9TH ANNUAL
DIGESTIVE DISEASES: NEW ADVANCES

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Review of Eosinophilic Esophagitis

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Disclosures

- **Ehsan Navabi, MD**
  - **Advisory Board:** Eli Lilly

Objectives

- Definition of EoE
- Genetics and immunopathogenesis
- Epidemiology
- Clinical Manifestation
- Diagnosis
- Treatment
- What is new?!

Definition

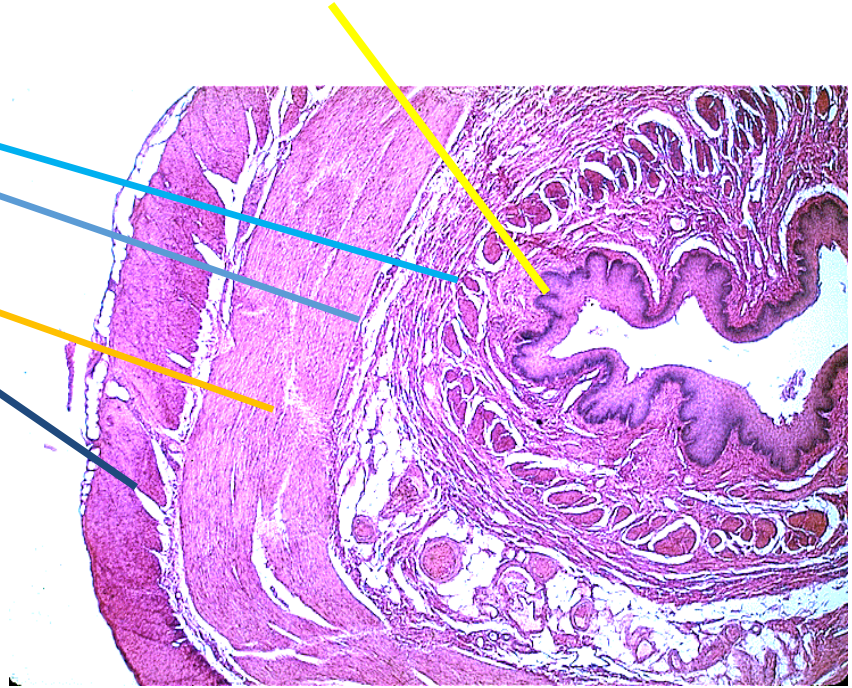
Chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.

Liacouras CA, Furuta GT, Hirano I et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128:3–20. e6.

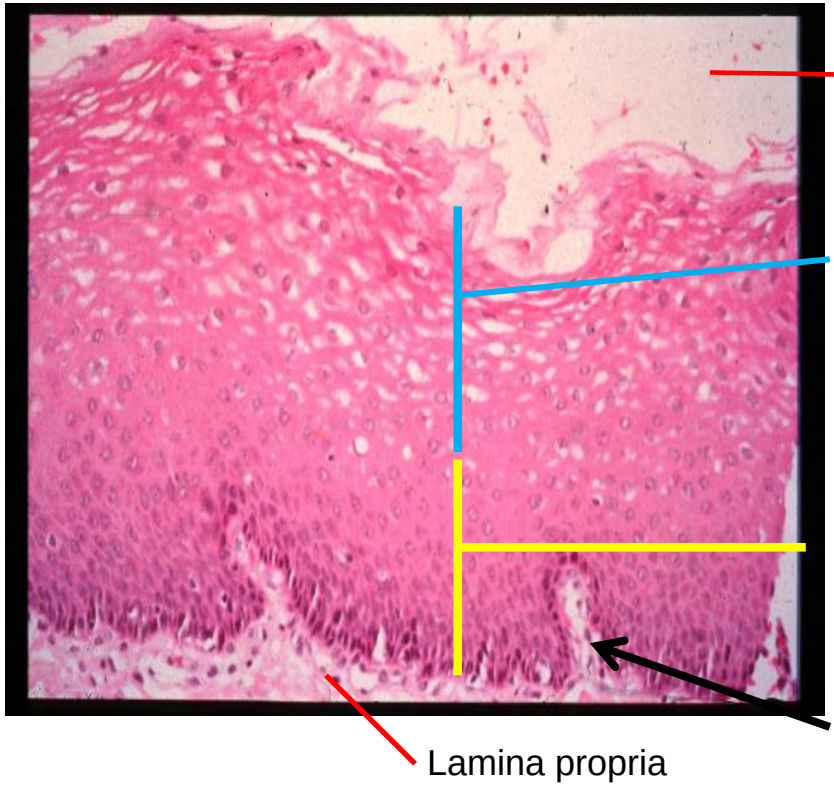
- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion for EoE.
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion for EoE.
- 15 eos/hpf (w60 eos/mm2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus.
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Normal Esophagus

- Stratified squamous, non-keratinized epithelium
- Surrounded by
  - Lamina propria
  - Muscularis mucosa
  - Submucosa
  - Muscularis propria



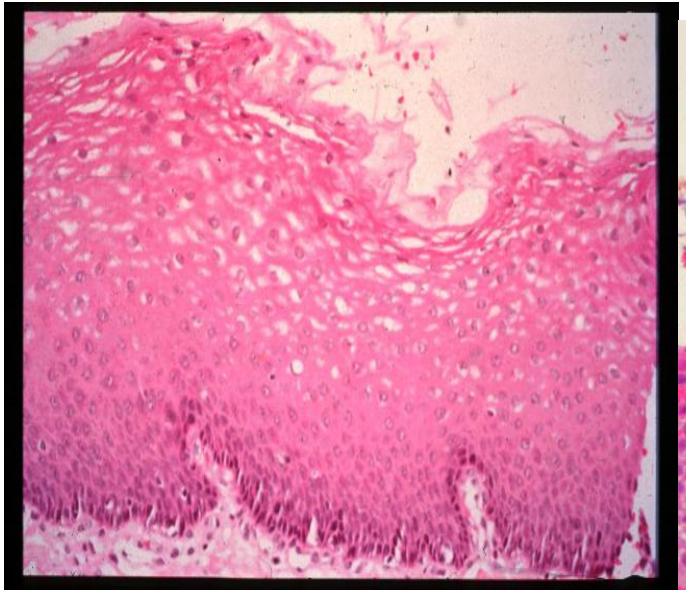
Normal Esophageal Histology
Stratified Squamous, Non-Keratinized, Epithelium



