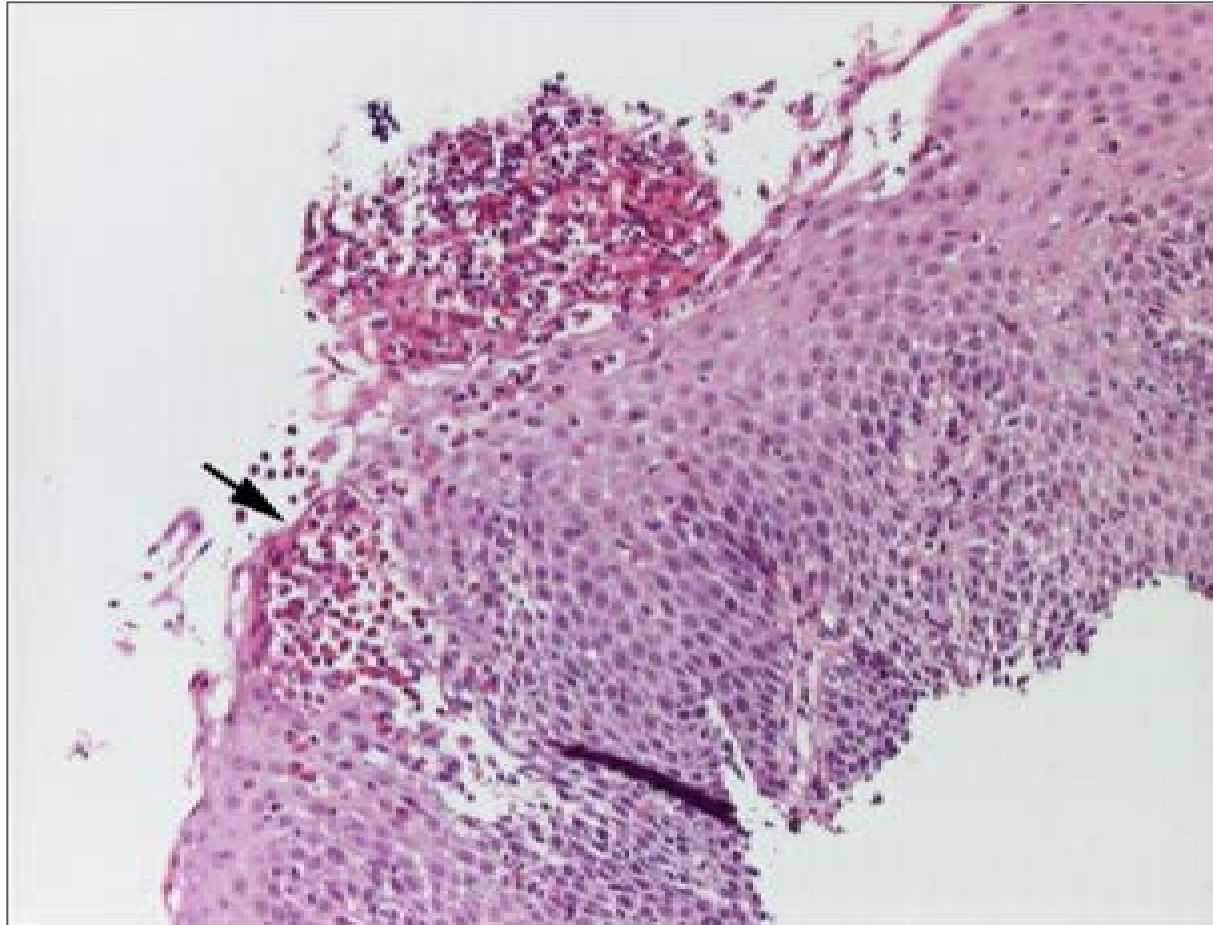
# Histology of EoE

# EoE Histology





# EoE Histology





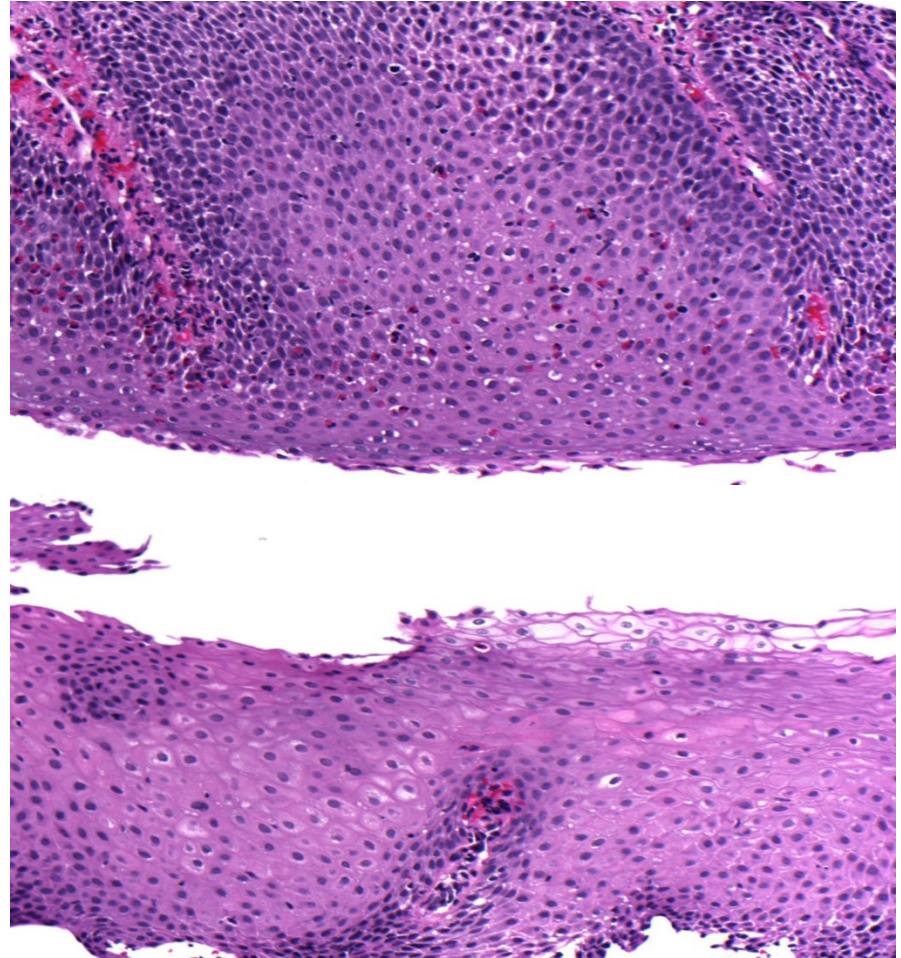


# Histology of EoE

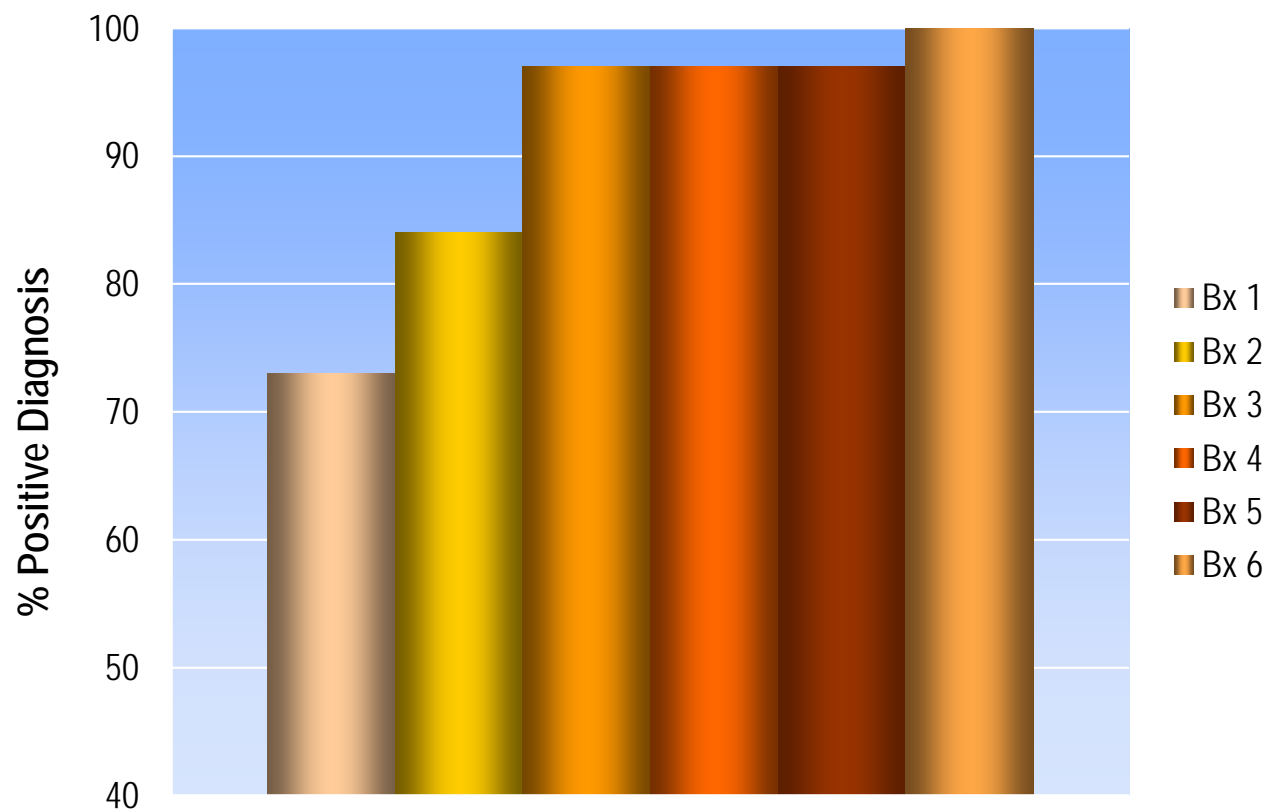
Eosinophilia is often patchy

Multiple biopsies are necessary

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



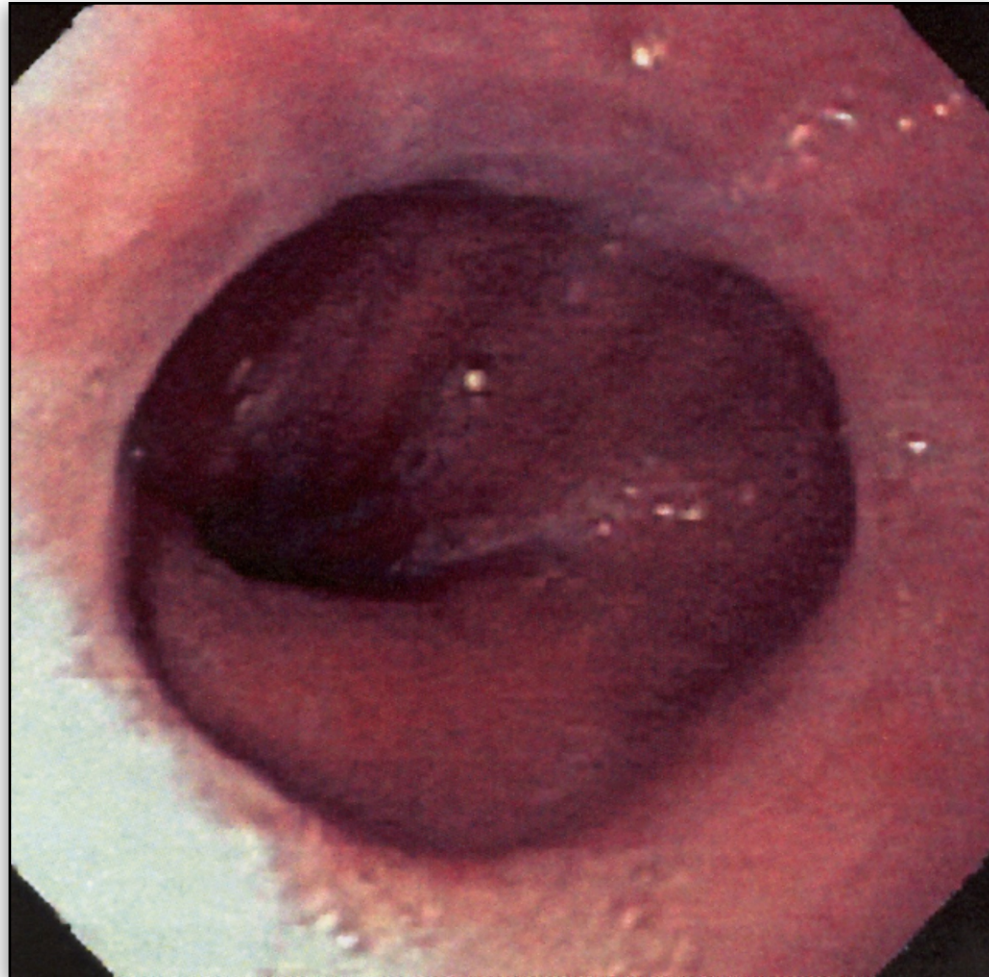
# Number of Biopsies to Diagnose Pediatric EoE



