EGID Pathogenesis

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EoE: A Clinicopathological Diagnosis
Differential Diagnosis of Esophageal Eosinophils

- Gastroesophageal Reflux Disease
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis with esophageal involvement
- Hypereosinophilic syndrome
- Parasitic infection
- Drug allergy
- Connective tissue disorder (scleroderma)
- ?Celiac with esophageal eosinophilia
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

Chris A. Liacouras, MD, Glenn T. Furuta, MD, Ikuo Hirano, MD, Dan Atkins, MD, Stephen E. Attwood, MD, FRCS, FRCSI, MCh, Peter A. Bonis, MD, A. Wesley Burks, MD, Mirna Chehade, MD, Margaret H. Collins, MD, Evan S. Dellon, MD, MPH,

Conceptual definition

Eosinophilic esophagitis represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

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Diagnostic guideline

EoE is a clinicopathologic disease. Clinically, EoE is characterized by symptoms related to esophageal dysfunction. Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded.
Histologic Features

>15 eosinophils per hpf
Eosinophil Degranulation
Basal Zone Hyperplasia
Dilated Intercellular Spaces
Histologic Features

Liacouras et al, 2011 Updated Consensus Recommendations, JACI
Endoscopic Features
Symptoms and Clinical Features
Pathogenesis: Triggers for Eosinophilia

- Acid
- Aeroallergens
Acid Driven Eosinophilia
Reflux Index To Eosinophilia

Steiner et al, Am J Gastroenterol, 2004
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Age (yr)/sex</td>
<td>14/M</td>
<td>25/M</td>
<td>13/F</td>
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<tr>
<td>Presentation</td>
<td>Pain</td>
<td>Food impaction</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Environmental Allergies</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment</td>
<td>Omeprazole 10 mg BID</td>
<td>Omeprazole 20 mg BID</td>
<td>Omeprazole 20 mg QD</td>
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<tr>
<td>Eosinophils/hpf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>37</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td>After treatment</td>
<td>1</td>
<td>3</td>
<td>0</td>
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An emerging body of literature and clinical experience describes a subset of patients whose symptoms and histopathologic findings are responsive to PPI treatment and who might or might not have well-documented GERD. Until more is known regarding this subgroup of patients, these patients should be given diagnoses of PPI-responsive esophageal eosinophilia. Future studies should be performed to determine whether PPIs help to diminish an immune/antigen-driven response, as is known to occur in patients with EoE.

- Eosinophils >15 per hpf
- 40% Responded to PPI

Molina-Infante et al, Clin Gastro Hepatol 2010
Dranove et al, JPGN 2010
Triggers: Aeroallergens

- Animal Models
- Human Disease
Aerollergens and EoE: Causal Link

- Instillation of:
  - Intranasal Aspergillus
  - Intranasal HDM
  - Intranasal Cockroach
  - Drives Murine EoE

Mishra et al., J Clin Invest 2001
Rayapaudi et al, J Leuko Biol 2010
### Pollen Driven Eosinophilia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Allergy</th>
<th>GERD</th>
<th>Normal</th>
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<tr>
<td>Any Esophageal Eos</td>
<td>10/38</td>
<td>5/24</td>
<td>0/25</td>
</tr>
<tr>
<td>Proximal Eos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Num Pts</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Num Eos</td>
<td>5 +/- 7</td>
<td>2 +/- 1.7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-20</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td>Distal Eos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Num Pts</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Num Eos</td>
<td>3 +/- 4</td>
<td>8 +/- 6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-12</td>
<td>3-14</td>
<td></td>
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</table>

Onbasi et al. Clin Exp Allergy, 2005
Pollens and EoE: Causal Link

Fogg et al, JACI 2003
Seasonal EoE?

Moawad et al Alim Pharm Ther 2009

Almansa et al Am J Gastro 2009
Recruiting Eosinophils to the Esophagus

- Chemokines
- Interleukins
- Vascular Activation
53-fold increase in Eotaxin-3 gene expression in EoE versus GERD pediatric patients

IL-5

- EoE patients have Increased IL-5
- IL-5 Deficient Mice are Protected from EoE
- IL-5 miniosmotic pump promotes murine EoE

Straumann et al, JACI 2001
Mishra et al, 2008
Anti-IL-5 in Children

Peak oesophageal eosinophils (mean±SD)

- 0.55 mg/kg
- 2.5 mg/kg
- 10 mg/kg

End of treatment
End of follow-up

Cells/high power field

Screening
Week 12
Week 24

End of treatment
End of follow-up
**IL-13**

- Instilling IL-13 Causes Murine EE
- Resolved with anti-IL-13 Antibody

Mishra & Rothenberg, Gastroenterology 2003
Blanchard et al, Clin Exp Allergy 2005

- IL-13 treatment promotes EoE transcriptome
- IL-13 induces the Eotaxin-3 promoter
IL-15

- Increased IL-15 on EoE Gene Chip
- IL-15Rα Deficient Mice: Protected from experimental EoE
- IL-15 Increased in Human Esophageal biopsies