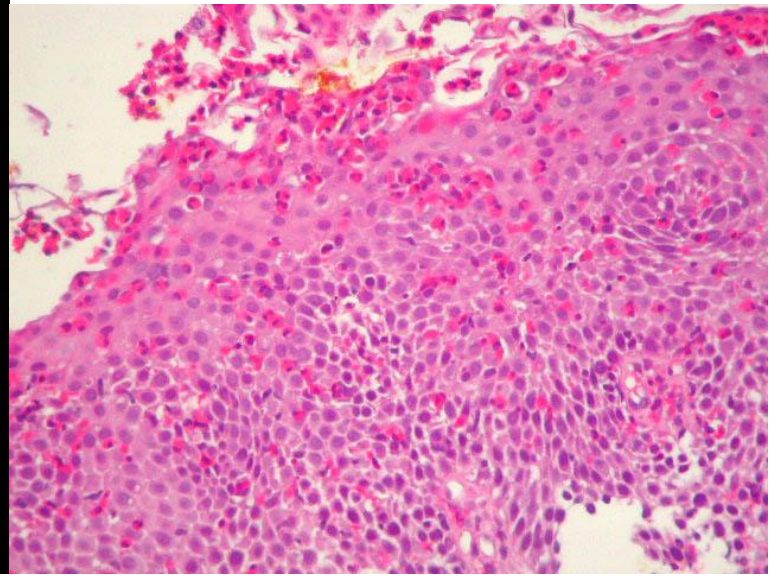
- Suprabasal layer
- Basal cell layer
- Rete peg

Normal Esophagus

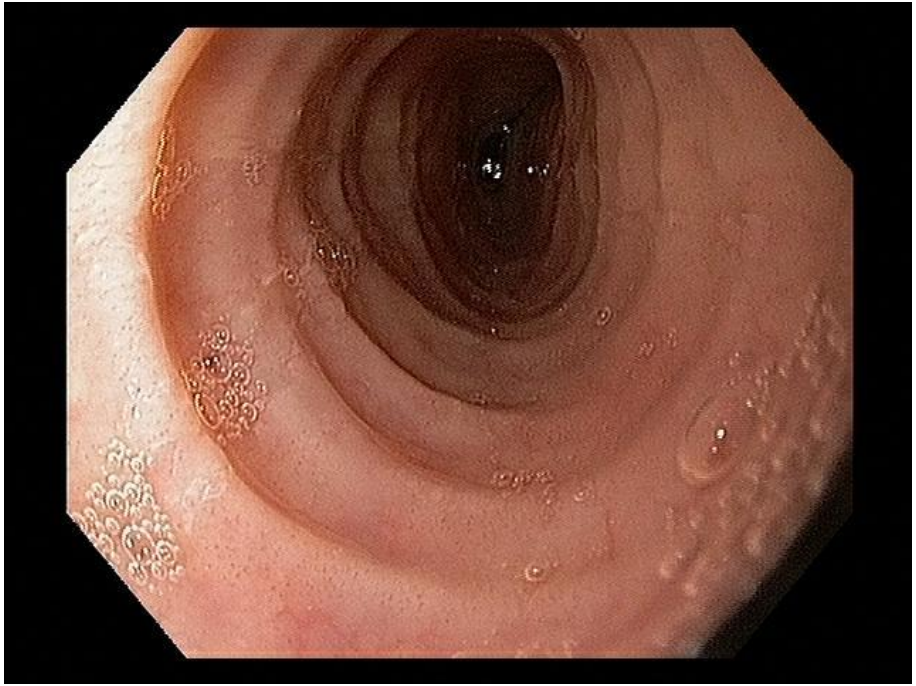
Normal Esophagus



Esophagitis



Mucosal Rings



Endoscopic Photograph of Distal Esophagus With Thickening and Furrowing

Exudate

Endoscopic Photograph Showing Typical Exudate (‘White Specks’)

Patchy Furrowing With Exudate

Conditions Associated With Esophageal Eosinophilia

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- Achalasia and other disorders of esophageal dysmotility
- Hypereosinophilic syndrome
- Crohn’s disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement (i.e., pemphigus)
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft vs host disease

Genetics and Immunopathogenesis

The pathogenesis of EoE is incompletely understood but involves an interplay between genetic, environmental, and host immune system factors.

Host immune system mechanisms in EoE appear to fall somewhere in between pure immunoglobulin E (IgE)-mediated and delayed T helper type 2 (Th2) responses.

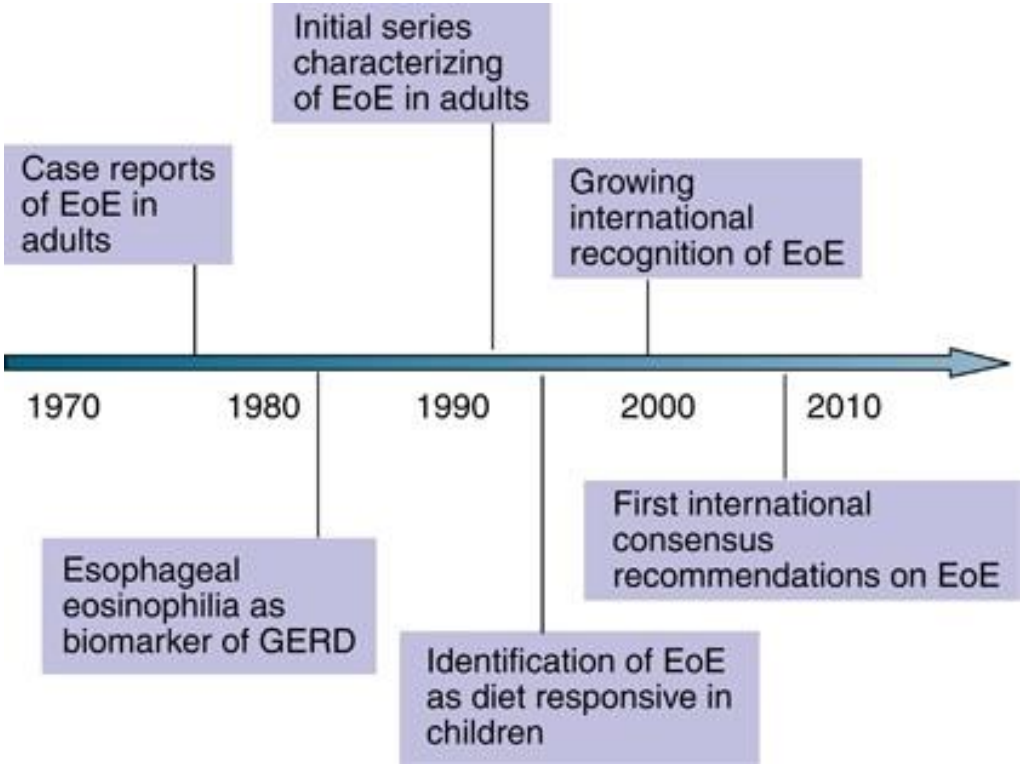
- Studies have identified contributory roles for allergens, cytokines, microRNAs (miRNAs), chemokines, and polarization of Th2 immunity in the disease pathophysiology.

A genetic predisposition to EoE is supported by evidence of familial clustering and twin studies.

- In addition, several genetic defects that may predispose to EoE have been identified, especially at 2p23, encoding for the esophagus specific gene product, calpain 14.