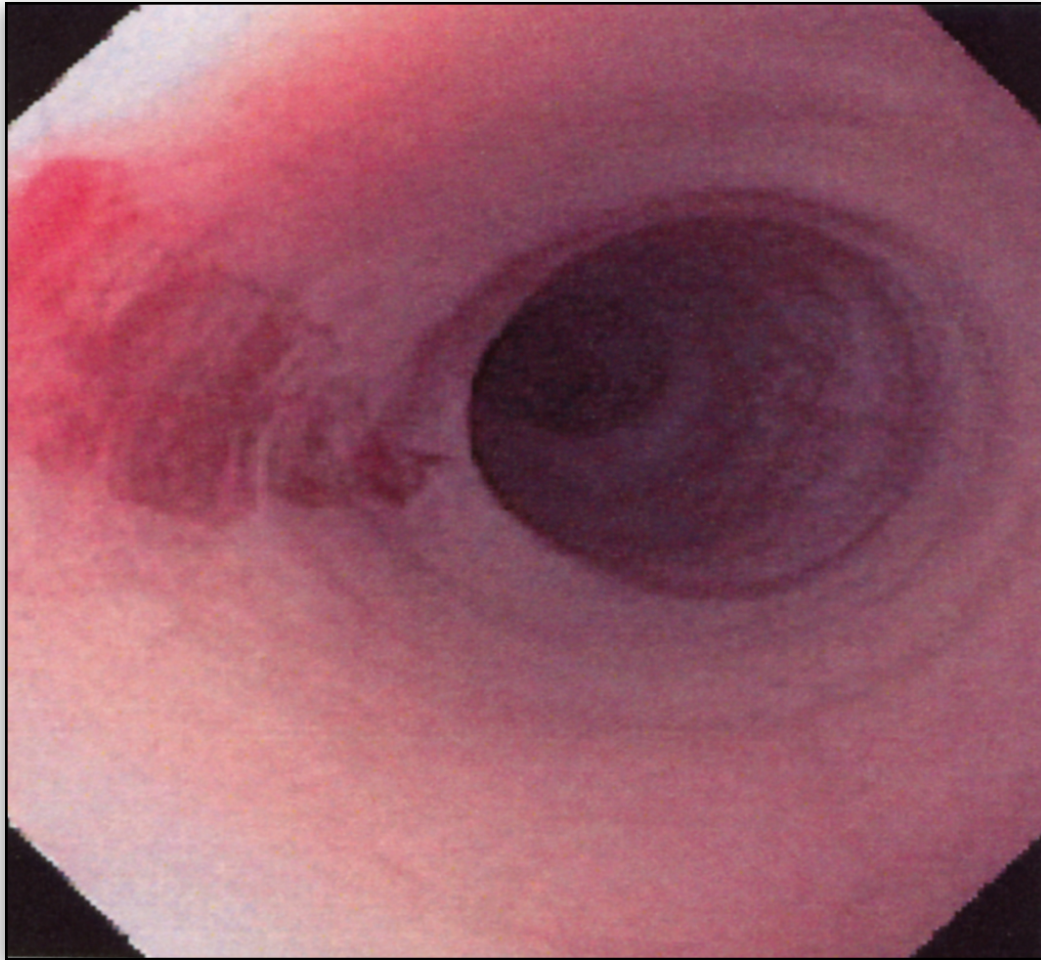
# Complications



# Distal Esophageal Stricture



# Small Caliber Esophagus





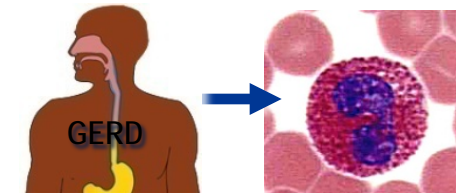
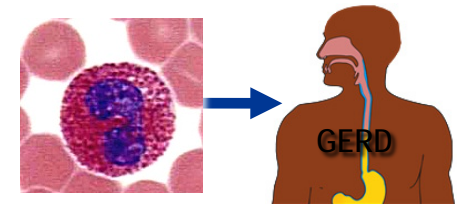
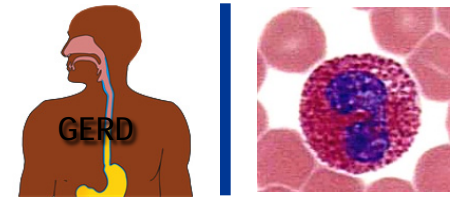
# Pill Impaction



