Eosinophilic Esophagitis Diagnosis & Management

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Jointly sponsored by NASPGHAN and The NASPGHAN Foundation in collaboration with The American Academy of Pediatrics: District II, III and Chapter 4 and The International Gastrointestinal Eosinophil Researchers

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Faculty

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Learning Objectives

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

- Define eosinophilic esophagitis (EoE) and present the updated 2011 diagnostic guidelines
- Understand the epidemiology, pathophysiology, and genetics of EoE
- Identify the clinical symptoms, allergic manifestations, and endoscopic and histologic features of EoE
- List and define the treatments of EoE, which include dietary restriction, pharmacologic therapy, and esophageal dilation
- Understand how to manage patients with EoE
- Provide information regarding ongoing and future research on EoE

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Background & Natural History

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Background

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

Kelly et al. *Gastroenterology.* 1995;109:1503-1512.
Straumann et al. *Schweiz Med Wochenschr*. 1994;124(33):1419-1429.
Attwood et al. *Dig Dis Sci.* 1993;38(1):109-116.

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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 antireflux 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.

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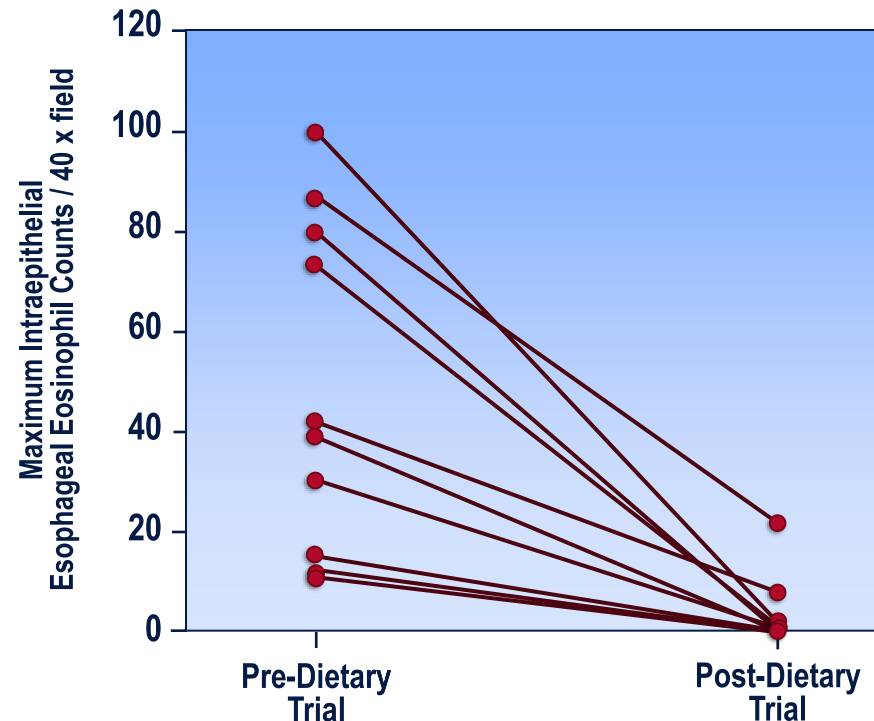
Diet and Eosinophilic Esophagitis

- 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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2013 Distribution of EoE

Switzerland
Spain
Belgium
England
Netherlands
Italy
Germany
France
Israel

Canada

United States

Mexico

Brazil

Middle East
Africa

Japan
Asia

Australia

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Definition

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Poll Question #1

The definition of “eosinophilic esophagitis” includes all of the following, EXCEPT:

A. Clinical symptoms that may include dysphagia, vomiting, abdominal pain, or heartburn
B. Esophageal eosinophilia with >15 eosinophils in at least 1 biopsy
C. Normal biopsies of the gastric antrum and duodenum
D. A patient with 75 esophageal eosinophils/hpf that completely resolve with the use of a proton pump inhibitor (PPI)
E. Eosinophilic esophagitis is a clinicopathologic diagnosis

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Esophageal Eosinophilia

Histologic Finding

- **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
- Graft-versus-host disease (GVHD)

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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.

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2011 Updated Consensus Report

Diagnostic Guideline

- EoE is a clinicopathologic disease
- Clinically characterized by esophageal dysfunction
- Pathologically 1 or more biopsies show eosinophil-predominant inflammation (15+ eos in peak hpf)
- Isolated to esophagus (need for other gastrointestinal [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.

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Poll Question #1 - Answer

The definition of "eosinophilic esophagitis" includes all of the following, EXCEPT:

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Epidemiology of Eosinophilic Esophagitis

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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.

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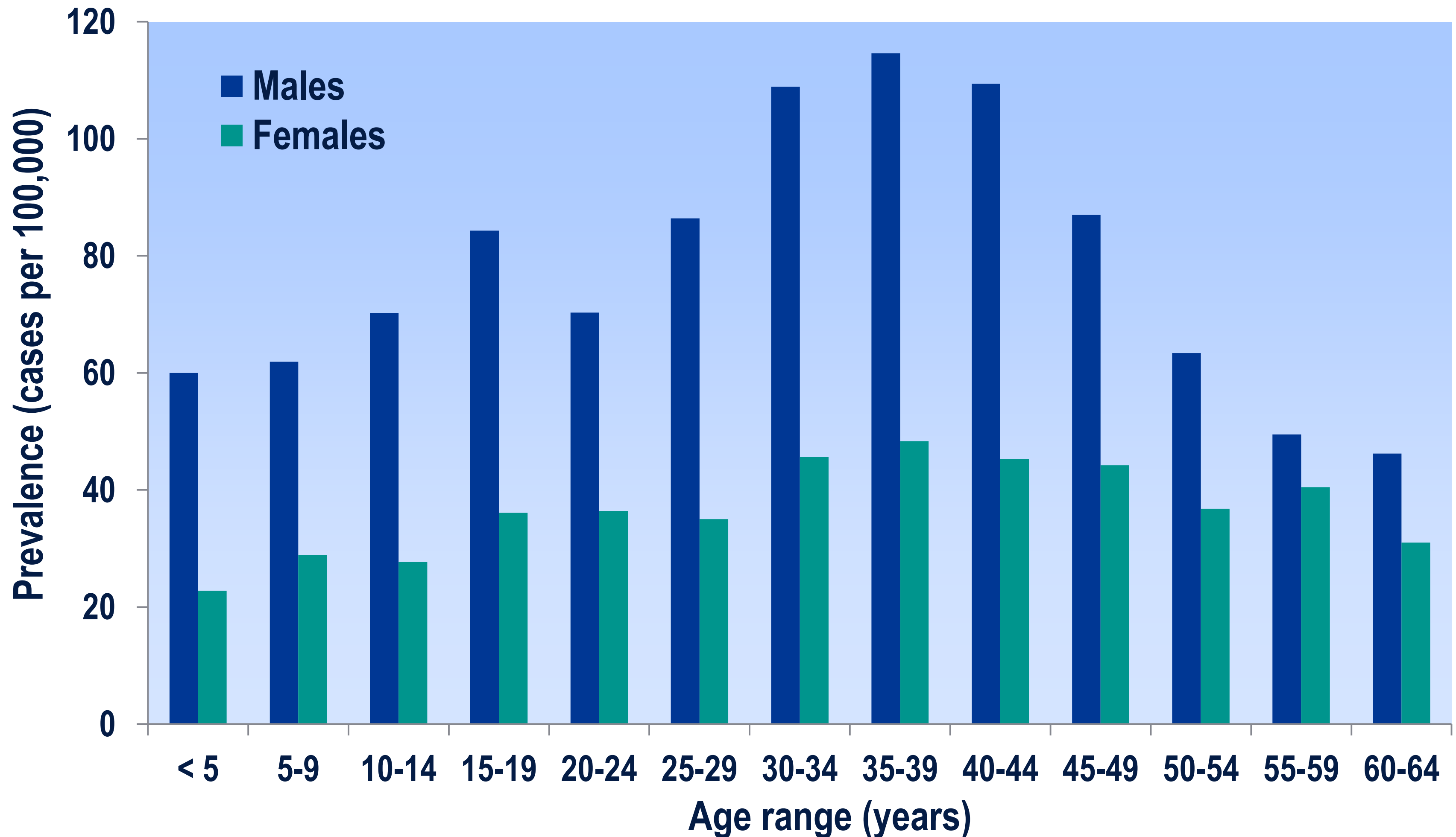
Prevalence of EoE by Age & Sex