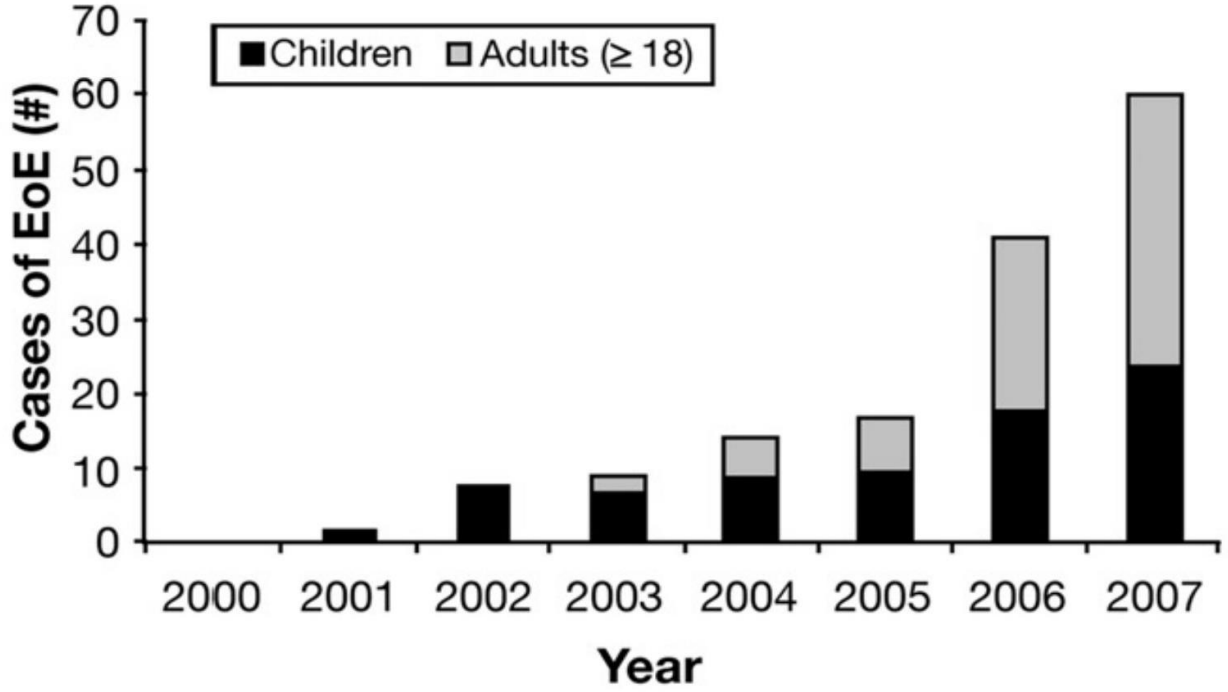
What It Really Is?

- Disorder of epithelial homeostasis
- Genetically susceptible individuals
  - Impaired barrier function: cell-cell adhesion
  - Dysregulation of the immune response toward Th2 mediated hypersensitivity
- Initiation and perpetuation of inflammation by dietary antigen exposure
  - Esophageal dysfunction (motor and sensory)
  - Mural remodeling with loss of compliance
  - Lumenal narrowing (focally or diffusely)
- Disease with eosinophils, not a disease of eosinophils



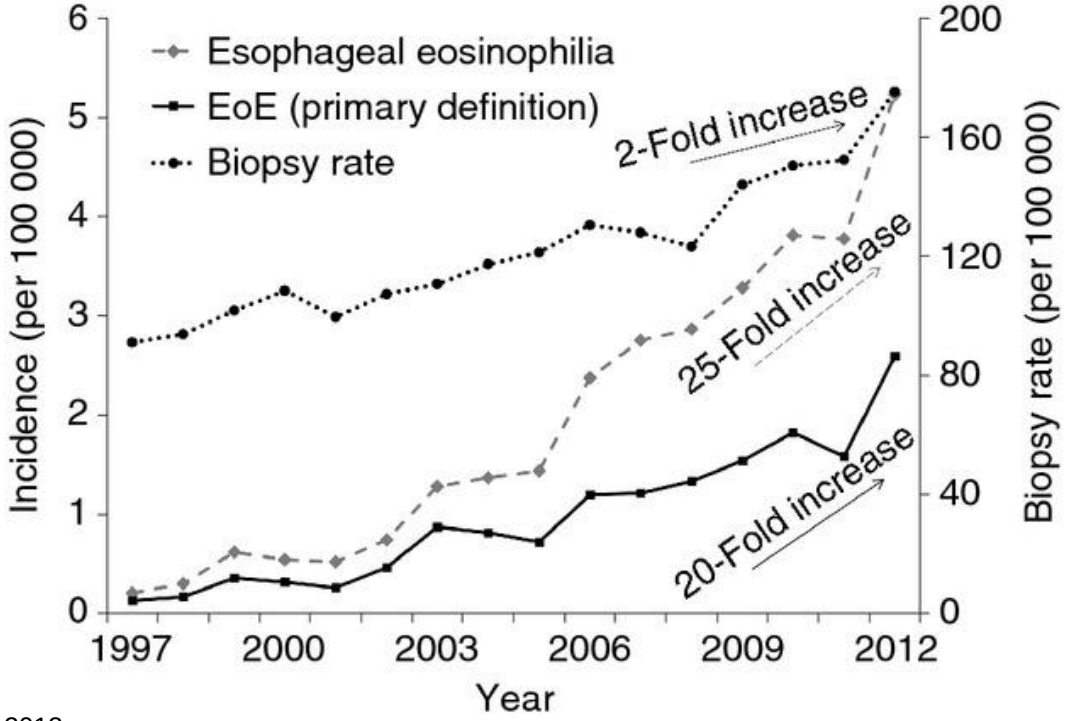
Hirano. *American Journal of Gastroenterology*. June 2016.

New Cases of EoE at UNC 2000-2007



Dallon E et al. *CGH.* 2009.

Incidence of EoE Rising More Rapidly than Esophageal Biopsy Rate



Danish Population Based Study 1997-2012.
Dellon E et al. *APT*. 2015.

Male predominant (~75%)

Familial clustering

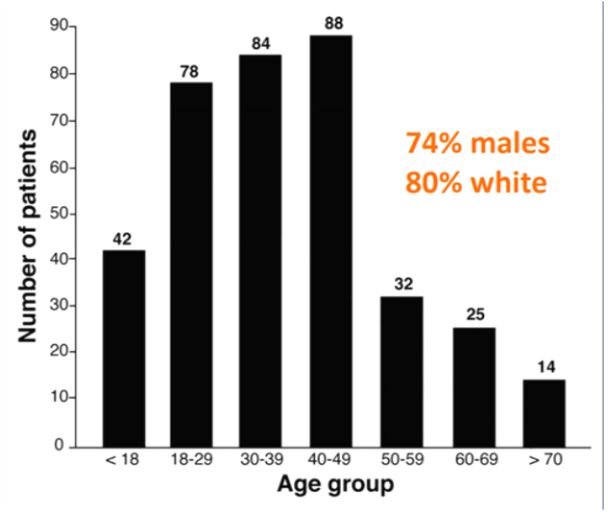
2/3 are otherwise atopic:

- Food allergies (IgE-mediated immediate hypersensitivity)
- Environmental allergies
- Asthma
- Eczema
- Chronic rhinitis

