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

Edaire Cheng, M.D.
Assistant Professor of Pediatrics
University of Texas Southwestern
Esophageal Diseases Center
Children’s Medical Center

I have no conflict of interests to disclose.

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.
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.


EoE in the United States

• Prevalence 56.7 per 100,000 (1 in 2,000)
  - Similar to pediatric inflammatory bowel diseases

• 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

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”
**EoE Endoscopic Reference Score (EREFS)**

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

*Endoscopic findings are not specific for EoE.*

**Histological Findings**

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

*Histological findings are not specific.*

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

Pathway diagram showing interactions between APC, Th2 cell, mast cells, food allergen, IL-5, IL-13, IL-4, and eotaxin-3 leading to esophageal epithelium inflammation and eosinophilia.
There Is No Diagnostic “Gold Standard” for Eosinophilic Esophagitis

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

Diseases Associated with Esophageal Eosinophils

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

History of Esophageal Eosinophilia

1980s
Histologic marker for GERD

1990s
EoE, a distinct entity
GERD or EoE?

Response to Proton Pump Inhibitors = GERD

GERD

EoE

GERD or EoE?

GERD EoE

Acid and bile upregulate adhesion molecules and chemoattractants involved in eosinophil trafficking.

Disrupted esophageal barrier function may increase esophageal permeability to swallowed antigens.

Inflammation and remodeling alter esophageal motility → delayed acid clearance, reduced lower esophageal sphincter pressure.

Inflammation may disrupt barrier and increase hypersensitivity to acid.

EoE and GERD Share a Complex Relationship

GERD

EoE

EoE and GERD Share a Complex Relationship

GERD

EoE

History of Esophageal Eosinophilia

Esophageal Eosinophilia

+PPI Response

GERD

EoE

2000 - 2010

GERD EoE

Esophageal Eosinophilia

+PPI Response

GERD

EoE

2000 - 2010
Most Patients with Symptomatic Esophageal Eosinophilia Respond to PPIs

712 patients with UGI symptoms
24 biopsies from mid-esophagus
677 (<15 eos/hpf)
35 (≥15 eos/hpf)
9 (25%) No Remission
26 (75%) Remission
4 Endo
5 Endo + GERD
12 endoscopic acid damage
12 pathologic pH monitoring
2 no evidence
of GERD
24 no evidence
of GERD

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%)

“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
**Clinical Features of GERD, EoE, and PPI-REE**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>GERD</th>
<th>EoE</th>
<th>PPI-REE</th>
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</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td></td>
<td>Dysphagia</td>
<td>Dysphagia</td>
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<tr>
<td>Regurgitation</td>
<td></td>
<td>Food impaction</td>
<td>Food impaction</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Erosive esophagitis</td>
<td>White plaques</td>
<td>White plaques</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>Furrows</td>
<td></td>
<td>Furrows</td>
</tr>
<tr>
<td>Peptic stricture</td>
<td>Rings/Stricture</td>
<td>≥ 15 eos/hpf</td>
<td>≥ 15 eos/hpf</td>
</tr>
</tbody>
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**Histology**

- <15 eos/hpf
- ≥ 15 eos/hpf

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

<table>
<thead>
<tr>
<th>Marker</th>
<th>GERD</th>
<th>EoE</th>
<th>PPI-REE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Basic Protein</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eotaxin-3</td>
<td></td>
<td></td>
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<tr>
<td>Tryptase</td>
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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.
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.

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

How might an immune/antigen mediated esophageal disease like EoE respond to anti-inflammatory effects of PPIs?
PPI effects were entirely independent of effects on gastric acid secretion.

Eotaxin-3 is a potent eosinophil chemoattractant.

Omeprazole might have eosinophil-reducing effects independent of effects on gastric acid secretion.

PPIs reduced Th2 cytokine gene profile in adult esophageal eosinophilia patients.

PPI reduced Eotaxin-3+ epithelial cells in the proximal esophagus of pediatric esophageal eosinophilia patients.

Anti-inflammatory rather than antisecretory effect of PPIs predominates in the proximal esophagus.
A trial of PPI therapy is recommended for patients with symptomatic esophageal eosinophilia, even if the diagnosis of eosinophilic esophagitis seems clear-cut.
Where are we now?

Esophageal Eosinophilia

GERD EoE

PPI-responsive

May the EOS be ever in your favor.