# 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







# 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





# 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

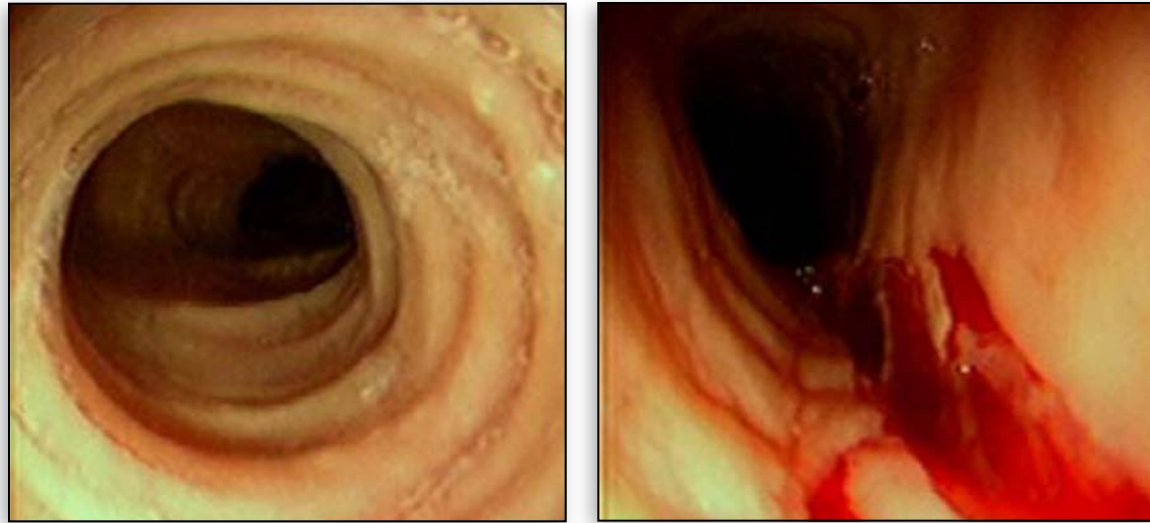
# Dilation



# 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.



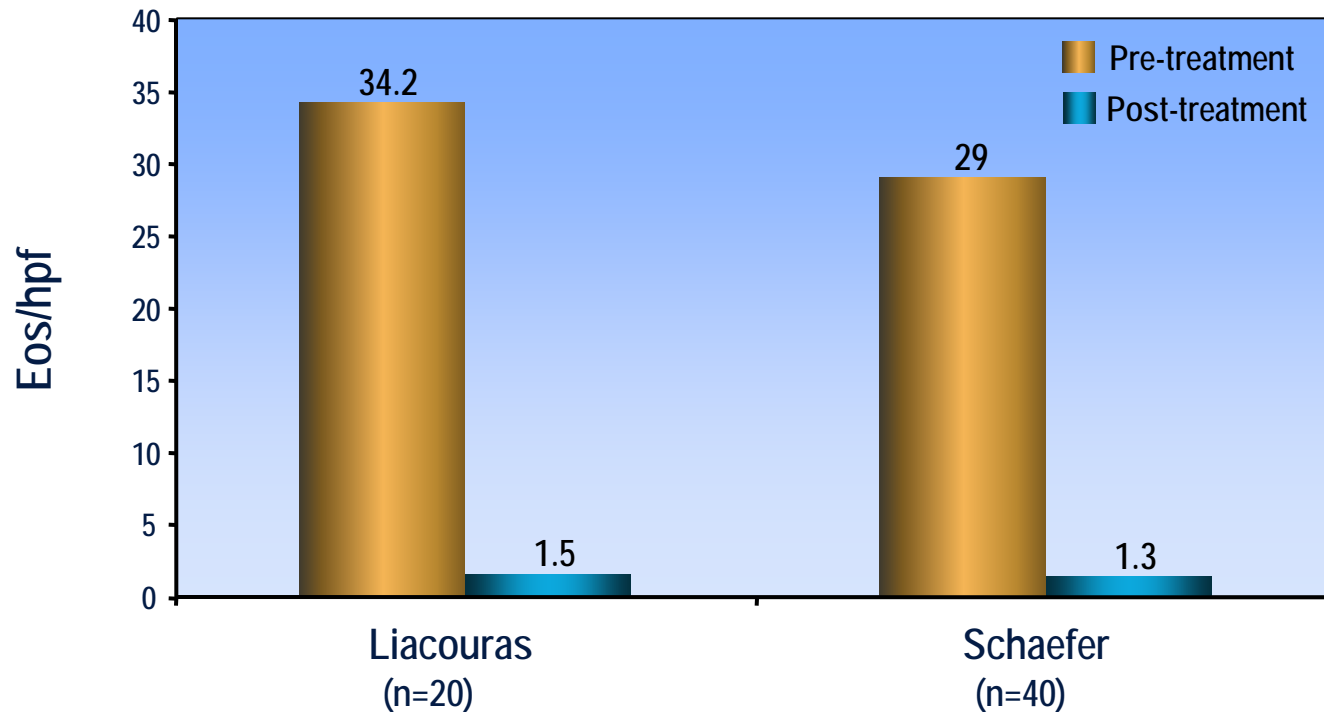
# Esophageal Dilation in EoE

- 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*

# Steroid Treatment in Pediatrics



# Oral Steroid Studies



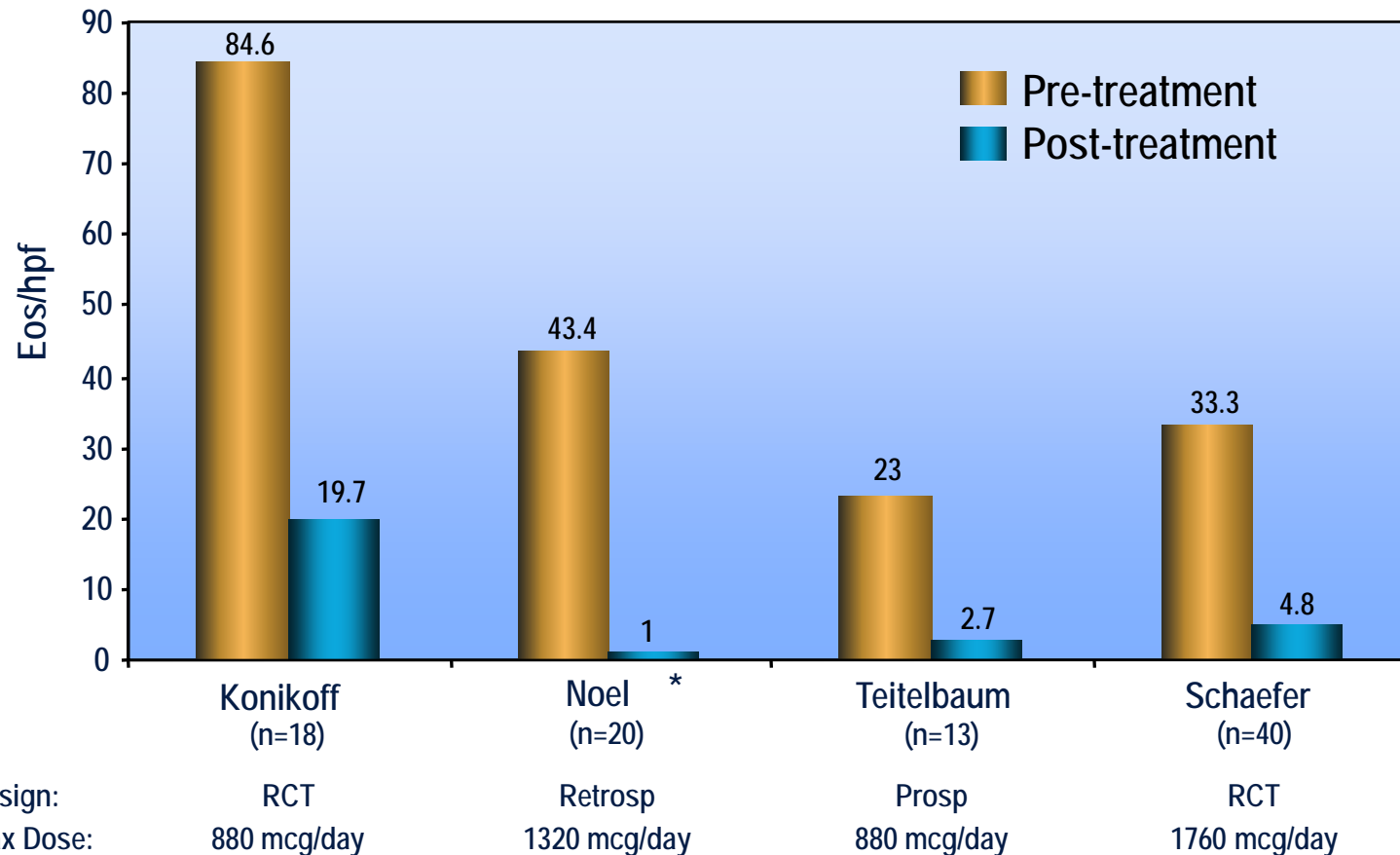