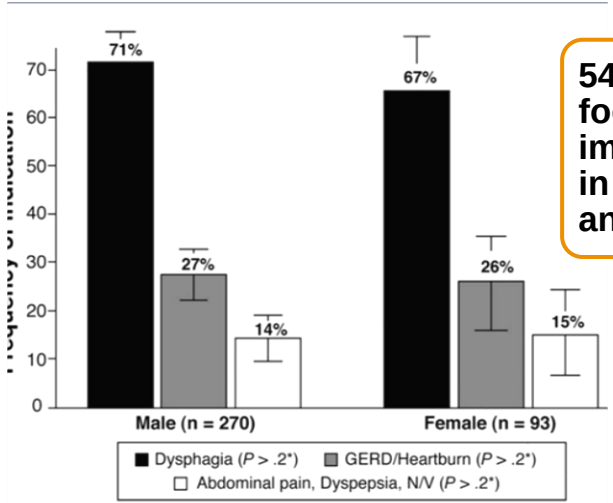
Food antigen-induced eosinophilia

- 95% respond to antigen removal
- Recurrent disease upon reintroduction of provocative antigens

Prevalence

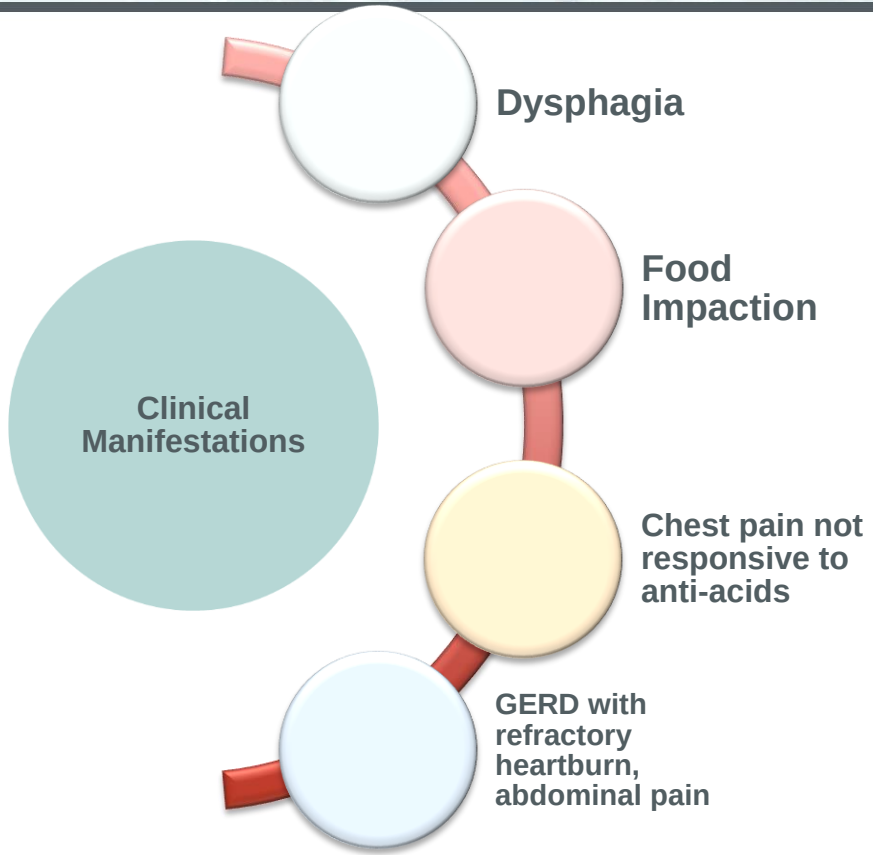


Symptoms



54% with food impaction in meta-analysis*

Karpel et al. *Gastroenterology.* 2008; * Hiremath GS el. *Dig Dis Sci*. 2015.


Clinical Manifestations
Dysphagia
Food Impaction
Chest pain not responsive to anti-acids
GERD with refractory heartburn, abdominal pain

Diagnosis

Clinical Suspicion and Evaluation

Symptoms

Esophageal dysfunction

History of atopic comorbidities

Family history

History of esophageal perforation or severe pain after dilation of a stricture should also raise suspicion of this disorder.

Endoscopic appearance

Stacked circular rings ("feline" esophagus) : 44 percent

Strictures (particularly proximal strictures) : 21 percent

Attenuation of the subepithelial vascular pattern: 41 percent

Linear furrows : 48 percent

Whitish papules (representing eosinophil microabscesses) : 27 percent

Small caliber esophagus: 9 percent

Histological findings

A threshold of 15 eosinophils per high power field is generally required for the diagnosis

Better to obtain biopsies from distal and proximal esophagus as well as stomach and intestine

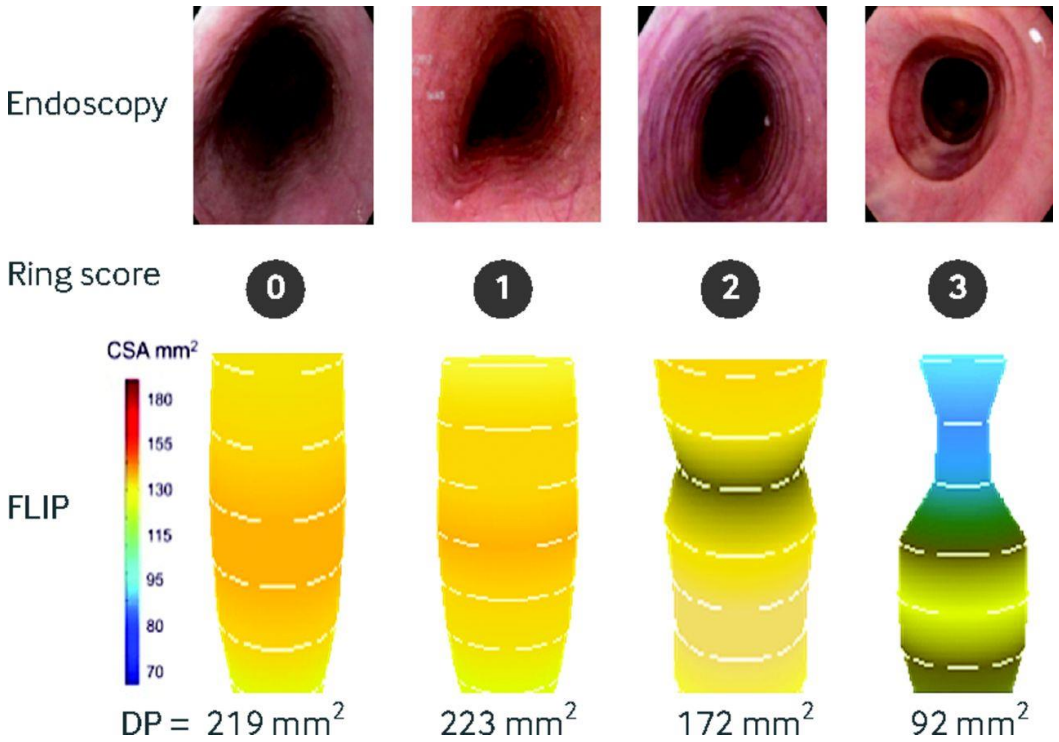
Diagnostic Criteria:

- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion for EoE.
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion for EoE.
- 15 eos/hpf (w60 eos/mm2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus.
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Other Diagnostic Measures:

- No role for radiology, but you may see

Functional Luminal Imaging Probe (FLIP)



Chen J W, Kao J Y. Eosinophilic esophagitis: update on management and controversies. *BMJ* 2017.