Dellon et al. *Clin Gastroenterol Hepatol.* 2014;12:589-596.

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Pathophysiology of EoE

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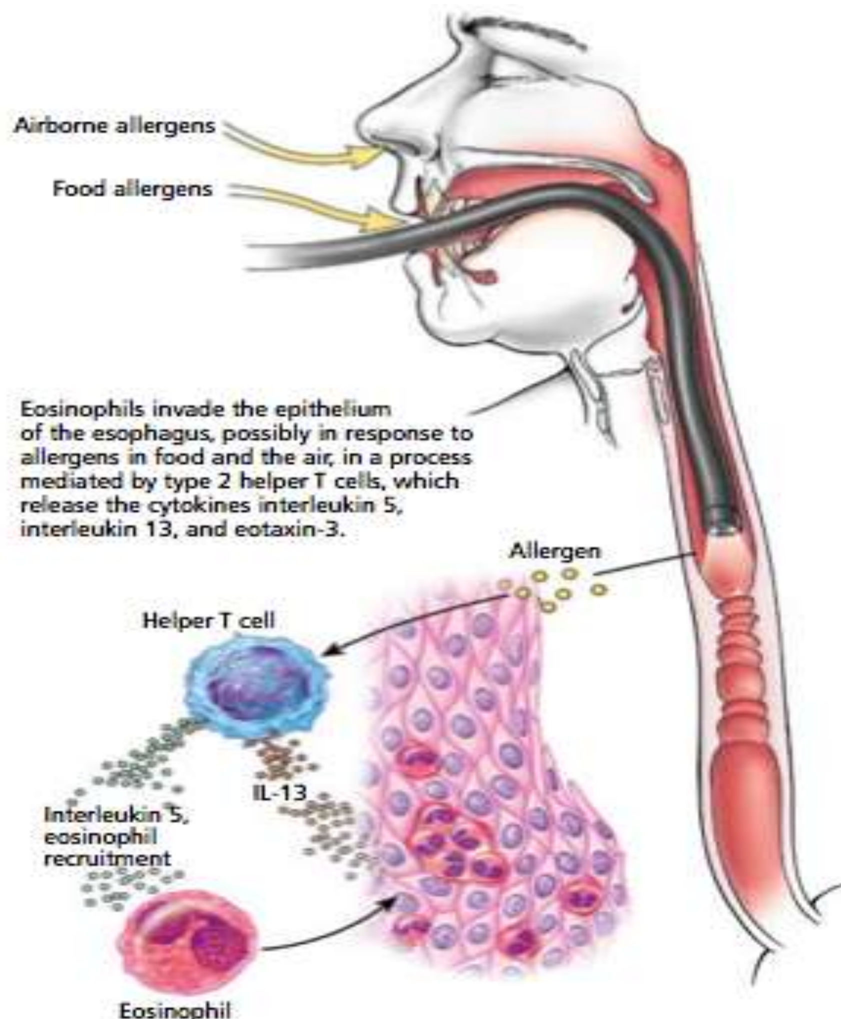
Potential Pathophysiology of EoE

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



Nonevski et al. *Clev Clin J Med.* 2008:75(9):623-626, 629-633.

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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

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Genetics

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EoE — Genetics

- Collaboration between CHOP and Cincinnati Children's Hospital – 2010
- Increased incidence in siblings and 1st degree relatives
- Identified gene locus at chromosome 5q22
- Thymic stromal lymphopoietin protein (TSLP) gene

Rothenberg et al. *Nat Genet.* 2010;42:289-291.

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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

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

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Clinical Symptoms — Pain

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

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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, and 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

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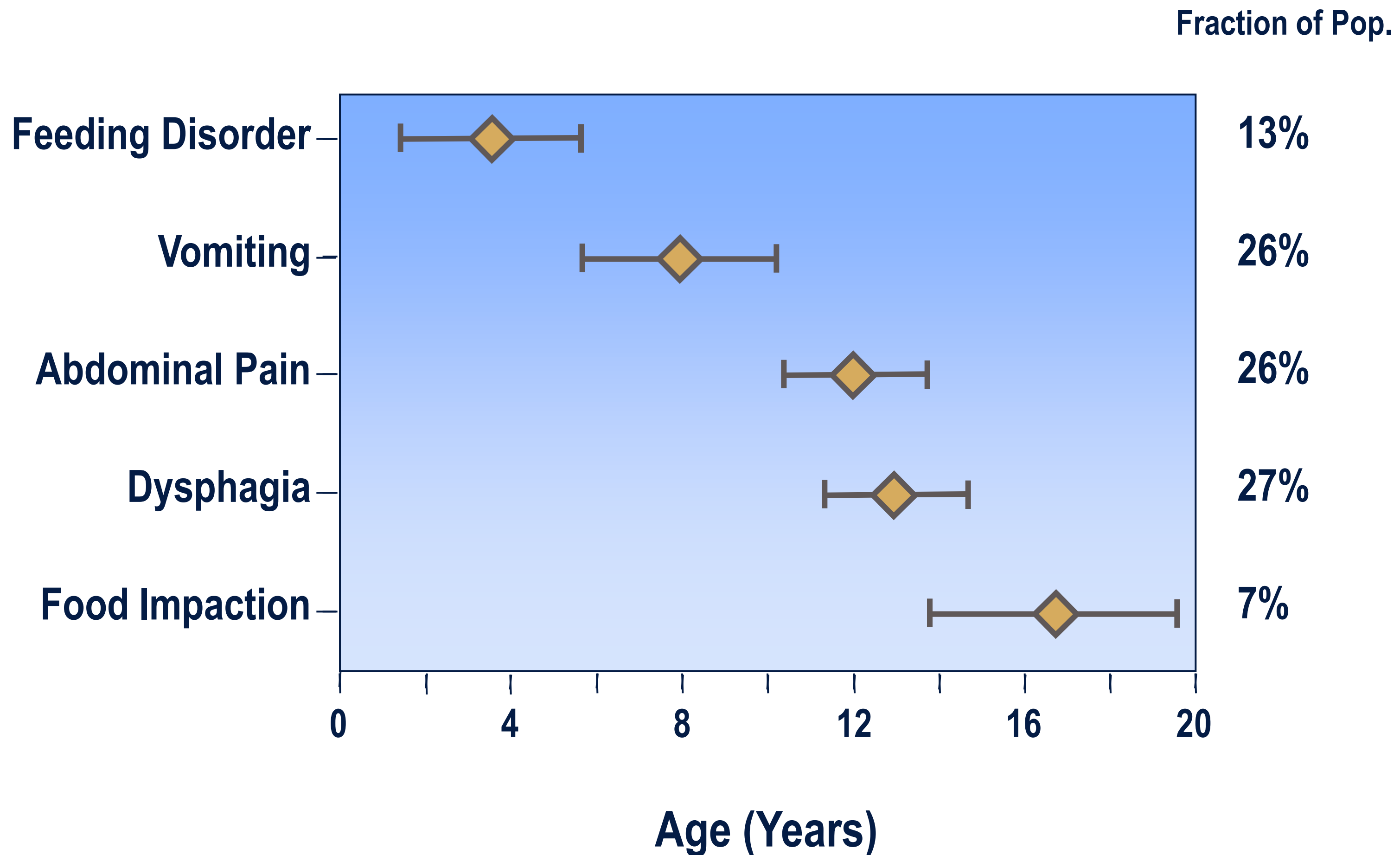
EoE Presentation by Age



