

## The EoE Hunger Games: PPI-REE is Catching Fire!

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Medical Center

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I have no conflict of interests to disclose.

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### Learning Objectives

- Recognize the similarities, differences, and relationship between GERD, EoE, and PPI-REE.
- Understand the mechanism of PPI response in PPI-REE patients.
- Evaluate and treat a patient with esophageal eosinophilia.

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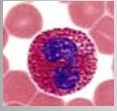
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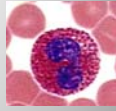
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## Eosinophilic Esophagitis (EoE) Conceptual Definition



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

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

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## EoE in the United States

- Prevalence 56.7 per 100,000 (1 in 2,000)  
- Similar to pediatric inflammatory bowel diseases  
*Dellon E. Clin Gastroenterol Hepatol 2014;12:589.*
- Most common cause of food impaction in patients seen in ER  
*Sperry S. Gastrointest Endosc 2011;74:985.*
- Health-care cost \$0.5-1.4 billion per year  
*Jensen E. Am J Gastroenterol 2015.*



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## Common Symptoms of EoE

- Dysphagia
- Odynophagia
- Food Impaction

### Children

- Vomiting
- Feeding intolerance
- Feeding aversion
- Failure to Thrive



### Adults

- Chest Pain
- Heart burn
- Epigastric pain
- Refractory "GERD"



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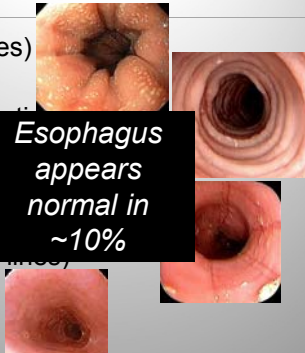
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### EoE Endoscopic Reference Score (EREFS)

- Exudates (plaques)
- Rings (tracheal)
- Edema (pallor)
- Furrows (vertical lines)
- Strictures

Esophagus  
appears  
normal in  
~10%



Endoscopic findings are not specific for EoE.

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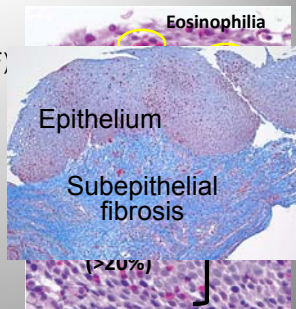
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### Histological Findings

- Esophageal Eosinophilia  
( $\geq 15$  intraepithelial eos/HPF)
- Eosinophil Microabscesses
- Basal Zone Hyperplasia
- Dilated Intercellular Spaces
- Subepithelial Fibrosis



Histological findings are not specific.

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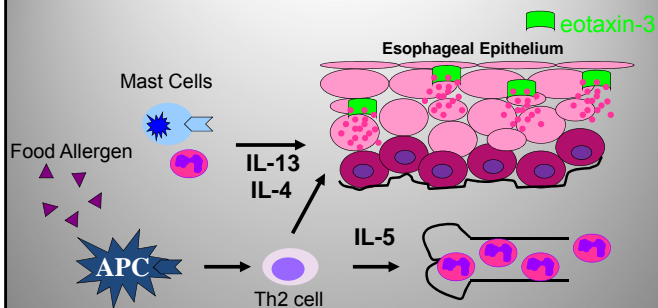
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### Eosinophilic Esophagitis Pathogenesis Model (Genetically-Susceptible Individual)



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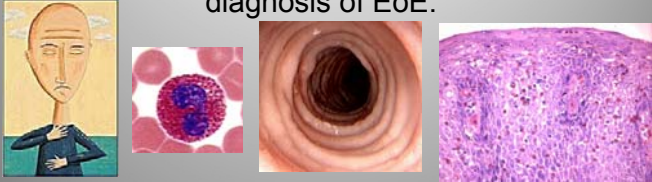
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## There Is No Diagnostic “Gold Standard” for Eosinophilic Esophagitis

No single clinical, laboratory, endoscopic, or histological feature establishes the diagnosis of EoE.



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## Diseases Associated with Esophageal Eosinophils

- EoE
- GERD
- Eosinophilic gastroenteritis
- Crohn’s disease
- Infections
- Connective tissue diseases
- Vasculitis
- Hypereosinophilic syndrome

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## History of Esophageal Eosinophilia

Esophageal Eosinophilia

GERD

EoE

1980s  
Histologic marker for GERD

1990s  
EoE, a distinct entity

Leape et al. J Pediatr Surg 1981.  
Winter et al. Gastroenterology 1982.  
Brown et al. Am J Surg Pathol 1984.  
Hyams et al. J Pediatr Gastroenterol Nutr 1988.

Attwood et al. Dig Dis Sci 1993.  
Straumann et al. Schweiz Med Wochenschr 1994.  
Kelly et al. Gastroenterology 1995.