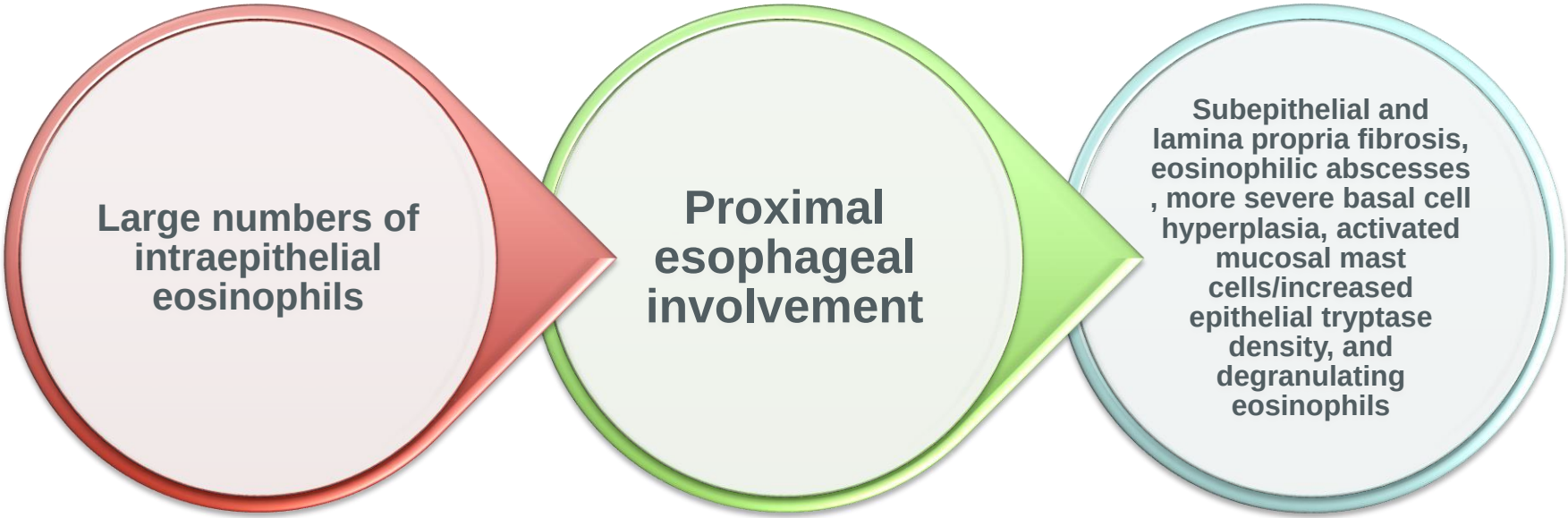
Other Diagnostic Measures:

- Lab Test:
  - Approximately 50 to 60 percent of patients with eosinophilic esophagitis will have elevated serum IgE levels (>114,000 units/L)
  - Peripheral eosinophilia is seen in 40 to 50 percent of patients but is generally mild.
  - A 96-gene EoE diagnostic panel, has been developed based upon analysis of esophageal biopsies.
    - This diagnostic panel, which appears to be able to differentiate EoE from control individuals, including those with GERD, may also be able to differentiate patients with active and inactive disease and identify glucocorticoid exposure.

Other Diagnostic Measures:

- Allergy Testing:
  - The primary method of food allergy testing used for patients with EoE is skin prick testing (SPT). Atopy patch testing (APT) is used infrequently. In general, these tests have good negative predictive values (NPVs) and poor positive predictive values (PPVs) for foods, with the exception of milk.
  - Allergy testing in EoE is used to identify and manage common comorbid atopic diseases (eg, asthma, allergic rhinitis) and to determine foods that may present a risk for acute allergic reactions/immediate-type allergy when eliminated foods are reintroduced into the diet during treatment. It may also help identify EoE triggers.

Histologic Features Suggestive of Eosinophilic Esophagitis Rather than GERD:

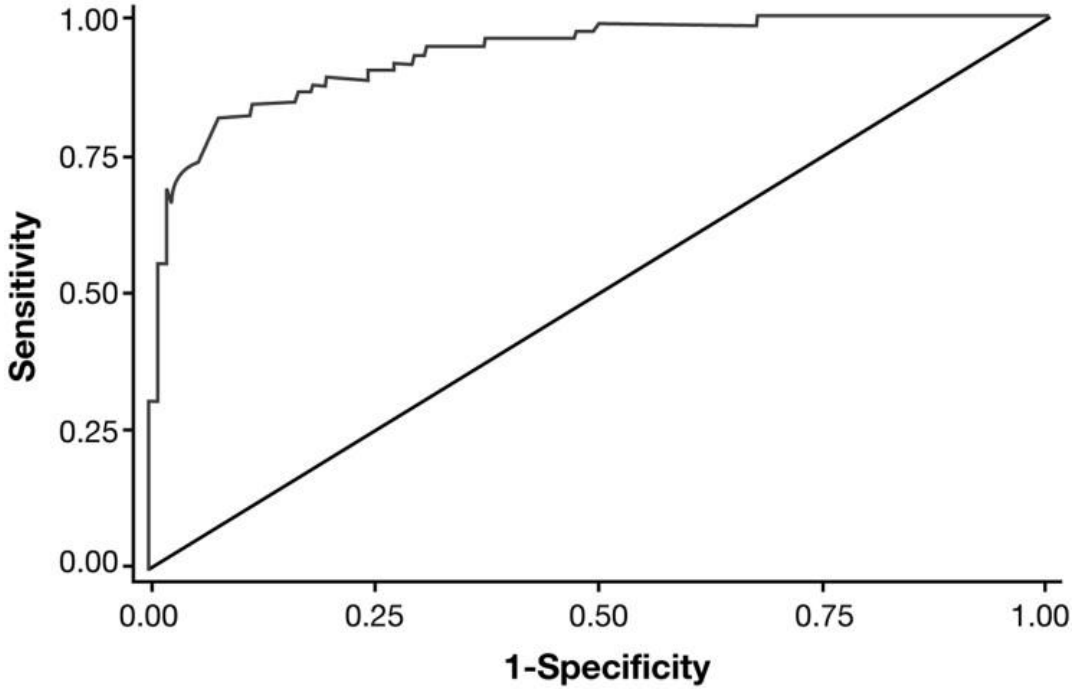


Multivariate Model Predicting EoE

Predictor	Odds ratio	95% CI	*P* value
Age at biopsy	0.98	0.95–1.00	.09
Dysphagia (symptom)	11.8	3.77–36.8	<.001
Food allergy (documented)	11.2	2.79–45.0	.001
Rings seen on EGD	9.9	1.93–51.1	.006
Linear furrows seen on EGD	6.4	0.62–65.5	.12
White plaques seen on EGD	5.4	0.49–58.5	.17
Hiatal hernia present on EGD	0.21	0.04–1.00	.05
Maximum eosinophil count	1.01	1.01–1.02	<.001
Degranulating eosinophils	4.81	1.52–15.2	.0

Dellon ES, Gibbs WB, Fritchie KJ, Rubinas TC, Wilson LA, Woosley JT, Shaheen NJ. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2009.