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

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Diagnostic Studies

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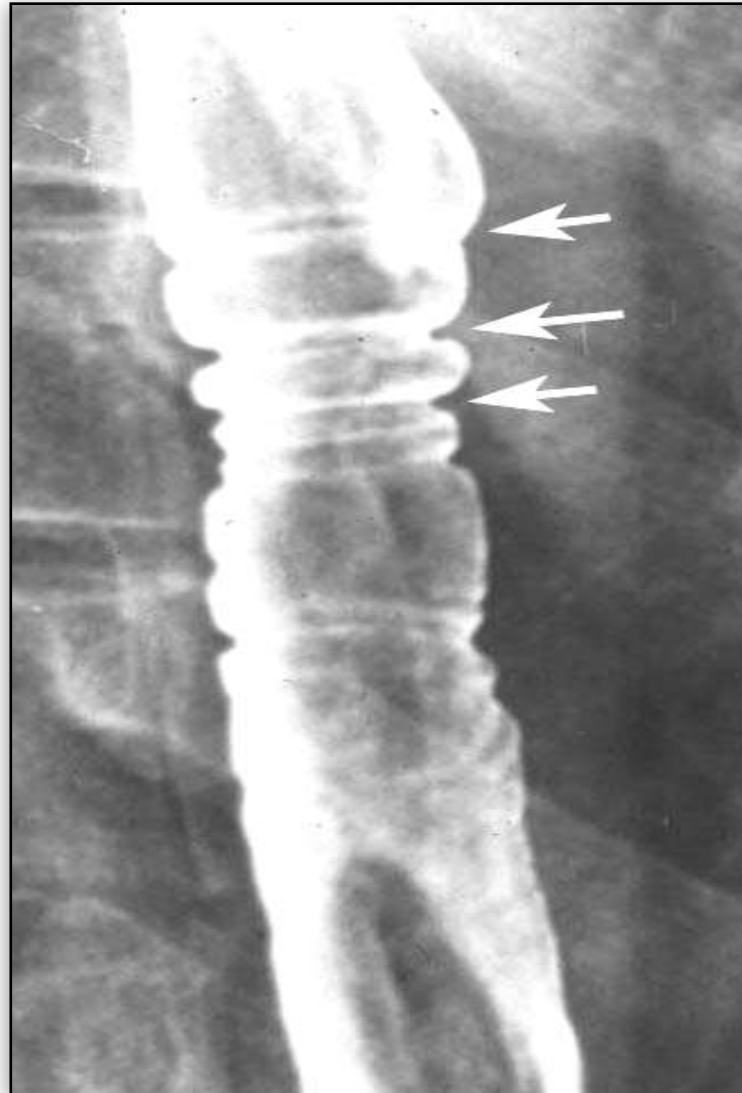
Esophageal Rings



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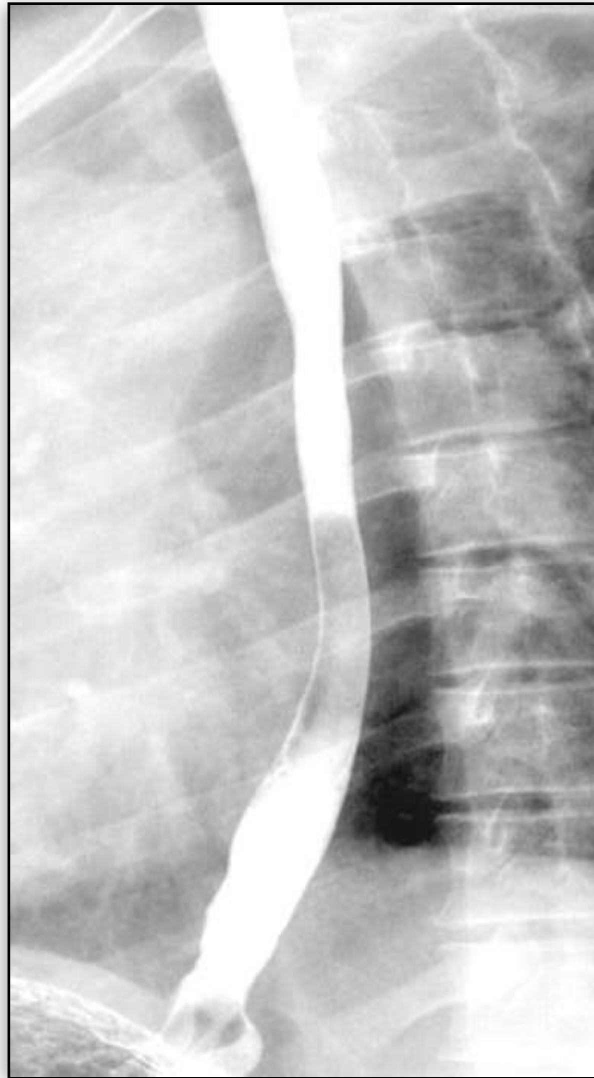
Small-Caliber Esophagus