1 mg/kg BID; max 30 mg BID

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

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



# Topical Steroids (*Swallowed Fluticasone*)



\* Post treatment data on 16 patients.

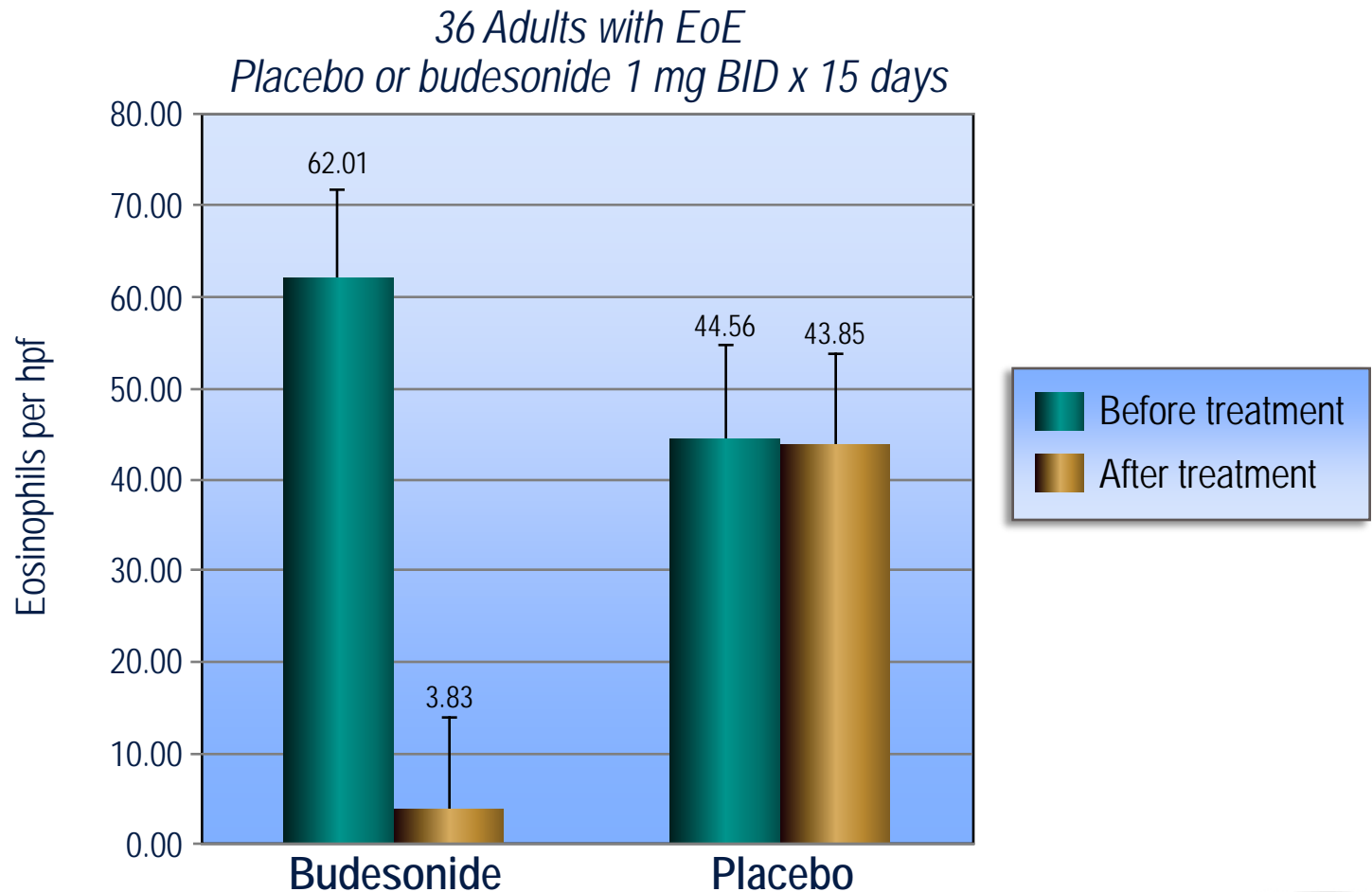
Konikoff et al. *Gastroenterology*. 2006; 131:1381-1391.  
Noel et al. *Clin Gastroenterol Hepatol*. 2004; 2(7):523-530.  
Teilbauam et al. *Gastroenterology*. 2002; 122:1216.  
Schaefer et al. *Clin Gastroenterol Hepatol*. 2008; 6:621-629.