Predictive Model Differentiating EoE From GERD

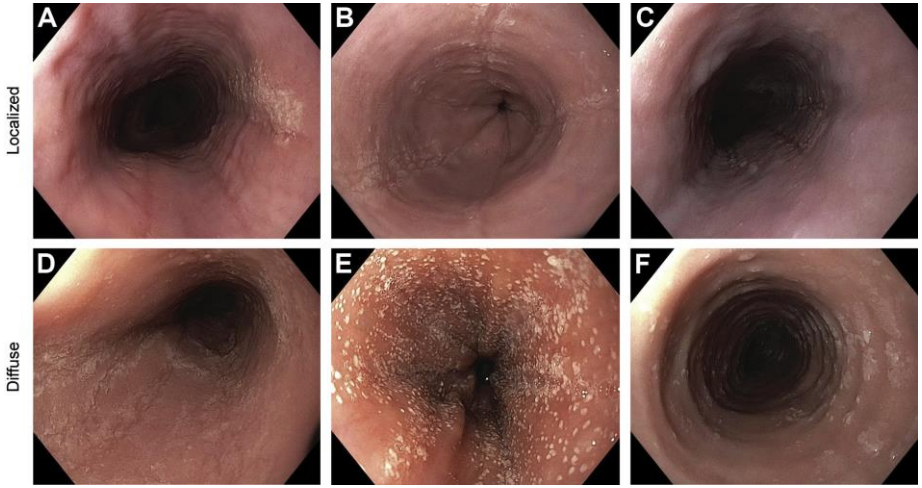


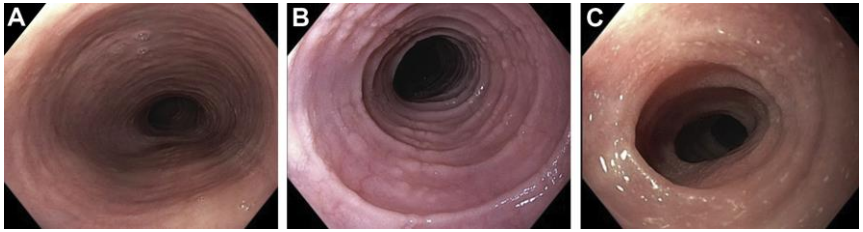
Area under ROC curve = 0.9339.

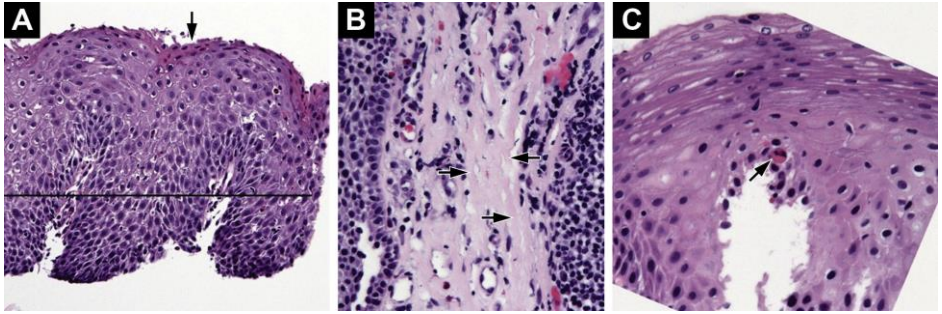
The Index of Severity for EoE (I-SEE)

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	--
Complications	--	Food impaction with ER visit or endoscopy (patient ≥18 years)	••Food impaction with ER visit or endoscopy (patient <18 years) ••Hospitalization due to EoE	••perforation ••Malnutrition •Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory • treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	--	--
Histology	15–60 eos/hpf	>60 eos/hpf	--	--
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope	--	Cannot pass standard upper endoscope; repeated dilations
Histology	--	BZH or LPF (or DEC/SEA if no LP)	--	--

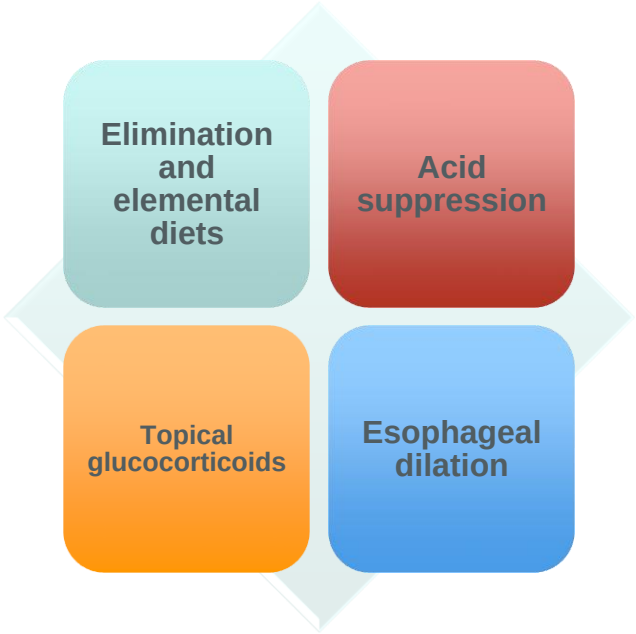
Figure 1







Treatment



Systemic glucocorticoids, antihistamines, immunosuppressants, and immunomodulators.

Dietary Therapy

Testing-directed Elimination Diet

- Skin prick testing (SPT) and occasionally atopy patch testing (APT) are performed to test for food allergies, with subsequent elimination of foods with positive test results

Empiric Elimination Diet

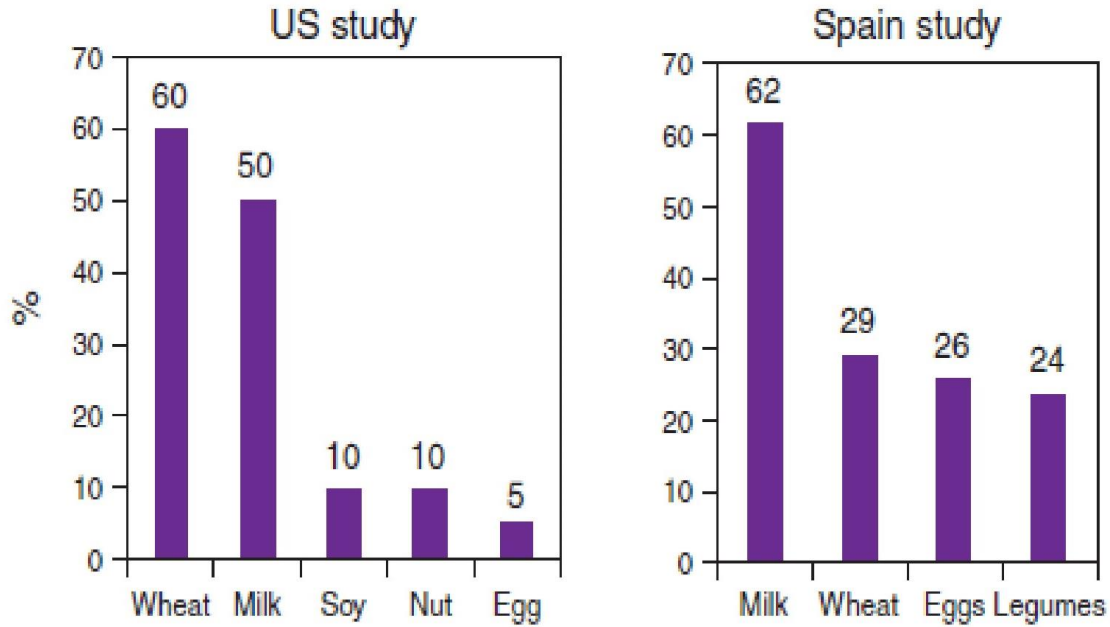
- This is called the six-food elimination diet (SFED)
- Four-food group elimination (milk, egg, legumes, wheat)