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Endoscopic Findings

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Esophageal Furrowing

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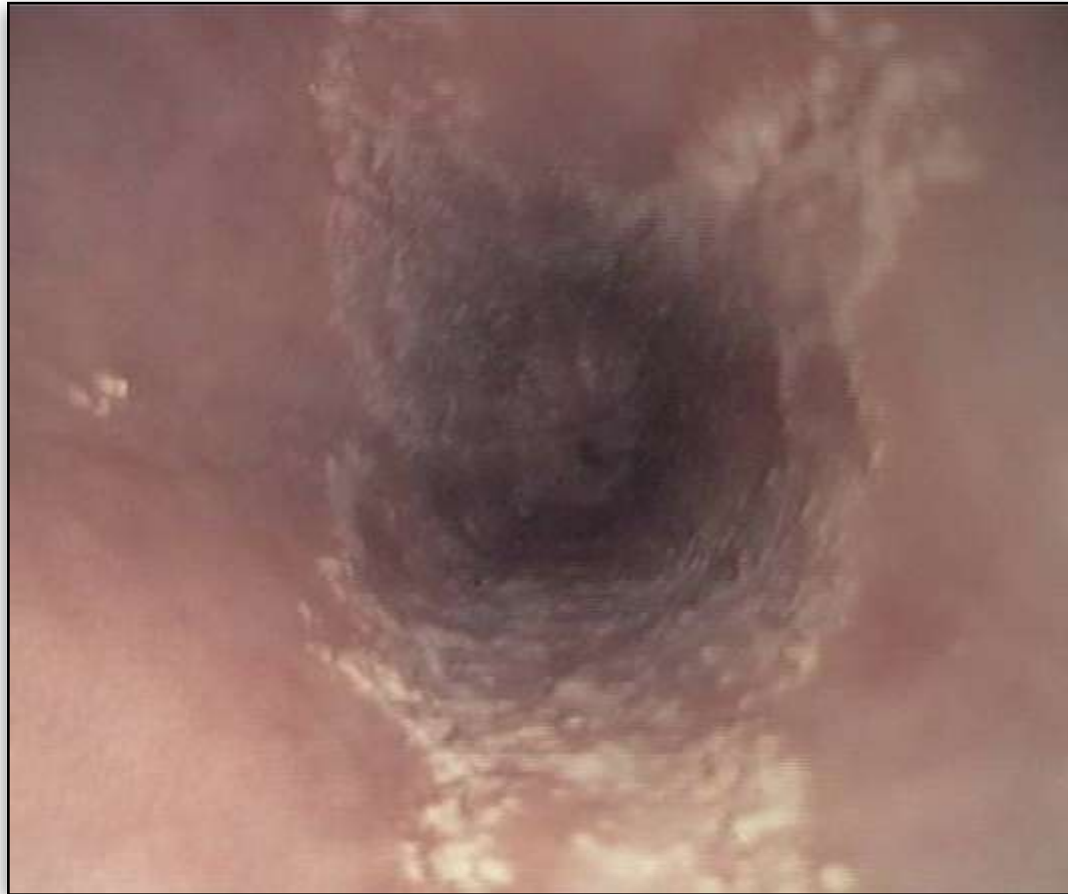
White Plaques



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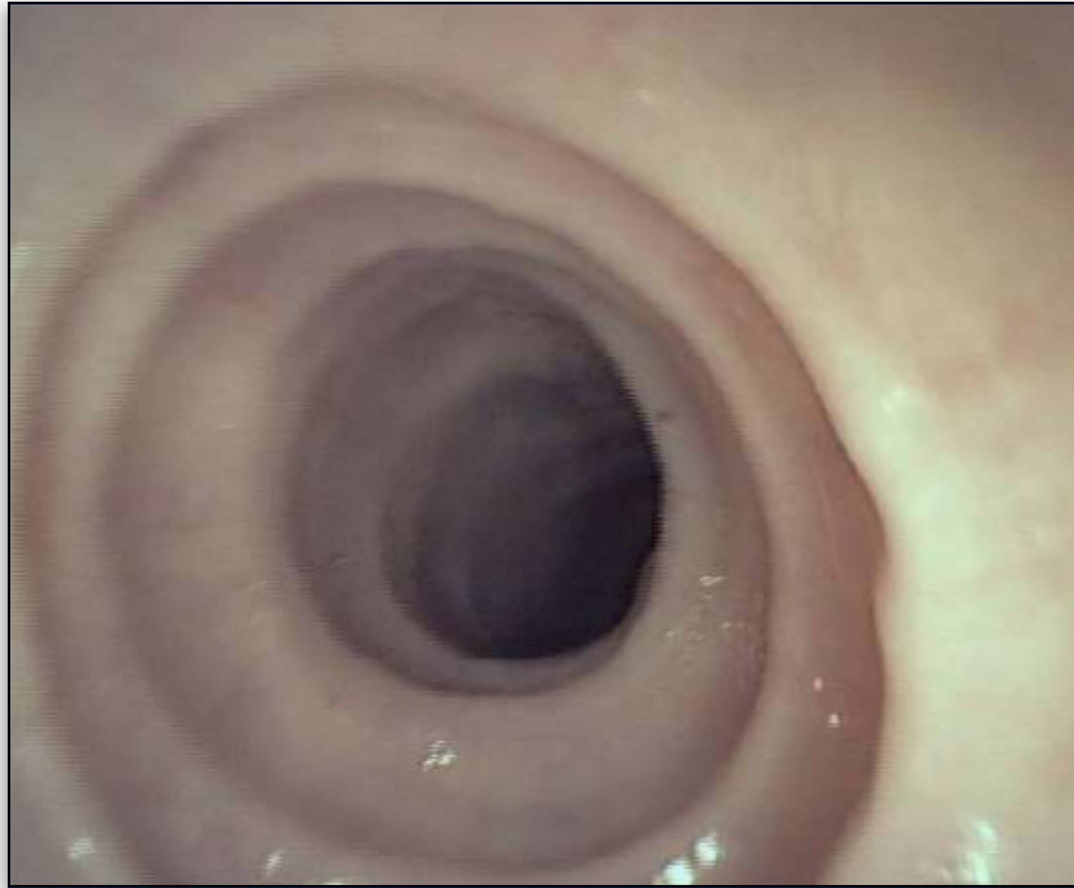
Esophageal Rings



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Esophageal Fragility

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EoE Histology

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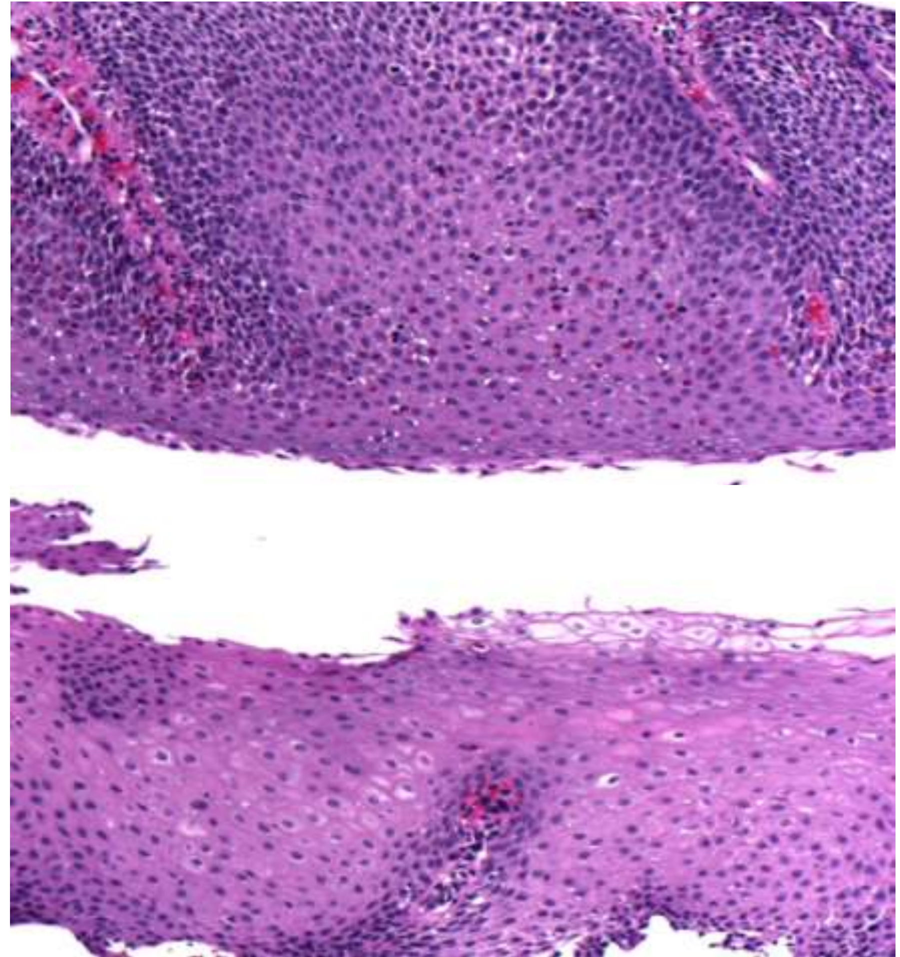
Histology of EoE

- Eosinophilia is often patchy
- Multiple biopsies are necessary
- EoE currently determined by the number of eosinophils in most-affected field



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Poll Question #2

Which of the following is not an accepted therapy for eosinophilic esophagitis?

