Eosinophilic Esophagitis and PPI-Responsive Esophageal Eosinophilia

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Disclosures

Consultant: Ironwood Pharmaceuticals

No treatment for eosinophilic esophagitis is FDA approved. I will discuss the use of proton pump inhibitors and topical steroids for eosinophilic esophagitis.

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

Incidence per 100,000 (Age and Sex Adjusted)

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>1976-1980</td>
<td>0</td>
</tr>
<tr>
<td>1981-1985</td>
<td>0</td>
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<tr>
<td>1986-1990</td>
<td>0</td>
</tr>
<tr>
<td>1991-1995</td>
<td>4</td>
</tr>
<tr>
<td>1996-2000</td>
<td>8</td>
</tr>
<tr>
<td>2001-2005</td>
<td>12</td>
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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

EoE Symptoms

Children
- Vomiting
- Feeding intolerance
- Feeding aversion
- Failure to thrive

Adults
- Dysphagia
- Food Impaction
- Chest Pain
- Heartburn
- Upper abdominal pain

Symptoms are not specific.
**EoE Endoscopic Reference Score (EREFS)**

- **Exudates (plaques)**
  0 = absent, 1 = mild, 2 = severe
- **Rings (trachealization)**
  0 = absent, 1 = present
- **Edema (pallor)**
  0 = absent, 1 = mild, 2 = severe
- **Furrows (vertical lines)**
  0 = absent, 1 = mild, 2 = severe
- **Strictures**
  0 = absent, 1 = present

EREFS Range 0-9
Score ≥ 2
88% sens. 92% spec.

- Esophagus appears normal in 5-10%


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**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.

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

- 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

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**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

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**If EoE is caused by food allergy, then why do eosinophils home to the esophagus?**
RNA Microarray Analysis of Esophageal Biopsies

<table>
<thead>
<tr>
<th>Controls</th>
<th>Pts. with EoE</th>
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</thead>
<tbody>
<tr>
<td>230 Genes Downregulated</td>
<td>344 Genes Upregulated</td>
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</table>

Eotaxin-3 (↑ >50-Fold)
A potent eosinophil chemoattractant

Immune System Activation

<table>
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<tr>
<th>Antigen Presenting Cell</th>
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<tbody>
<tr>
<td>Activate Immune System</td>
</tr>
<tr>
<td>Naive CD4+ T Cells</td>
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</table>

Th1 and Th2 Differentiation

| Th1 (T-helper 1) |
| Th2 (T-helper 2) |

- TNF-β, IFN-γ
- IL-4, IL-5, IL-13

Eosinophilic Esophagitis Pathogenesis Model

(Genetically-Susceptible Individual)

- Food allergen activates immune system
- Th2 Response
- ↑ IL-4
- ↑ IL-13
- ↑ eosinophil production, activation, recruitment
- ↑↑↑ eotaxin-3

Eotaxin-3 is a potent eosinophil chemoattractant

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

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

*Eotaxin-3 Stimulated EoE Cells (pg/ml per 250,000 cells)

* p<0.001


EoE or GERD?

Eosinophilic Esophagitis in a Patient with Vaginal Achalasia

R. T. Lander, M.D., G. G. R. Kunte, M.D., and W. B. Shiram, M.D.
Department of Medicine and Surgery, Barnes Jewish Medical Institutions, St. Louis, California

A patient with vagal achalasia is presented who had marked smooth muscle hypertrophy and eosinophil infiltration of the esophagus identical to that seen in patients with eosinophilic gastroenteritis. Eosinophilic infiltration of the esophagus probably represents a variant of eosinophilic gastroenteritis gastroenteritis with vagal involvement in an esophageal motor disorder.