Elemental Diet

- Patient is placed on an elemental formula, which eliminates all potential food allergens

- Milk
- Soy
- Eggs
- Wheat
- Peanuts/tree nuts
- Shellfish/Fish

Specific Food Triggers Identified in Adult Series of Elimination Diet



Hirano. *Am J Gastro*. 2016.

Eosinophil Response to Reintroduction of Foods

Common food triggers

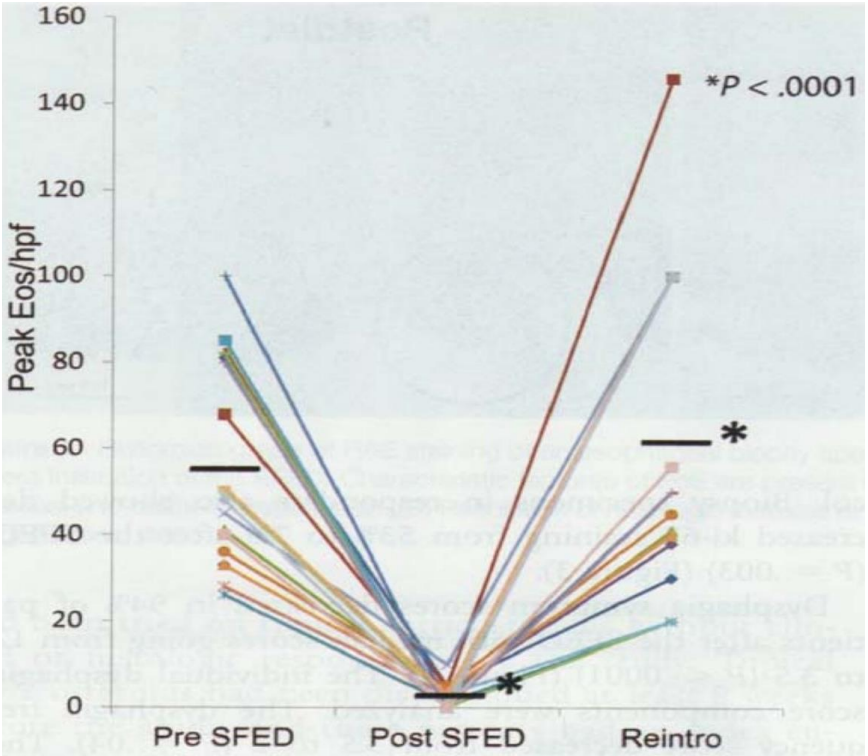
Wheat – 60%

Milk – 50%

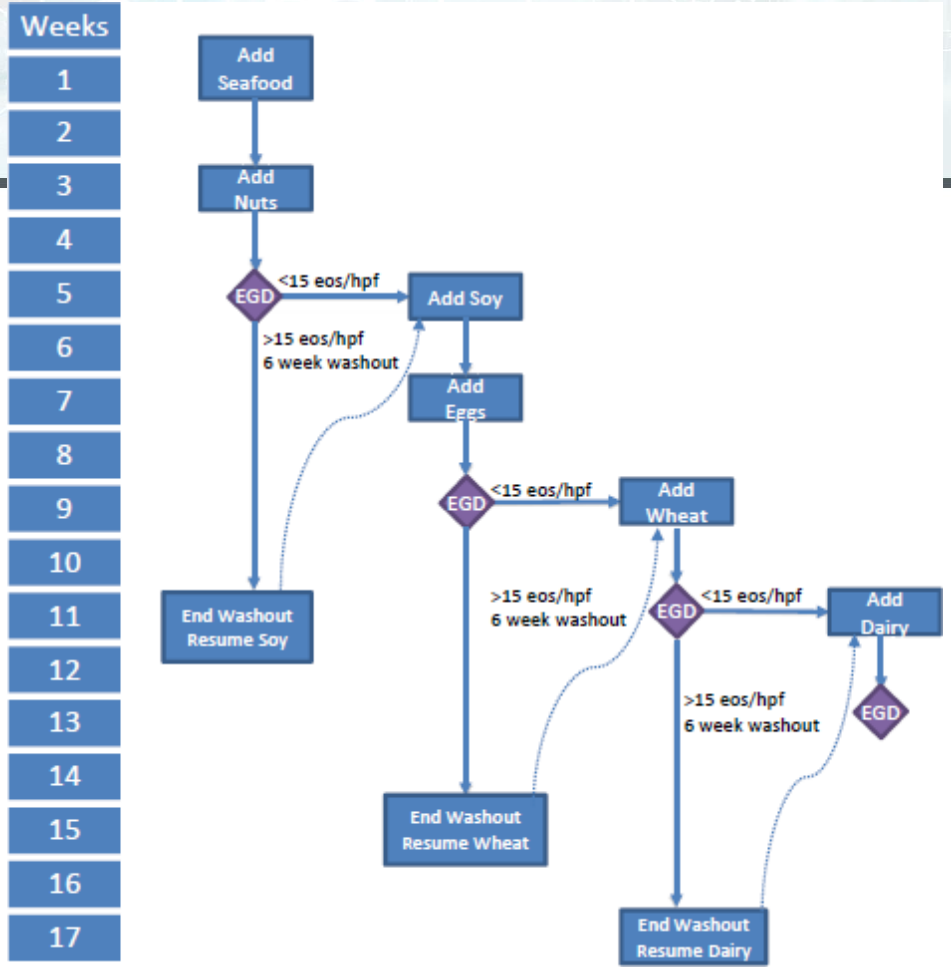
Soy – 10%

Nuts – 10%

Egg – 5%



Gonsalves et al. *CGH*. 2012.



Doerfler et al. *Disease of the Esophagus*. 2015.

Acid Suppression (Based on AGREE Consensus This Is Part of Treatment and Not Diagnosis Anymore).

- Start if dietary therapy not accepted or failed.
- Treat for 8 weeks.
    - Begin with standard full dose PPI
    - Increase to double dose if standard dose fails to improve symptoms after four weeks
- The clinical response should be evaluated after an eight-week course of treatment:
    - For patients with continued symptoms, repeat upper endoscopy
    - For patients who have a clinical response, we continue the PPI at the lowest dose successful at controlling symptoms

Topical Steroids

- Most patient respond with decrease in eosinophil counts.
- No formulation has been approved specifically for EoE. But Fluticasone and Budesonide have been best studied.