A. Topical swallowed steroids
B. Dietary restriction
C. Proton pump inhibitors
D. Systemic steroids
E. Esophageal dilation

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Treatment With PPIs

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PPI Therapy and EoE

- Acid suppression with PPIs
  - 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

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Steroid Treatment in Pediatrics

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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;26:380-385.

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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 (candidal overgrowth seen)

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

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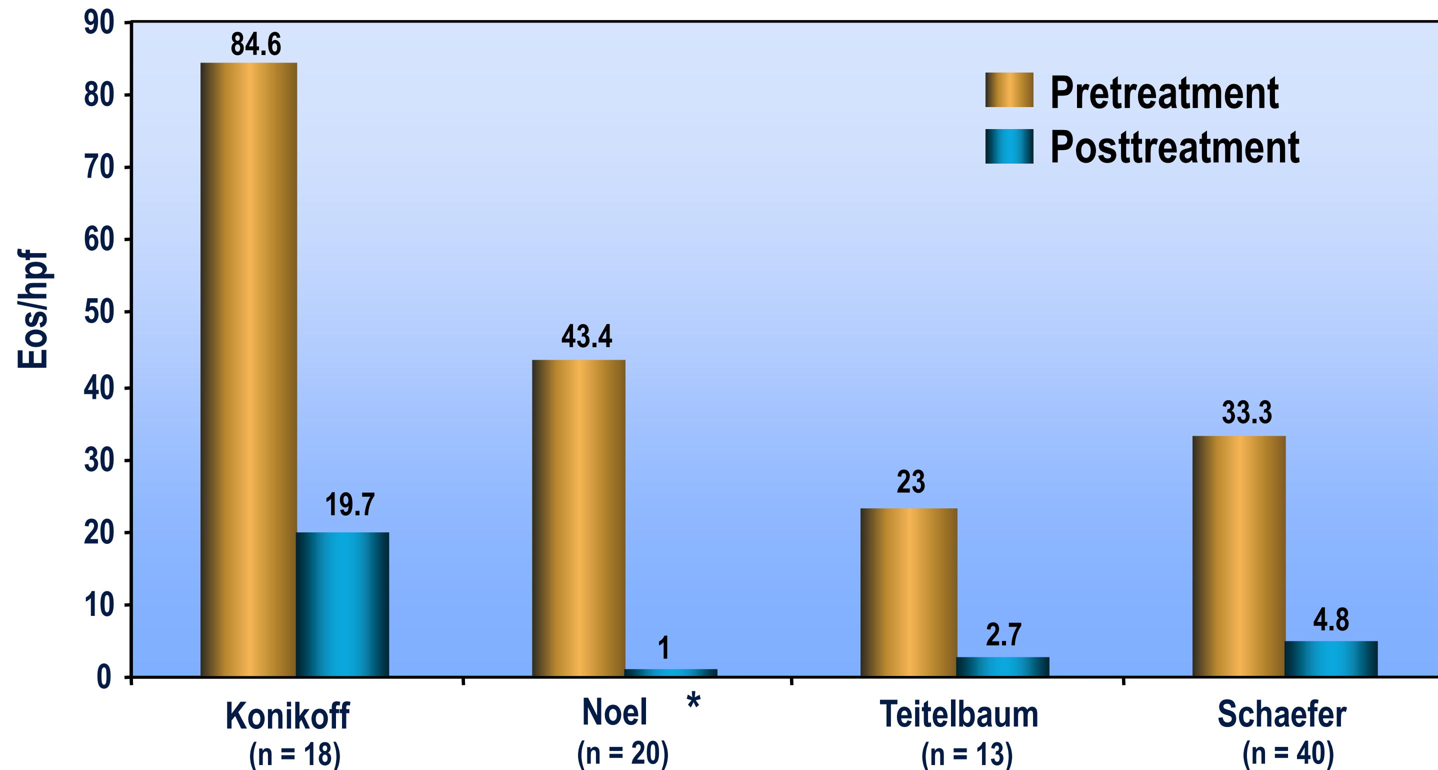
Topical Steroids *(Swallowed Fluticasone)*



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

*Posttreatment data on 16 patients

Konikoff et al. *Gastroenterology* 2006;131:1381-1391.
Noel et al. *Clin Gastroenterol Hepatol.* 2004;2(7):568-575.
Teitelbaum et al. *Gastroenterology* 2002;122:1216-1225.
Schaefer et al. *Clin Gastroenterol Hepatol.* 2008;6:165-173.

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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 nonresponder (no change in eos) after 3–4 months of treatment
  - No significant adverse effects; esophageal candida in one

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

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Corticosteroids in EoE

- Systemic and topical corticosteroids effectively resolve the acute clinicopathological 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;133:1342-1363.
Liacouras et al. *J Allergy Clin Immunol.* 2011;128:3-20.

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Poll Question #2 - Answer

Which of the following is not an accepted therapy for eosinophilic esophagitis?

A. Topical swallowed steroids
B. Dietary restriction
C. Proton pump inhibitors
D. Systemic steroids
E. Esophageal dilation

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Poll Question #3

Of the following dietary therapies, which is not an accepted therapy for EoE?

A. A restricted diet based on the removal of the most likely 6 foods causing disease
B. The strict use of an amino acid–based formula
C. A restricted diet simply based on a patient's symptoms
D. A restricted diet based on skin prick and atopy patch allergy testing

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Dietary Treatment in Pediatrics

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Types of Dietary Therapy for EoE

- Total elimination diet
  - Amino acid–based formula
- Selective diet
  - Empiric diet
  - Directed (targeted) diet

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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	Prediet	Postdiet	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.

