Eosinophilic Esophagitis: The New Kid on the Block

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Disclosures

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Eosinophilic Esophagitis (EoE)

Eosinophils infiltrate esophageal squamous epithelium, releasing secretory products that mediate:

• Tissue damage
• Tissue remodeling
• Symptoms

Incidence of Eosinophilic Esophagitis (EoE) in Olmsted County, Minnesota

EoE in the United States

- Prevalence 50-100 per 100,000
  - Similar to ulcerative colitis
  

- 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
  

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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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EoE Symptoms

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Feeding intolerance</td>
<td>Food Impaction</td>
</tr>
<tr>
<td>Feeding aversion</td>
<td>Chest Pain</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Heartburn</td>
</tr>
<tr>
<td></td>
<td>Upper abdominal pain</td>
</tr>
</tbody>
</table>

Symptoms are not specific.

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EoE Endoscopic Reference Score (EREFS)

- Exudates (plaques)
  
  None of these findings are specific for EoE

- Rings
  
  Esophagus appears normal in ~10%

- Edema (pallor)

- Furrows (vertical lines)

- Strictures

### EoE Histology

- ≥15 eosinophils per HPF
- Eosinophil microabscesses
- Basal zone hyperplasia
- Dilated intercellular spaces
  - Subepithelial fibrosis

The finding of ≥15 eosinophils per HPF has no established biological importance. 
*Histological findings are not specific.*

### EoE Affects Children and Adults of All Ages in All Racial and Ethnic Groups

- Earlier studies suggested a predilection for whites
- Recent studies suggest whites and African Americans affected with similar frequency


Furrows, rings uncommon in blacks
*Bohm M. J Clin Gastroenterol 2011.*

- Reports of EoE from US, Canada, Australia, New Zealand, Europe, Mexico, India, Israel, Saudi Arabia, Iran, Japan, China

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### EoE Affects Both Sexes

Male:Female = 3:1

### Eosinophilic Esophagitis

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

Eosinophilic Esophagitis (EoE) Consensus Diagnostic Guideline 2011

- EoE is a clinicopathologic disease.
  - **Clinico:** Symptoms related to esophageal dysfunction
  - **Pathologic:** ≥1 esophageal biopsy shows eosinophil-predominant inflammation with ≥15 eos per HPF (recommend 2-4 biopsy specimens from both proximal and distal esophagus)
  - Disease should be isolated to the esophagus
  - Disease should remit with treatments of dietary exclusion, topical corticosteroids or both


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Hypotheses Proposed to Explain Recent Appearance and Rising Incidence of EoE

- **Hygiene Hypothesis**
  - ↓ encounters with infectious stressors in childhood leads to allergies in adults
- **Changes in Food Composition**
  - Pesticides, fungicides, water, additives, processing, packaging
- **Changes in Environmental Exposures**
  - Pollution
- **Antisecretory Medications**

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Incidence of Eosinophilic Esophagitis (EoE) in Olmsted County, Minnesota


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Incidence of Eosinophilic Esophagitis (EoE) in Olmsted County, Minnesota

Proton Pump Inhibitor (PPI) Use Becomes Widespread

Peptic Digestion of Potential Protein Allergens

PPI
Pepsin (Acid)

Protein Allergen

Undigested Protein Allergen Delivered to Duodenum

PPI
Pepsin (Acid)

Protein Allergen

Hypothesis:
Acid reducing medications contribute to the development of eosinophilic esophagitis

- Raise gastric pH → pepsin not active
- Allergenic peptides not degraded in the stomach
- PPIs increase gastric mucosal permeability
  - Facilitates uptake of undegraded peptide allergens and exposure to immune cells
- Effects on gut microbiome

Merwat and Spechler, Am J Gastroenterol 2009;104:1897.

Evidence that Eosinophilic Esophagitis is an Allergic Disorder

- 50-60% of patients have history of atopic disease (rhinitis, asthma, atopic dermatitis)
- Most patients exhibit sensitization to food and/or aeroallergens
  - 15% have food anaphylaxis
- During oral immunotherapy for food allergy, 3% of patients develop EoE
- In animal models, EoE can be induced by allergen sensitization
- Dramatic response to elemental diet

If EoE is caused by food allergy, then why do eosinophils home to the esophagus?

RNA Microarray Analysis of Esophageal Biopsies
EoE Patients Abnormally Express 1% of Genome

Controls  Pts. with EoE

- 1230 Genes Downregulated
- 344 Genes Upregulated

Eotaxin-3
(↑ >50-Fold)

Immune System Activation
Th1 and Th2 Differentiation

Antigen Presenting Cell

Activate Immune System
Naive CD4+ T Cells

Th1
(T-helper 1)
TNF-β, IFN-γ

Th2
(T-helper 2)
IL-4, IL-5, IL-13

Allergic Disorders

IL-13 (a Th2 cytokine) Stimulates Eotaxin-3 Secretion in Esophageal Cells from EoE Patients

Eotaxin-3 is a potent eosinophil chemoattractant

Eotaxin-3 (pg/ml per 250,000 cells)

- Unstimulated
- IL-13 (10 ng/ml)

*p<0.001

IL-4 (a Th2 cytokine) Stimulates Eotaxin-3 Secretion in Esophageal Cells from EoE Patients