  Fluticasone: ACG 2013 → 880 to 1760 mcg/day in divided doses

  8 weeks treatment, with rapid response. Though chance of relapse is high after stopping the treatment. So, need either dietary treatment or continue fluticasone. (maintenance is 880 mcg daily

  - ✓ Expensive
  - ✓ Infection (candida, herpes)
  - ✓ Cataract ?

  Budesonide: 2 mg daily for 8 weeks. (maintenance 1 mg daily)

  Almost no role for systemic steroids. Also, no difference between fluticasone vs budesonide.

First EoE Study in Adults With Fluticasone vs Placebo

- Fluticason 220 micrograms – 4 puffs BID for 6 weeks vs Placebo
- Initially 21 EoE patients in each group

Table 2. Dysphagia Response

	Fluticasone	Placebo	*P* value
ITT complete	42.9% (9/21)	28.6% (6/21)	.52
PP complete	47.4% (9/19)	40.0% (6/15)	.74
ITT partial or complete	57.1% (12/21)	33.3% (7/21)	.22
PP partial or complete	63.2% (12/19)	46.7% (7/15)	.49
PP complete 2 weeks	42.1% (8/19)	26.7% (4/15)	.47
PP complete 4 weeks	47.4% (9/19)	26.7% (4/15)	.30

Table 3. Histologic Response

	Fluticasone	Placebo	*P* value
ITT complete	61.9% (13/21)	0% (0/21)	<.001
PP complete	68.4% (13/19)	0% (0/15)	<.001
ITT partial or complete	81.0% (17/21)	4.8% (1/21)	<.001
PP partial or complete	89.5% (17/19)	6.7% (1/15)	<.001

*Despite nearly eliminating eosinophils, symptom relief no better than placebo.
Alexander JA et al. *Clinical GI and Hepatology*. 2012.

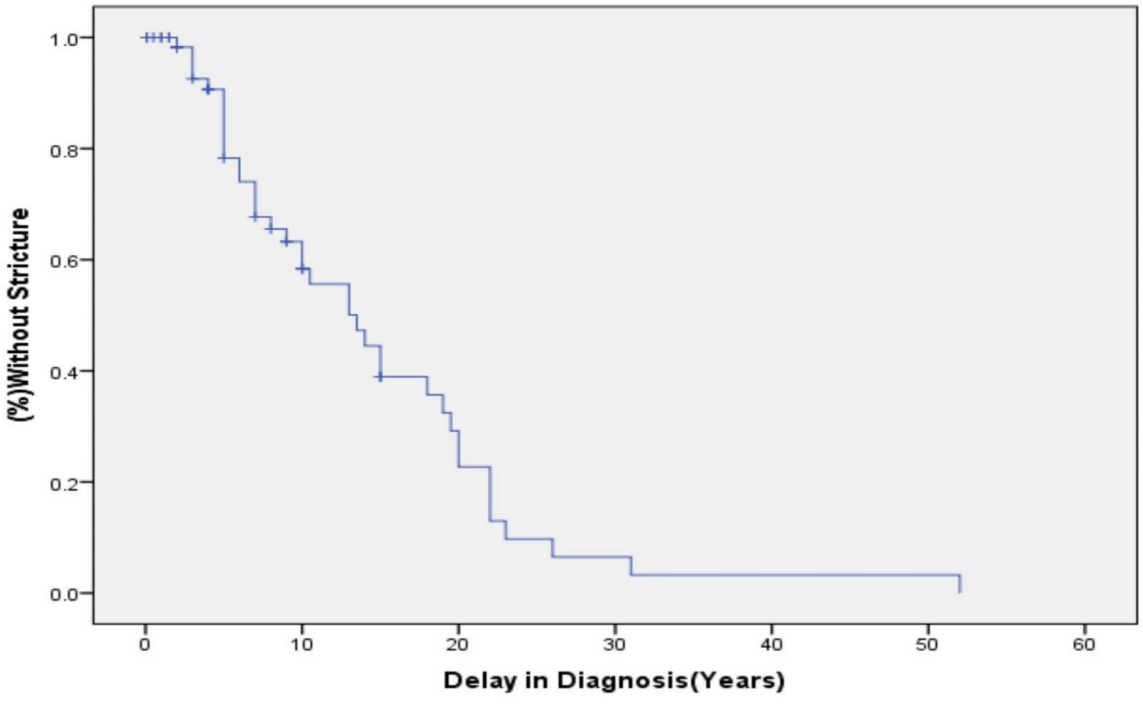
Large Clinical Experience With Steroids in Adult EoE Patients

- 221 EoE received steroids
- Only 57% had histologic remission
- Only 48% responded to second line therapies
- Need for esophageal dilation was predictor of poor outcomes

Therapy (no. receiving)	Responded with <15 eosinophils, n (%)
Dietary (16)	6 (38)
Increased dose (14)	2 (14)
Changed topical agent (7)	2 (29)
Singular (7)	1 (14)
Prednisone (5)	1 (20)
Ciclesonide (3)	0 (0)
Compounded budesonide (2)	1 (50)
Ketotifen (1)	0 (0)
6-mercaptopurine (1)	0 (0)
Total	13 (48)

Wolf WA et al. *Clinical GI and Hepatology*. 2015.

Duration of Symptoms Predict Stricture Disease in EoE – USF Experience



Lipka et al. *J Clin Gastro*. 2015.

Esophageal Dilation

- Dilation of esophageal strictures is effective for relieving dysphagia but has no effect on underlying inflammation.
- Usually reserved if no response to therapy.
- Patient should be forewarned that there is a risk of perforation, bleeding and chest pain.
  - No more than 3 mm per session.
  - Goal of 15 to 18 mm.
    - While older studies suggest that the perforation risk was as high as 7% but 2017 meta-analysis of 977 patient with 2034 dilations shows that post procedure hospitalization just occurred in 0.03 to 0.7 with no increased risk in perforation and chest pain.

Natural History of EoE Treated With Esophageal Dilation Over 13 Years

14 patients (11 men)–average age 32

Average follow-up–13 yrs (5-24)yrs

Lipka S, Richter JE, et al. *GI Endoscopy*. 2014.

Dupilumab (Dupixent)

- Monoclonal antibody to the alpha subunit of the interleukin-4 [IL-4] receptor inhibits signaling of IL-4 and IL-13 cytokines, which is important in the generation of inflammation mediated by T-helper type 2 cells.

FDA NEWS RELEASE

FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder

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For Immediate Release: May 20, 2022

Today, the U.S. Food and Drug Administration approved Dupixent (dupilumab) to treat eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms (which is about 88 pounds). Today's action marks the first FDA approval of a treatment for EoE.

"As researchers and clinicians have gained knowledge about eosinoph[illegible]
[illegible]itis i[illegible]nt years, more cases of the disorder have beco[illegible]
[illegible]Jessica Lee, M.D., directo[illegible]

12 years and older
weigh at least 88 lb. (40 kg).

300mg injection QW