Rayapudi et al, Gastroenterology 2010
Siglecs and EoE

A. No OVA

B. OVA + Control Ab

C. OVA + Control Ab (x40)

D. OVA + anti-Siglec-F Ab
Esophageal Remodeling: Vascularity

VWF Positive Vessels

VCAM-1 Positive Vessels

Normal GERD EE

vWF Positive Vessels per hpf

VCAM positive vessels per hpf

Normal GERD EE

Normal GERD EE
Eosinophil Activation
Eosinophil Derived Neurotoxin

Kephart et al, Am J Gastro 2010
Major Basic Protein

Mueller et al
More Than Just Eosinophils

- T Cells
- B Cells
- TSLP
T Cells

- Increased CD3+, CD8+
- Murine EoE Induction Relies on T cells

Lucendo et al, 2007; Mishra et al, 2007
- Increased TSLP expression in EoE
- Genetic variants in TSLP and Eotaxin-3 associate with EoE

Rothenberg et al, Nature Genetics 2010
B Cells and Local IgE Production

Increased B cells in:
- Epithelium
- Vascular Papillae
- Lamina Propria

Increased IgE Class Switch Genes

Vicario et al, Gut 2009
Mast Cells

Inflammation and Complications
Mast Cells

- Mast Cells: Elevated, Specific Gene Profile
- May help distinguish EoE from GERD

Dellon et al, Am J Gastro 2011
Abonia et al, JACI 2010
Smooth Muscle Inflammation

- Mast Cells are Increased in the Smooth Muscle
- Mast cells make TGFβ1

Aceves et al, JACI 2010
TGFβ1 Causes Smooth Muscle Contraction

- TGFβ1 induces esophageal smooth muscle cell contraction

Aceves et al, JACI 2010
Esophageal Remodeling: Eosinophils Produce TGFβ1

Esophageal Fibrosis

EoE Patients have Increased Fibrosis

Animals without IL-5 and Eosinophils are Protected from Fibrosis

Aceves et al, JACI 2007
Mishra et al, Gastroenterology 2008
Esophageal Eosinophils: Periostin

Increased periostin expression induced by TGFβ

Periostin increases eosinophil trafficking and adhesion

Blanchard et al, Mucosal Immunol 2008
Esophageal Remodeling: The Key to the Pathogenesis of Complications?

Strictures
Dysmotility
Esophageal Rigidity
Food Impactions

GI Motility online (May 2006)
Inflammation Can Correlate with Endoscopy, Symptoms

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Endoscopy</th>
<th>Symptom</th>
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<tbody>
<tr>
<td><strong>Epithelial:</strong></td>
<td>Thickened/Furrows r=0.82*</td>
<td>Dysphagia + Anorexia/Early Satiety r=0.32*</td>
</tr>
<tr>
<td>Average Epithelial Score Prox+Mid+Distal</td>
<td>White Plaques, r =0.64*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pallor r=0.62*</td>
<td></td>
</tr>
<tr>
<td><strong>Lamina Propria:</strong></td>
<td>Thickened/Furrows r=0.64*</td>
<td>Dysphagia r= 0.45*</td>
</tr>
<tr>
<td>Fibrosis + Eosinophils</td>
<td></td>
<td></td>
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</tbody>
</table>

* *p<0.05

Aceves et al, Annals of All Immunol 2009
Decreased Esophageal Distensibility

Kwiatek et al, Gastroenterology 2011
Smooth Muscle

- Thickened esophagus
- Dis-coordinated smooth muscle contraction
- Episodes of dysmotility correlate with dysphagia

Nurko et al, Am J Gastro, 2009
Korsapaati et al, Gastroenterol 2009
Fox et al, Gastrointest Endosc, 2003
EGE: Beyond the Esophagus
Different or Disease Extension?
Eosinophilic Gastroenteritis

- Diagnostic criteria not established
  - Eosinophilia is normal in the non-esophageal intestine
- Often does not involve the esophagus
- Mucosal, Muscularis, Serosal Forms
- Primary – Atopic vs Non-atopic
- Secondary – Rule out
  - HES, Vasculitis
  - Celiac, IBD, Scleroderma, Infection
Eosinophilic Colitis

- **Primary: Atopic vs Non-Atopic**
  - Allergic Colitis of Infancy

- **Secondary**
  - HES, EGE
  - Rule out: IBD, Infection
Animal Model of GI Eosinophilia

Ovalbumin induces Gastric and Esophageal Eosinophilia

Hogan et al, 2001
Animal Model of GI Eosinophilia

Song et al, Clin Exp Allergy 2008
Disease Mechanisms

- Increased CD4+ peripheral cells that are antigen specific

- Eosinophilic gastroenteritis patients have increased IL-5+, IL-4- cells compared to Non-allergic and Peanut Allergic Patients

Prussin et al JACI 2009
Conclusions

- Eosinophilic esophagitis is more than eosinophils
- Pathogenesis includes Eosinophil Activation
- Pathogenesis includes T cells, B cells, Mast Cells, and Degranulated Mast Cells
- Remodeling may explain the pathogenesis for Disease Complications
- EGE is likely a Distinct Disease from isolated EoE