Intraepithelial Eosinophils: A New Diagnostic Criterion for Reflux Esophagitis

HARLAND S. WINTER, JAMES L. MADARA, RICHARD J. STAFFORD, RICHARD J. GRAND, JO-ELLEN QUINLAN, and HARVEY GOLDMAN

Department of Medicine, Division of Gastroenterology, Children’s Hospital Medical Center, Department of Pathology, Children’s Hospital Medical Center, Brigham and Women’s Hospital and Beth Israel Hospital, Departments of Pediatrics and Pathology, Harvard Medical School, Boston, Massachusetts

Gastroenterology 1982;83:818-23.

12 adults with dysphagia, esophageal biopsies showing >20 eosinophils/HPF, normal endoscopy and normal pH monitoring.

Esophageal Eosinophilia with Dysphagia
A Distinct Clinicopathologic Syndrome

STEPHEN E.A. ATTWOOD, MS, FICS, THOMAS C. SMYK, MD, TOM R. DIERENSTEER, MD, and JAMES B. JONES, MD


Eosinophilic Esophagitis Attributed to Gastroesophageal Reflux: Improvement With an Amino Acid-Based Formula

KEVIN J. KELLY,* AUDREY J. LACENELI,† PETER C. ROME,* JOHN H. YANCEY,‡ JAY A. MEDERIAL,‡ and SUSI A. SAVADOFF*****

University of Washington Gastroenterology/Hepatology Program, Department of Medicine, School of Medicine, University of Washington, Seattle, Washington, and Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama


Eosinophilic Esophagitis in Children: Immunopathological Analysis and Response to Fluticasone Protopionate

JONATHAN E. TETI,*JULIE L. FRAZER,‡ KIMBERLY A. FERRIS,* SARAH A. SCHEINSTEIN,* DAN WOOD,* GEORGE GREER,* and LEIGH T. FURCH®

*Department of Pediatrics and *Division of Gastroenterology and Hepatology, University of Washington School of Medicine, Seattle, Washington, and *Department of Pathology, University of Alabama School of Medicine, Birmingham, Alabama.


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

EoE

GERD

sinophilic 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

“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 (PPI-REE)

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

30% to 50% of patients with symptomatic esophageal eosinophilia respond to PPIs

Possible Explanations for PPI-Responsive Esophageal Eosinophilia (PPI-REE)

1) **Pts have subclinical GERD**, not Ag-driven eosinophilia
   Responds to anti-secretory and anti-inflammatory effects of PPIs
   Non-Erosive Reflux Disease (NERD)

2) **Pts have Ag-driven eosinophilia (EoE)**, not GERD
   Responds to anti-inflammatory effects of PPIs

3) **Patients have GERD exacerbating Ag-driven EoE**
   Responds to both anti-secretory and anti-inflammatory effects of PPIs

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Other Potential Anti-Inflammatory Effects of PPIs

• Anti-oxidant properties
• Inhibitory effects on inflammatory cells
• Decrease adhesion molecule production by endothelial cells and neutrophils
• Decrease pro-inflammatory cytokine production by endothelial and esophageal epithelial cells

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

Reflux

- For patients with esophageal symptoms and eosinophilia, a clinical and/or histological response to PPIs…
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PPIs and Esophageal Eosinophilia in GERD and in EoE

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

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Eosinophilic Esophagitis (EoE) vs. PPI-Responsive Esophageal Eosinophilia (PPI-REE)

- Clinical, endoscopic, histologic and gene expression features of EoE and PPI-REE are virtually identical.

- Multivariate analyses have not identified any feature that distinguishes EoE from PPI-REE.
  - Probably because they are the same disorder

- Diseases not defined by response to a single medication
  - e.g. Ulcerative colitis vs. mesalamine-responsive colitis

- Persistent notion: Gastric acid inhibition is the only possible therapeutic effect of PPIs, so GERD is the only esophageal disease that can respond to PPIs

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Topical Steroid Therapy for EoE

(Fluticasone Inhaler, Oral Viscous Budesonide, Fluticasone Diskus)

- 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

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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%)

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Arias A. Gastroenterology 2014;14:1639.

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