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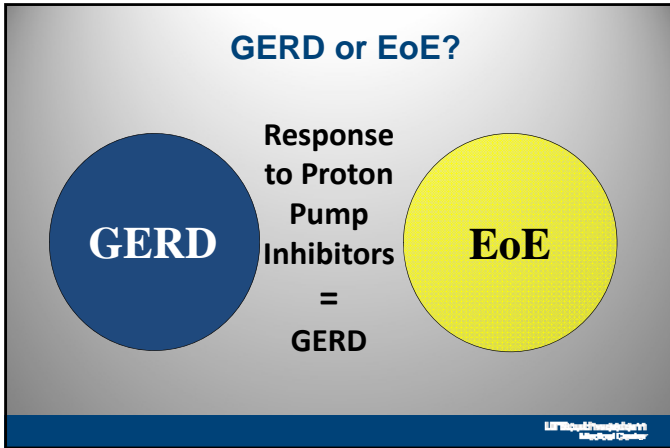
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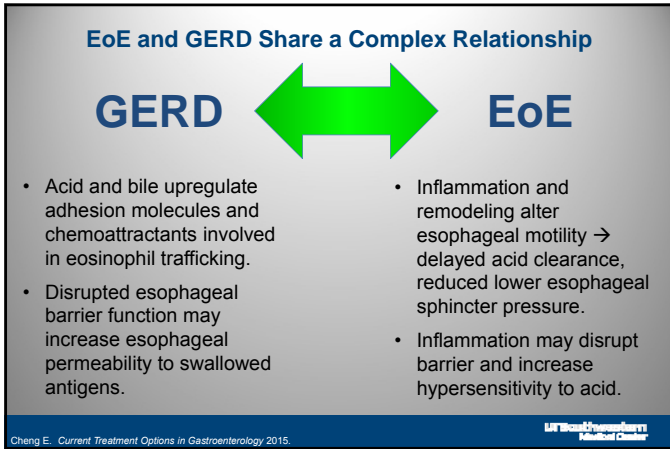
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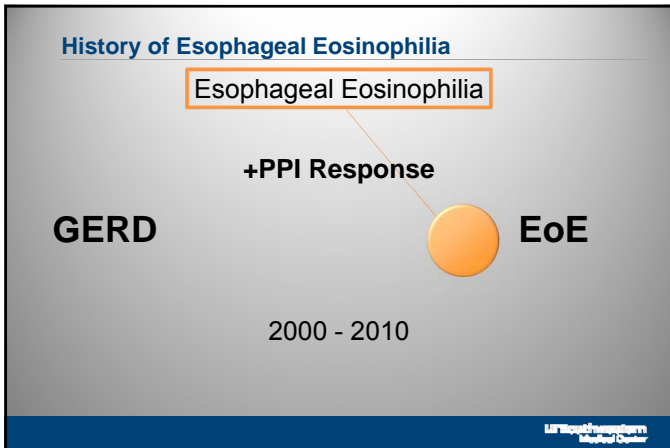
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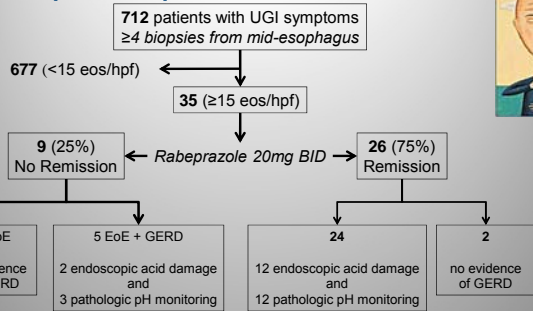
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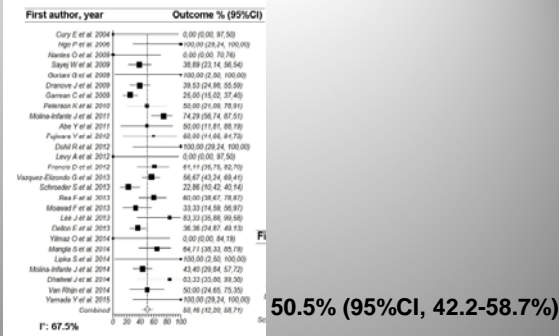
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## Most Patients with Symptomatic Esophageal Eosinophilia Respond to PPIs



Patients who have EoE symptoms and histology but no evidence of GERD can respond to PPIs.

## PPIs Induce Histologic Remission in Symptomatic Esophageal Eosinophilia



50.5% (95%CI, 42.2-58.7%)

Lucendo, Arias, Molina-Infante. Clin Gastroenterol Hepatol 2015.

U.S. Department of Health and Human Services  
 National Center for Human Genome Research

## “PPI-Responsive Esophageal Eosinophilia”



- Have typical **EoE** symptoms and histology
- No evidence of GERD by endoscopy or pH monitoring
- Exhibit a clinical and histological response to PPIs

Liacouras et al. J Allergy Clin Immunol 2011.