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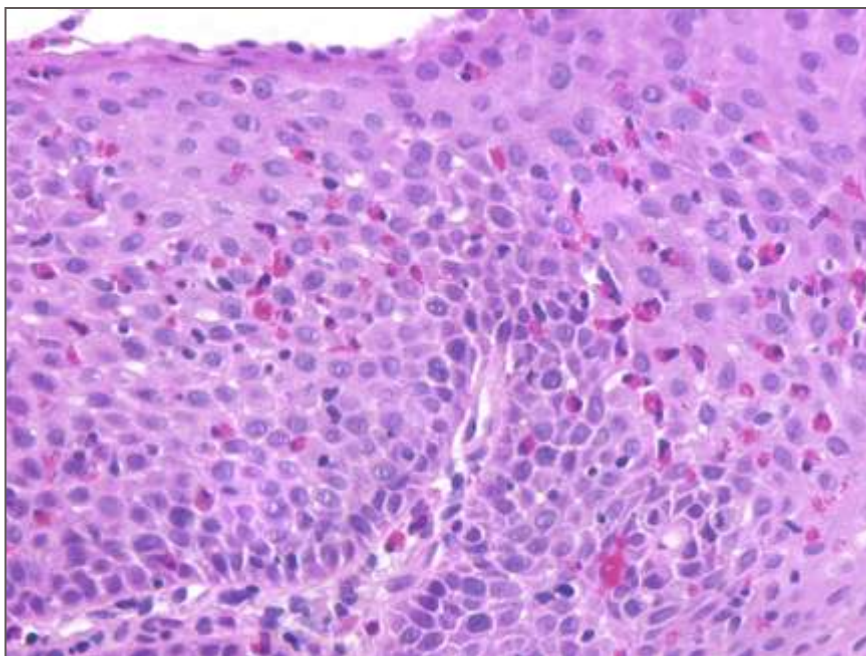
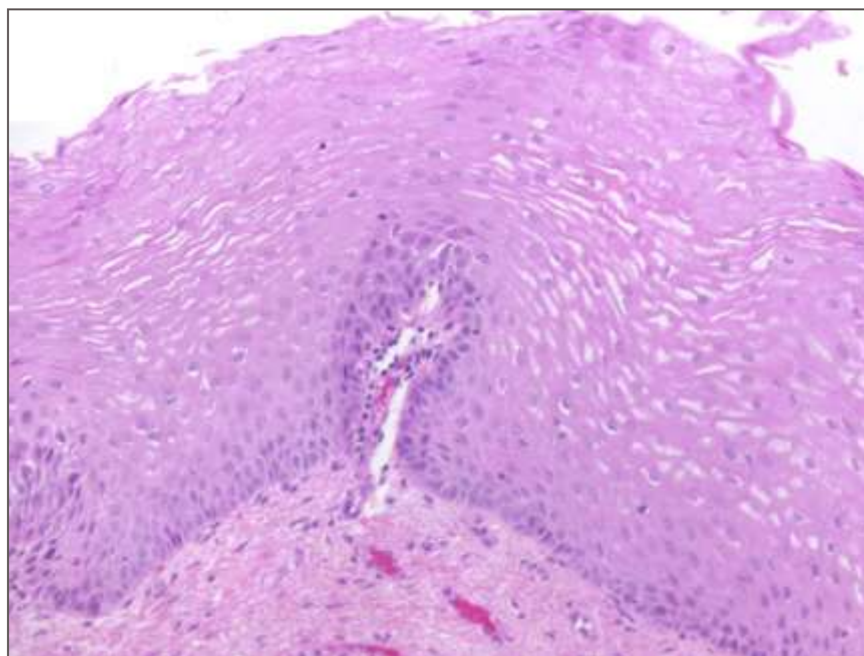
EoE – Elemental Diet



Before



After

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Advantages of Elemental Diet

- When administered correctly:
  - >95% demonstrate clinical and histologic response
  - Allows systematic reintroduction 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)

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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;4:1097-1102.

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Empiric Diet Elimination

- Easy, does 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 reintroduction

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Allergy Testing

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Types of Allergy Testing

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

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Prick Skin Test

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

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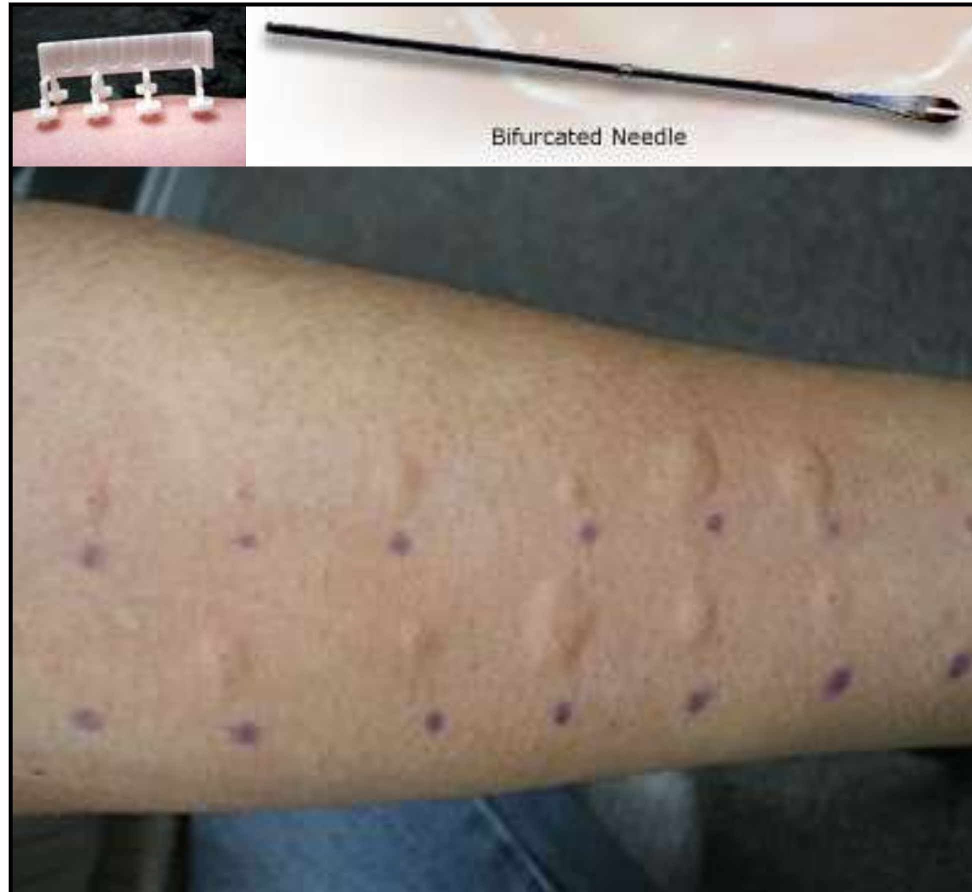
Skin Test Devices/Reactions



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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 eosinophilic gastrointestinal diseases (EGIDs)
- Reagents are not standardized