# 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

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







# 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.

# Dietary Treatment in Pediatrics



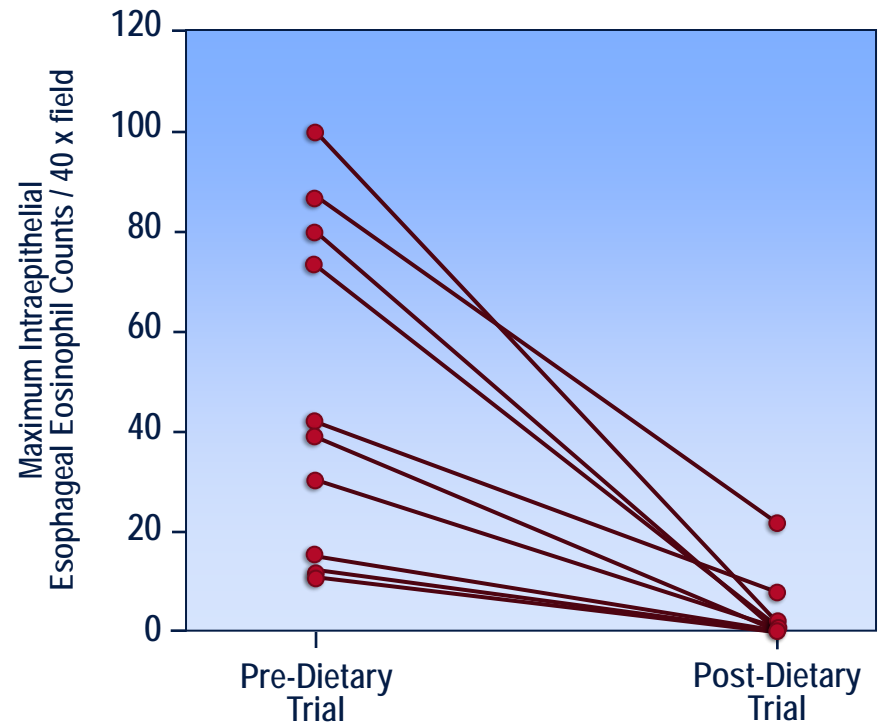
# History of Diet and EoE

- 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



# 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



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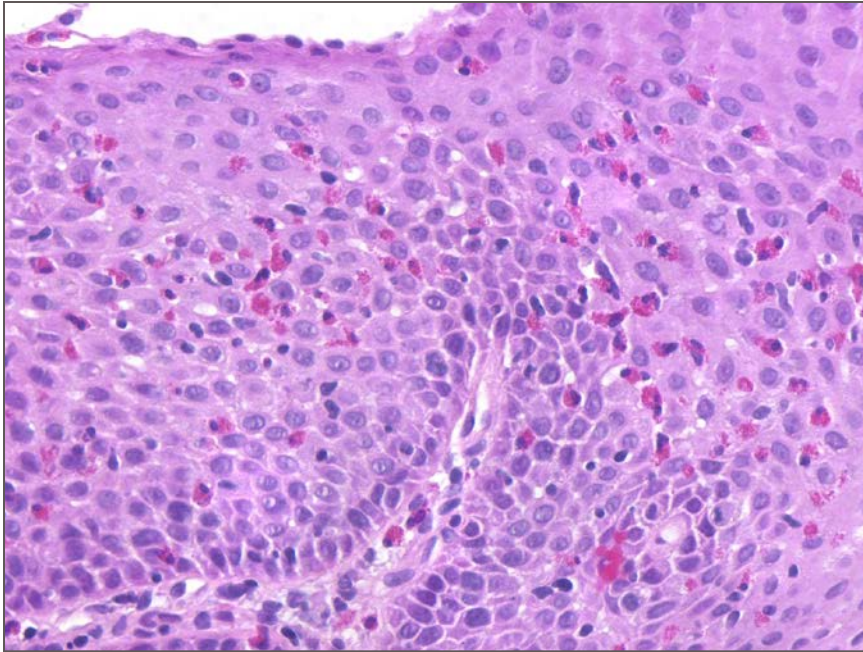
# Dietary Management

## Amino Acid–Based Formula

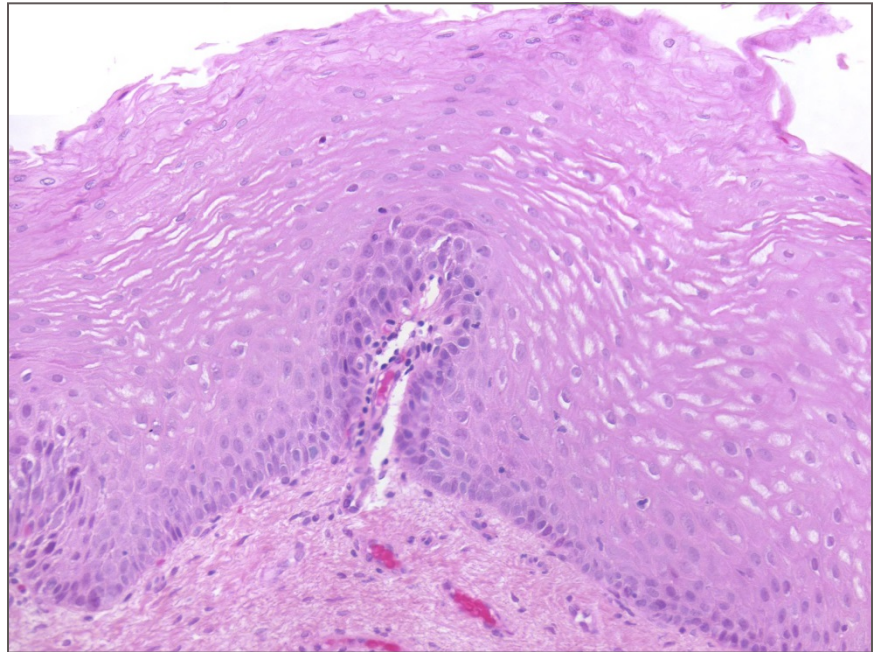
- 172 Patients (128 nasogastric tube, 32 oral, 4 failed, 8 noncompliant)
  - 160 patients completed therapy
- Patients evaluated 4-6 weeks after instituting diet