U.S. Department of Health and Human Services  
 National Center for Human Genome Research

### Clinical Features of GERD, EoE, and PPI-REE

	GERD	EoE	PPI-REE
<b>Symptoms</b>	Heartburn	Dysphagia	Dysphagia
	Regurgitation	Food impaction	Food impaction
	Abdominal pain	Atopy/food allergy	Atopy/food allergy
<b>Endoscopy</b>	Erosive esophagitis	White plaques	White plaques
	Hiatal hernia	Furrows	Furrows
	Peptic stricture	Rings/Stricture	Rings/Stricture
<b>Histology</b>	<15 eos/hpf	≥ 15 eos/hpf	≥ 15 eos/hpf

No PPI response      + PPI response

Dellon et al. Clin Gastroenterol Hepatol 2009. Mulder et al. J Pediatr Gastroenterol Nutr 2013. University of Washington Medical Center  
 Dellon et al. Am J Gastroenterol 2013. Schroeder et al. J Pediatr Gastroenterol Nutr 2013.

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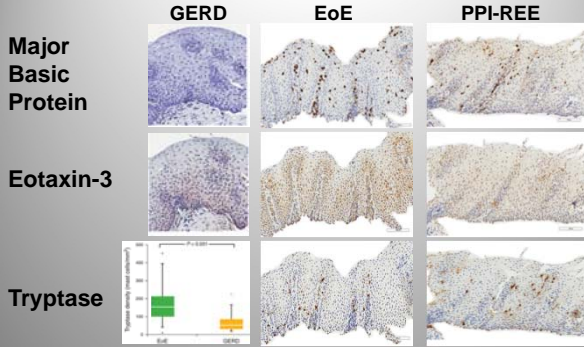
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### Inflammatory Markers Can Distinguish GERD but not PPI-REE from EoE



Dellon et al. Am J Gastroenterol 2011. Dellon et al. Am J Gastroenterol 2012. Dellon et al. Clin Gastroenterol Hepatol 2014. University of Washington Medical Center

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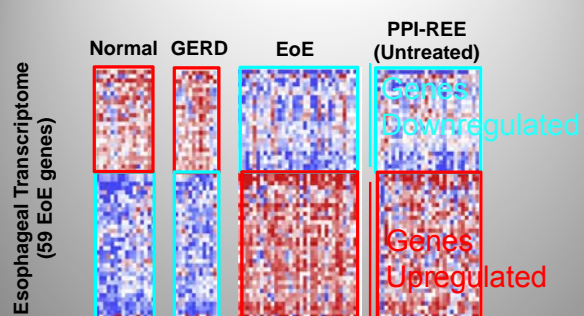
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### Esophageal Transcriptome Overlap Between EoE and PPI-REE



EoE and PPI-REE are part of the same spectrum of a Th2-mediated esophageal disease.

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### Possible Mechanisms for PPI-Responsive Esophageal Eosinophilia

- Patients have GERD with acid reflux causing esophageal eosinophilia, even though endoscopy and pH monitoring are normal
- Patients have EoE that responds to anti-inflammatory effect of PPIs independent of effects on acid inhibition

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### PPIs Do More Than Just Inhibit Gastric Acid Production

#### Potential Anti-Inflammatory Effects

- Anti-oxidant properties



- Inhibitory effects on neutrophil function
- Decrease cytokine production by endothelial and epithelial cells
- Decrease adhesion molecule production by endothelial cells and neutrophils

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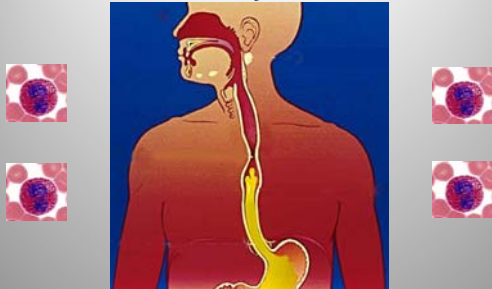
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### How might an immune/antigen mediated esophageal disease like EoE respond to anti-inflammatory effects of PPIs?