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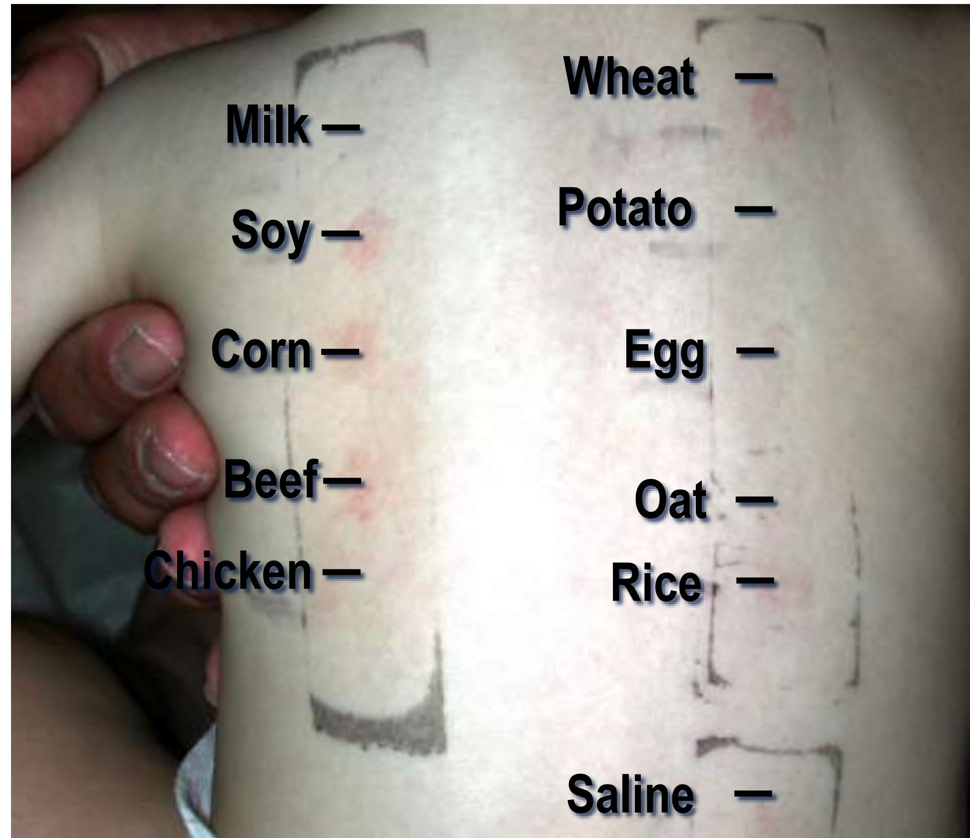
Atopy Patch Testing



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Food Testing in EoE

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

  -1/8 have both negative skin prick test (SPT) and APT
  - Wheat, corn, soy, milk, beef, rice, chicken, egg, rye, oat, and potato

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

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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 4–5 foods
- Up to 25% have severe food allergies—unable to tolerate ANY food without symptoms and histologic changes

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Diet Choice

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 4 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 negative likelihood ratio (NLR)/positive likelihood ratio (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 and Wang. *J Allergy Clin Immunol Pract.* 2013;1(6):602-607.

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Dietary Therapy in EoE

- Dietary therapy (amino acid [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;133:1342-1363.
Liacouras et al. *J Allergy Clin Immunol.* 2011;128:3-20.

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Poll Question #3 - Answer

Of the following dietary therapies, which is not an accepted therapy for EoE?

A. A restricted diet based on the removal of the most likely 6 foods causing disease
B. The strict use of an amino acid–based formula
C. A restricted diet simply based on a patient's symptoms
D. A restricted diet based on skin prick and atopy patch allergy testing

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EoE and Atopy

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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% and 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

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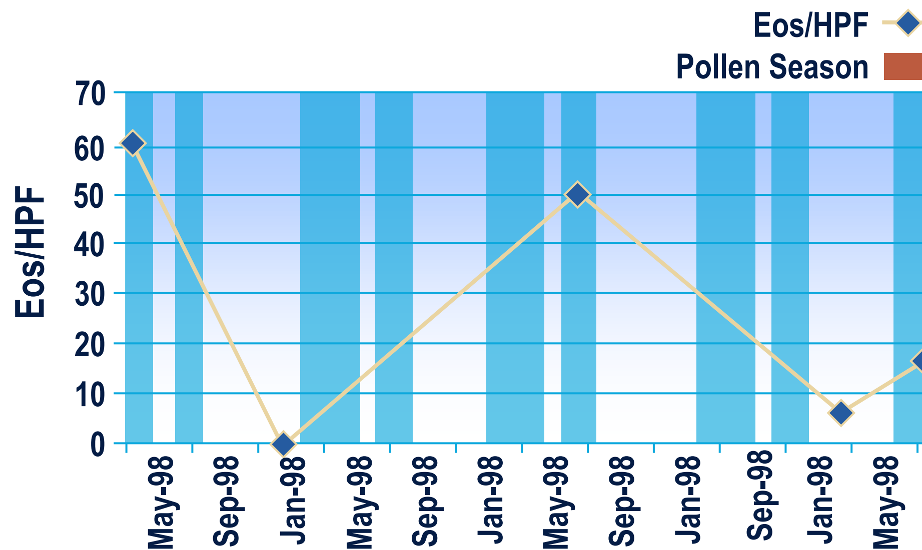
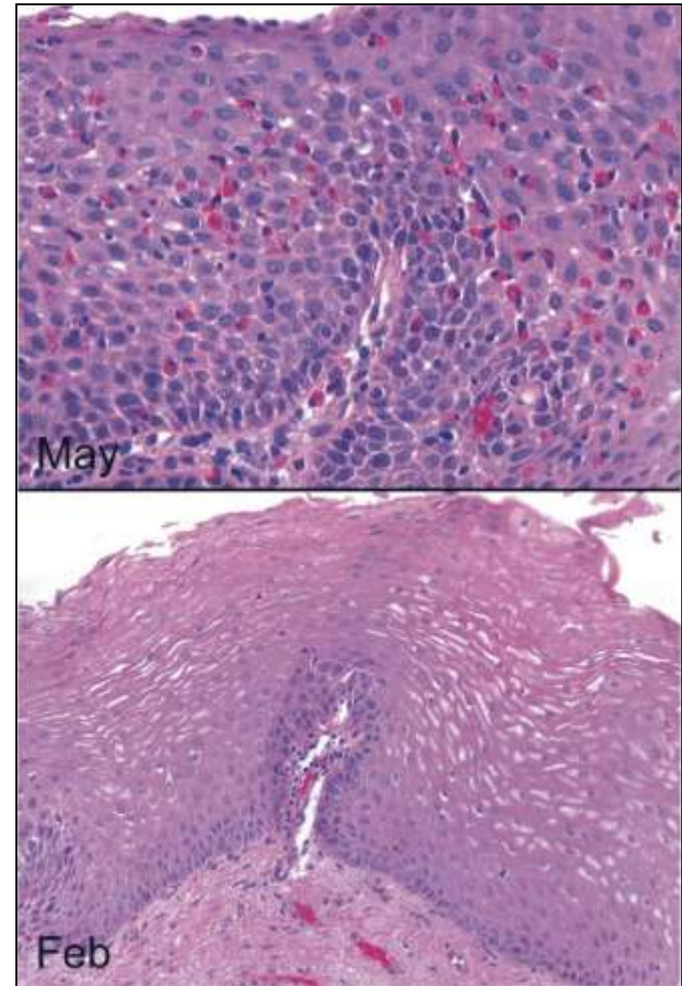
Seasonal Variation in EoE

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





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

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Poll Question #4

The role of a dietitian in patients with EoE include all of the following, EXCEPT:

A. Performs allergy testing—skin or patch testing
B. Helps patients and families understand how to read food labels in order to avoid "allergic foods"
C. Works closely with allergists and gastroenterologists to help treat patients with EoE
D. Monitors height and weight in order to outline adequate caloric intake

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Nutrition in EoE

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Role of Dietitian 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

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Components of Nutrition Assessment

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

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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

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Elimination Diets

Essentials

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

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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: Food Allergen Labeling and Consumer Protection Act (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

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Elemental Diet

- 100% amino acid–based formula as sole source of nutrition (Neocate®, Elecare®, etc.)
- Can use in combination with elemental semisolid (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

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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

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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)

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Family Support

- Work with schools to educate staff and minimize risk of allergen exposure (Food Allergy Research & Education [FARE] program)
  - Provide safe, nonperishable foods for snack time, parties
  - Emergency kit /epi must be available
  - Other FARE resources (restaurants, camps, etc.)
- Thorough, updated, and 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.