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

# 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



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# 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%



# Empiric Diet Elimination

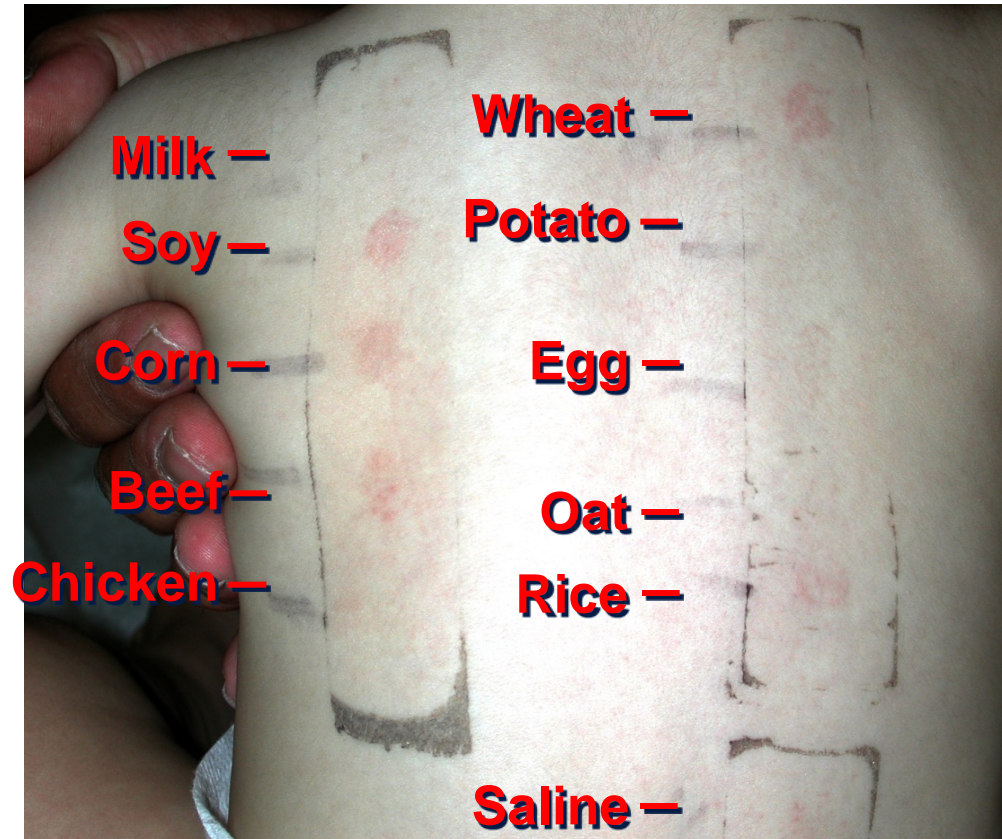
- Easy, do not need testing
- Few studies in the literature
- May not eliminate all foods necessary to induce remission
- May eliminate foods that are not necessary to be eliminated
- May prolong the process of food elimination and re-introduction



# Directed Diet Elimination

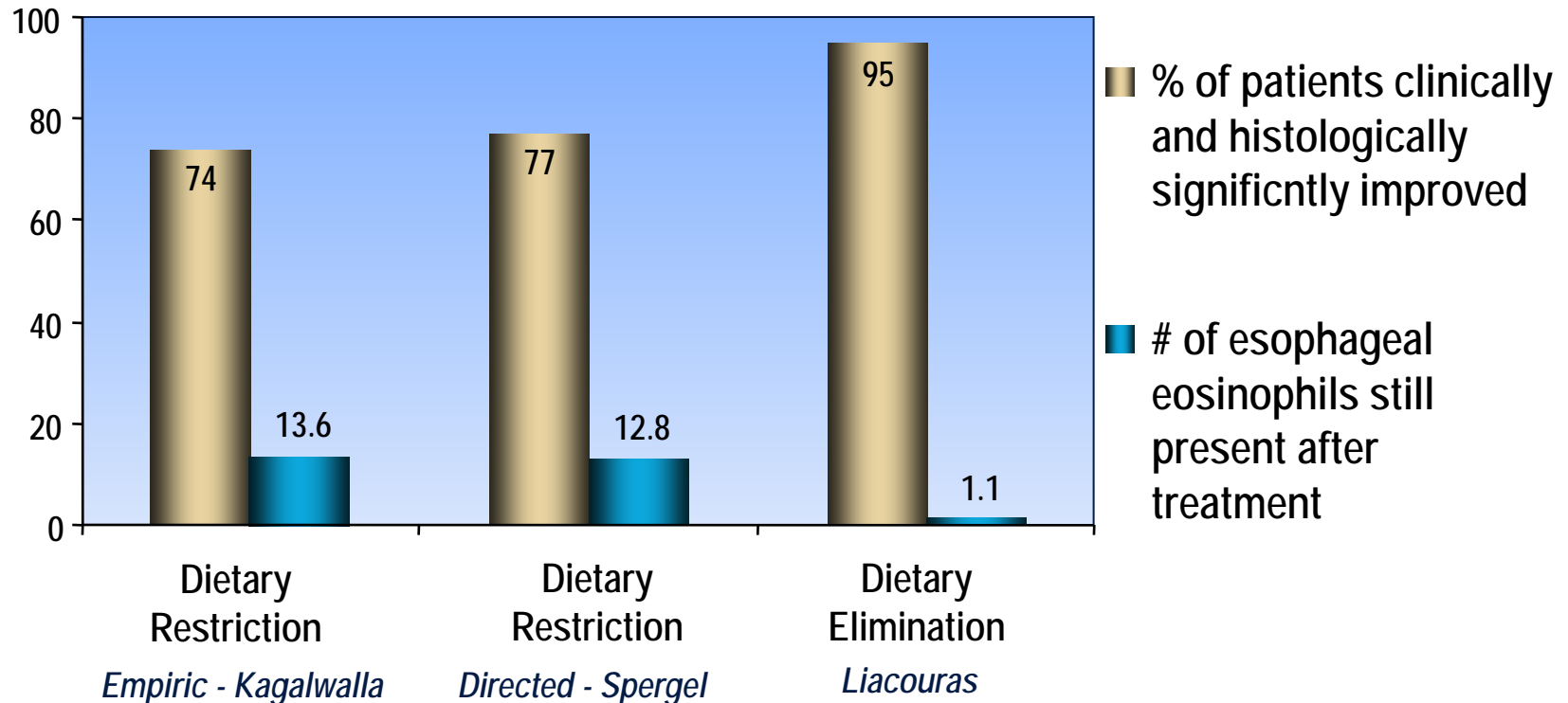
- Elimination by history/symptoms (or guessing) is challenging
  - Reactions may be delayed several days after exposure
  - Reactions may persist several days after exposure
  - More than one food may be causing reaction
- Elimination based on diagnostic testing is inaccurate