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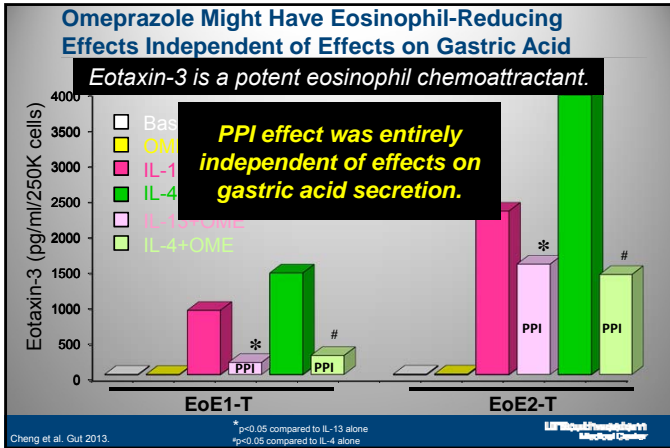
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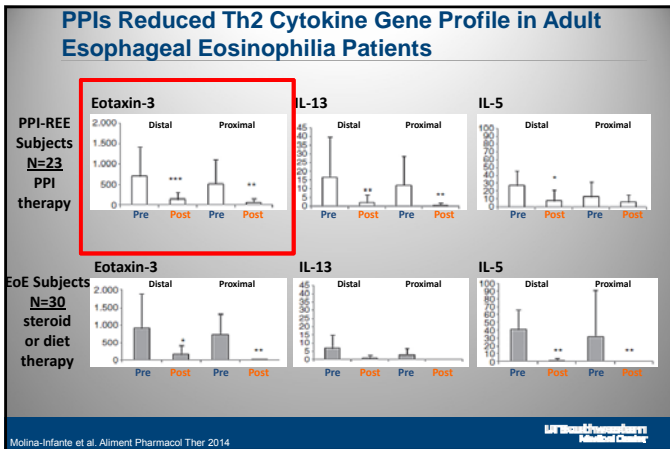
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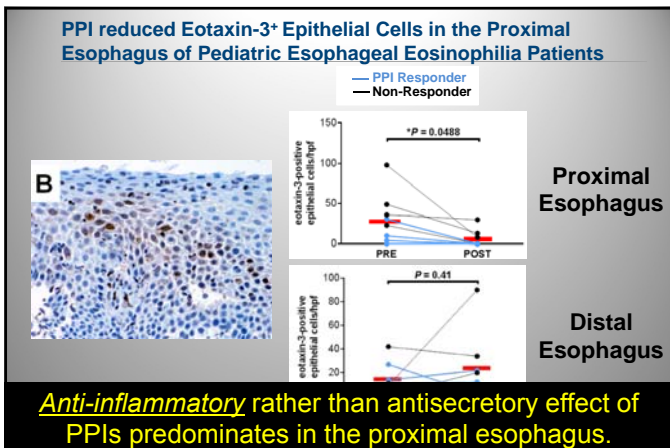
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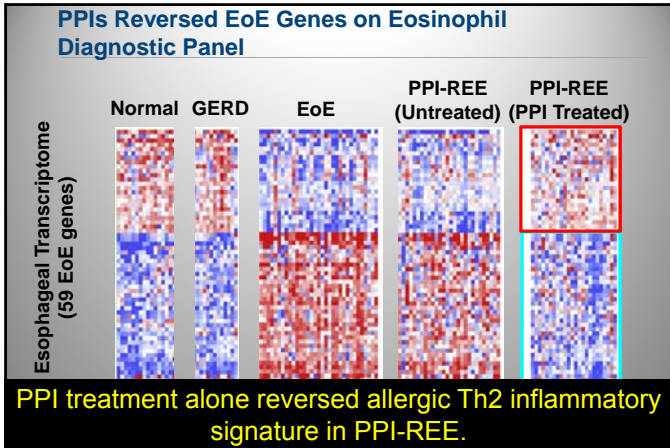
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**Anti-inflammatory** rather than antisecretory effect of PPIs predominates in the proximal esophagus.




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**A trial of PPI therapy is recommended for patients with symptomatic esophageal eosinophilia, even if the diagnosis of eosinophilic esophagitis seems clear-cut.**

Cheng E, Souza RF, Spechler SJ. Gastroenterology Clinics of North America 2014.

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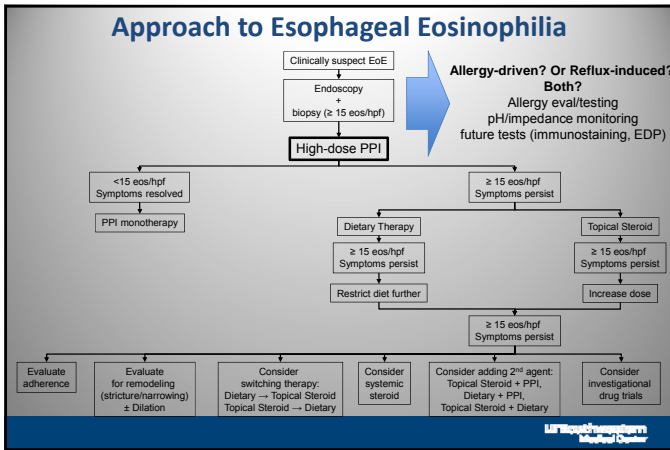
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Where are we now?

Esophageal Eosinophilia



*May the EOS be ever in your favor.*

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