Eotaxin-3 is a potent eosinophil chemoattractant

*Unstimulated
* IL-4 (10 ng/ml)

Eotaxin-3 (pg/ml per 250,000 cells)

EoE1-T  EoE2-T

*p<0.001


Eosinophilic Esophagitis Pathogenesis Model
(Genetically-Susceptible Individual)

Food allergen activates immune system

→ Th2 Response

↑ IL-5  ↑ IL-13  ↑ IL-4

↑ eosinophil production, activation, recruitment

↑↑↑ esophageal production of eotaxin-3

GERD

AGA Institute 2007 Definition of EoE
Gastroenterology 2007;133:1342.
A primary disorder of the esophagus characterized by UGI symptoms, esophageal biopsy ≥15 eos/hpf, and the absence of pathologic GERD

GERD  EoE  GERD eosinophilic esophagitis

Possible Reasons for the Association of GERD and Esophageal Eosinophils
• GERD causes mild eosinophilia (<7 eos/hpf)
• GERD and EoE co-exist but are unrelated
• EoE contributes to or causes GERD
  – Eosinophil secretory products alter esophageal motility and permeability, and induce remodeling
• GERD contributes to or causes EoE
  – Reflux might cause esophageal mucosa to produce chemokines that attract eosinophils
  – Increased esophageal permeability might expose deep layers of esophageal epithelium to antigens

PPIs might help these EoE patients

“A trial of PPI therapy is recommended for patients with eosinophilic esophagitis, even if the diagnosis seems clear-cut.”


Rationale for a Trial of PPI Therapy in Patients with Esophageal Eosinophilia

PPIs only affect gastric acid secretion
Only acid-peptic disease can respond to PPIs
Response to PPIs = GERD

“PPI-Responsive Esophageal Eosinophilia”

• Have typical EoE symptoms and histology
• Do not have GERD by endoscopy or pH monitoring
• Exhibit a clinical and histological response to PPIs

Possible Explanations for PPI- Responsive Esophageal Eosinophilia

1) Patients have GERD with acid reflux causing esophageal eosinophilia, even though endoscopy and pH monitoring are normal.

2) Patients have EoE (or an EoE-like disorder) that responds to anti-inflammatory effects of PPIs (independent of their effects on acid inhibition).
Omeprazole Blocks Th2 Cytokine-Stimulated Eotaxin-3 Secretion in Squamous Cells from EoE Patients

Effects of Lansoprazole on IL-4-Stimulated Eotaxin-3 Protein Secretion in EoE Squamous Cell Lines

Topical Steroid Therapy for EoE (Fluticasone, Oral Viscous Budesonide)

- RCTs show that topical steroids significantly reduce esophageal eosinophil levels
- Most patients experience symptomatic relief during treatment with steroids
- Symptoms recur frequently when steroids are stopped
- Limited data on efficacy and safety of long-term steroid therapy for EoE

Topical Steroid Therapy for EoE in Adults

- Fluticasone 2-4 puffs (220 µg/puff)
- BID, after breakfast and dinner
- Do not use spacer (designed for lung delivery)
- Inspire deeply first, depress inhaler, swallow
- Do not eat or drink for at least 30 minutes
Randomized Trial: 8 weeks of Fluticasone (440 µg BID) or Esomeprazole (40 mg QD) for Esophageal Eosinophilia
- 42 adults with ≥1 symptom (dysphagia, food impaction, heartburn)
- ≥15 eosinophils per high power field on esophageal biopsy
- 24-hour esophageal pH monitoring → 8 patients with GERD

Proton Pump Inhibitors (PPIs) and Esophageal Eosinophilia in GERD and in Eosinophilic Esophagitis (EoE)
- PPIs have anti-secretory (gastric acid inhibitory) effects that might be beneficial both for GERD and for EoE.
- PPIs have anti-inflammatory effects (independent of their anti-secretory effects) that might be beneficial both for GERD and for EoE.
- For patients with esophageal symptoms and eosinophilia, a clinical and/or histological response to PPIs...
  - Does not rule in GERD
  - Does not rule out EoE

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

• **Directed elimination diet**
  – Based on skin prick testing
  – 46% success (95% CI, 35-56%)

• **Empiric elimination diet**
  – Prohibit most common food allergens (milk, soy, eggs, wheat, nuts, seafood)
  – 72% success (95% CI, 66-78%)
  – Prohibit 4 foods – 54% success

• **Elemental diet**
  – Use amino acid-based formulas
  – 91% success (95% CI, 85-96%)

Arias A. Gastroenterology 2014;146:1639.

Management of EoE 2015

Suspected EoE (≥15 eos/hpf)

- **Trial of PPI BID 4-8 weeks**
- **Dx: GERD or PPI-Responsive Eosinophilia**
  - Continue PPI Rx
  - **Symptoms Persist**
  - Stop PPI or consider pH testing
- **Dx: EoE**
  - Directed or Empiric Elimination Diet
  - Continue Diet Rx
  - **Symptoms Persist**
  - Topical Steroids 6-8 weeks
  - Follow, Resume Steroids PRN
  - **Dysphagia Persists**
    - Rule Out Infection (Candida, HSV)
    - Esophageal Stenosis
    - Esophageal Dilation