# Methods of Direct Allergy Testing for EoE





# 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	<ul style="list-style-type: none"><li>• Hypoallergenic</li><li>• Nutritionally comprehensive</li><li>• Reduces symptoms and eosinophil counts</li></ul>	<ul style="list-style-type: none"><li>• Taste (may require feeding tube)</li><li>• Expense</li><li>• Age appropriateness</li><li>• Excludes all food</li><li>• May have adverse impact on quality of life</li></ul>
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)	<ul style="list-style-type: none"><li>• Allergy testing not required</li><li>• Studied across all ages</li><li>• Reduces symptoms and eosinophil counts</li></ul>	<ul style="list-style-type: none"><li>• Some avoidance may be unnecessary</li><li>• Only four foods may be necessary</li><li>• Expense</li><li>• May be nutritionally incomplete</li></ul>
Targeted diet	Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)	<ul style="list-style-type: none"><li>• Most specific therapy</li><li>• Can preserve diet</li><li>• Established sensitivity, specificity, and NLR/PLR to assist with add-back</li><li>• Reduces symptoms and eosinophil counts</li></ul>	<ul style="list-style-type: none"><li>• Testing precision and technique is inconsistent across centers</li><li>• Milk testing precision very poor when negative</li><li>• Empiric milk elimination as an addition greatly improves response</li><li>• Some avoidance may be unnecessary (sensitization without clinical allergy)</li></ul>





# 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



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# Food Reintroduction

## *After Normal Biopsy*

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



# 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

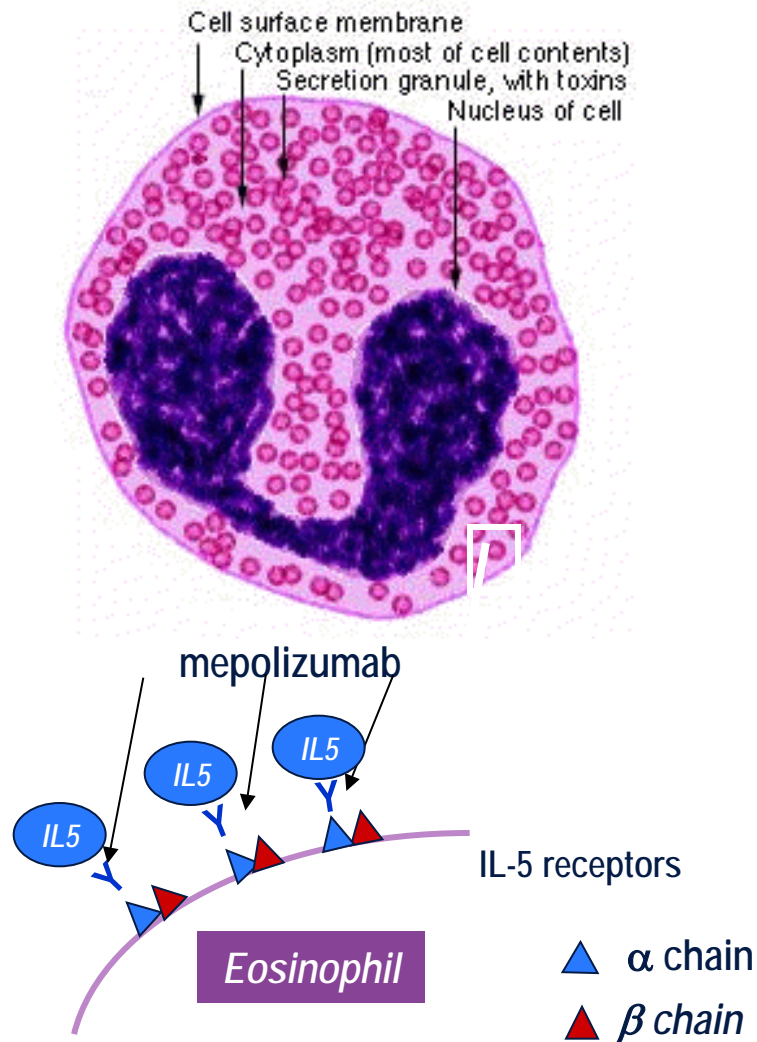


# Guidelines for Dietary Therapy in EoE

- 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.

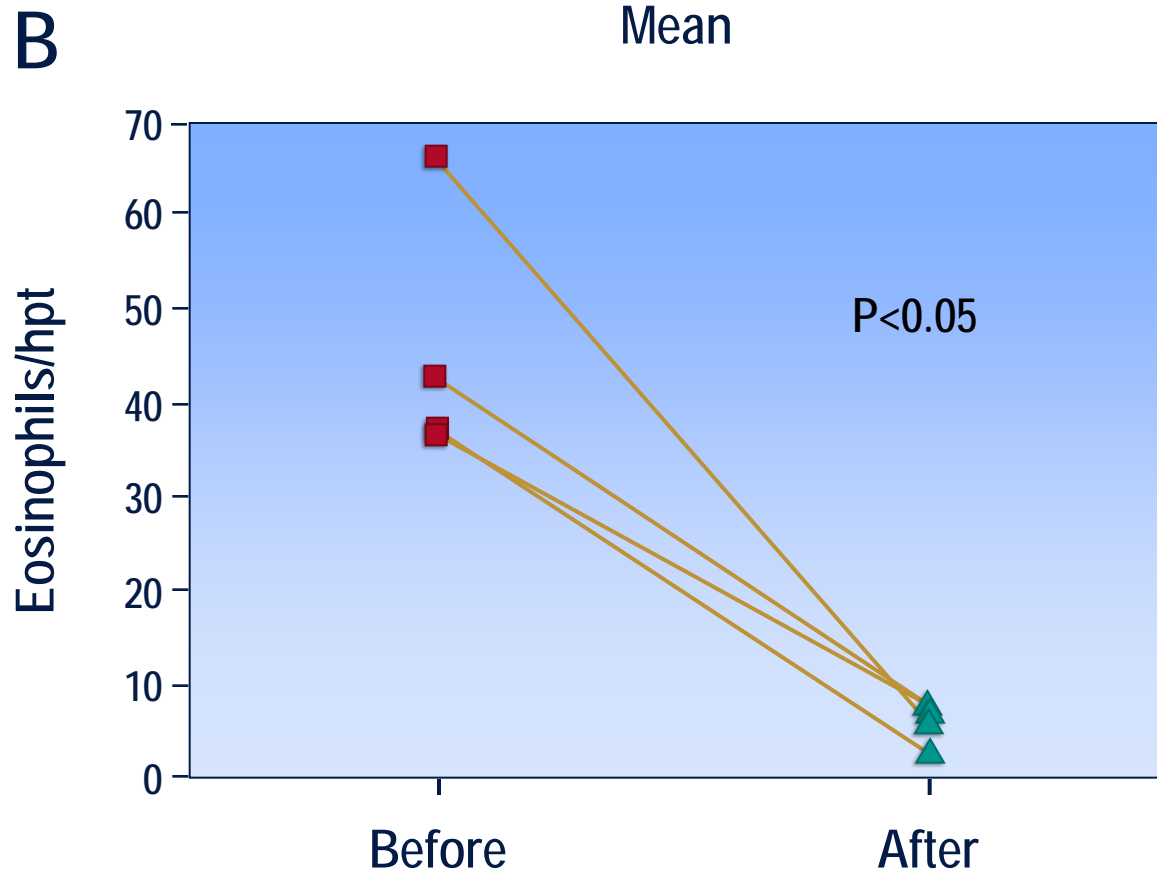
# Biologic Treatment

# 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.

# Anti-IL5 on Esophageal Eosinophils



# 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



# 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



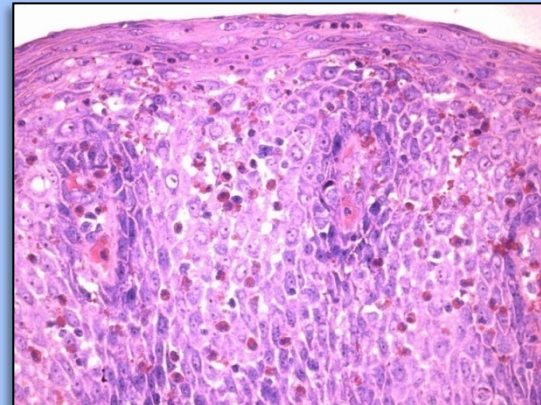
**A trial of PPI therapy is required for patients with presumed eosinophilic esophagitis, even if the diagnosis seems clear-cut.**