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Poll Question #4 - Answer

The role of a dietitian in patients with EoE include all of the following, EXCEPT:

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Biologic Treatment

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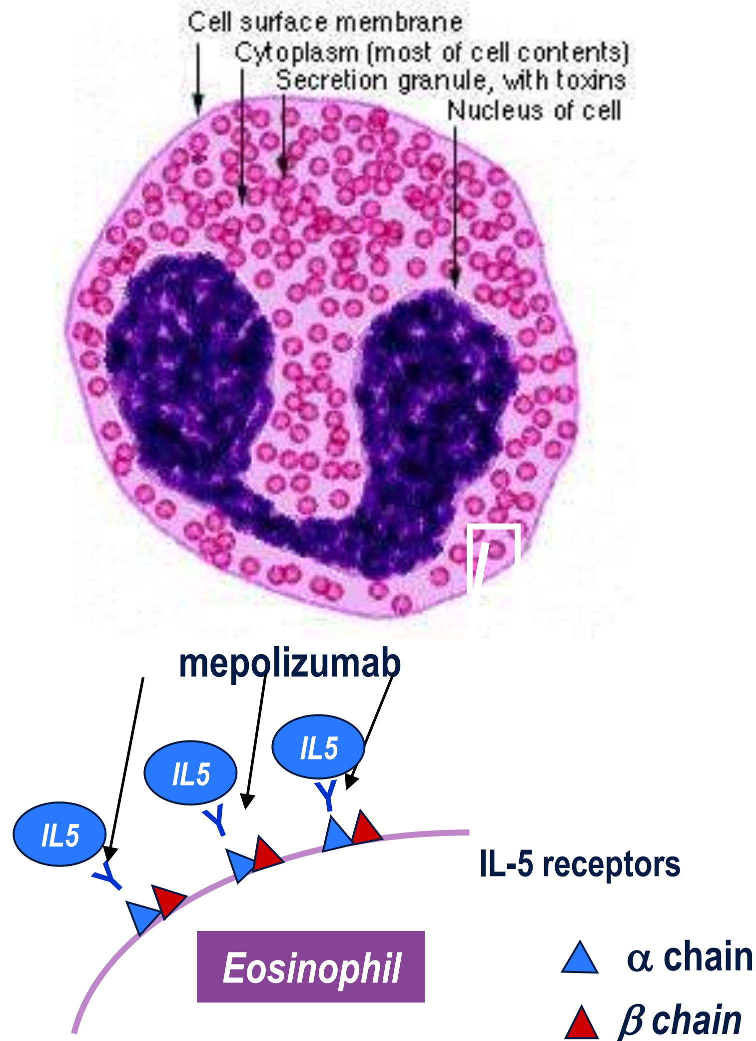
Anti-Interleukin 5



- Interleukin (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 number. No change in symptoms in adults.

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

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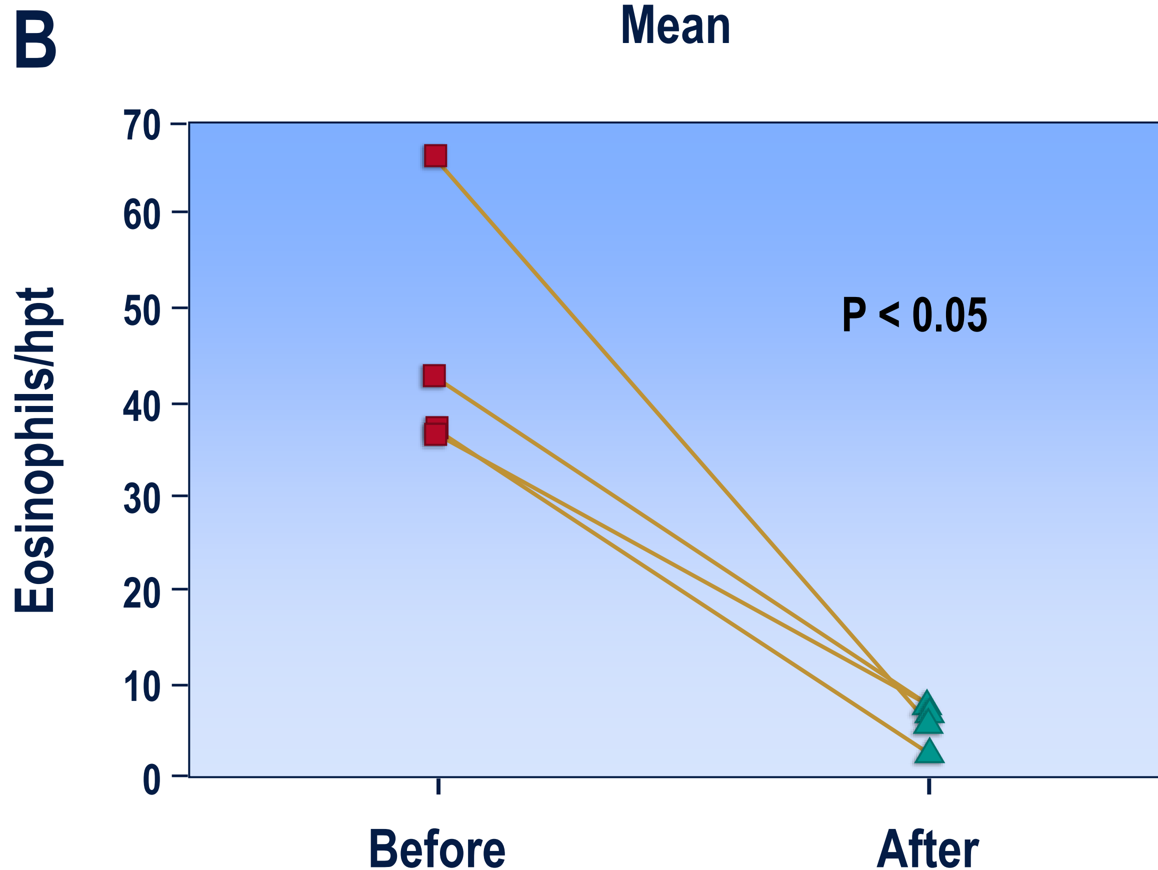
Anti-IL-5 on Esophageal Eosinophils



Stein et al. *J Allergy Clin Immunol.* 2006;118:1312-1319.

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Anti-IL-5 — Current Studies

- Mepolizumab
  - Utilized 3 different doses of anti-IL-5 via 4-week infusions
  - Significantly reduced esophageal eosinophilic inflammation
  - Symptom improvement difficult to assess
- Reslizumab
  - Placebo-controlled trial
  - Anti-IL-5 significantly reduced esophageal eosinophils
  - Symptom improvement similar between placebo and anti-IL-5

Assa'ad et al. *Gastroenterol*. 2011;141:1593-1604.
Spergel et al. *J Allergy Clin Immunol.* 2012;129:456-463.

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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”
- ? cotherapy 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.
Bhardwaj and Ghaffari. *Ann Allergy Asthma Immunol*. 2012;109:155-159.

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Advocacy Groups

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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

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Conclusions

- EoE is a clinicopathologic 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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Questions & Answers

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