# Proposed Endpoints for Treatment of Eosinophilic Esophagitis

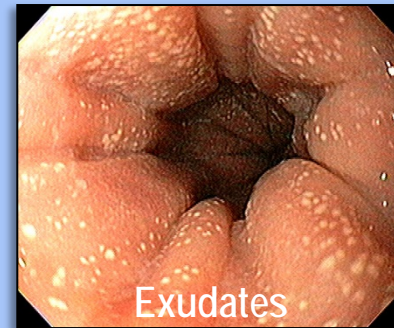
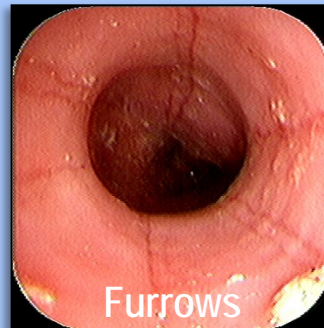
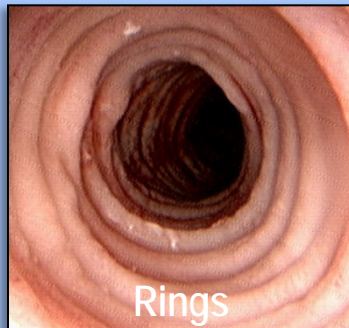
## Symptomatic Remission



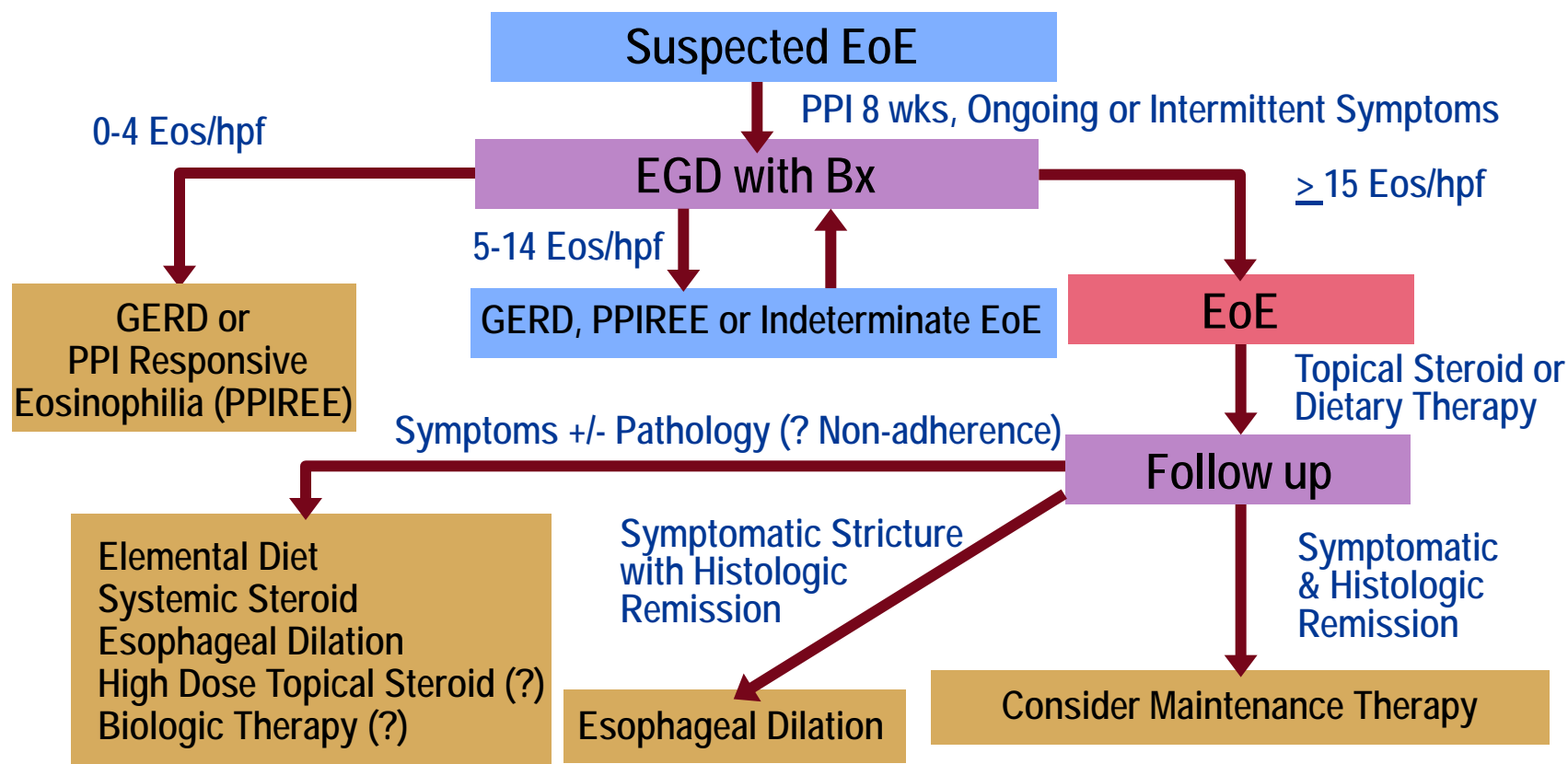
## Histological Remission



## Endoscopic Remission



# Suggested Algorithm for Management of Eosinophilic Esophagitis



# Future



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# 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



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# 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





# Advocacy Groups



# Advocacy Groups

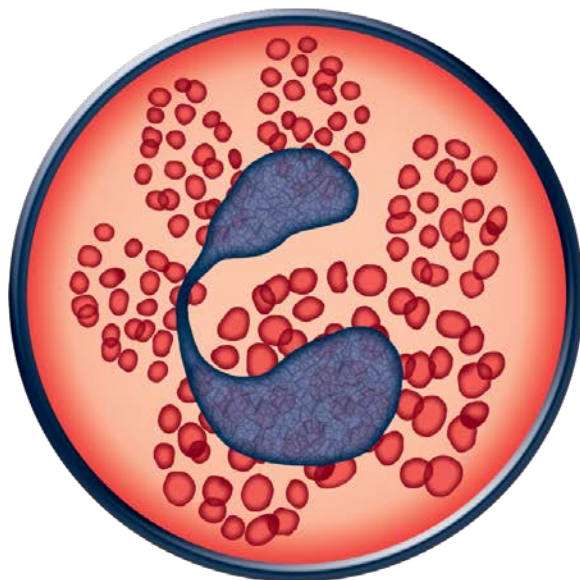
- American Partnership for Eosinophilic Disorders
  - [www.apfed.org](http://www.apfed.org)
- Campaign Urging Research for Eosinophilic Disorders
  - [www.curedfoundation.org](http://www.curedfoundation.org)
- Food Allergy Network
  - [www.foodallergy.org](http://www.foodallergy.org)

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# 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 Eosinophilia
  - “PPI-responsive” esophageal eosinophilia
- “Stay tuned”
  - Expect changes to occur within the guidelines as therapy, research and interest continues



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