Eosinophilic Esophagitis (EoE)

**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 eos/hpf 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

Epidemiology of EoE in US

Health insurance database 2009-11 of 11.5 million; Prevalence based on ICD9 (530.13) 57/100,000

EoE Update

- Why should patients with suspected EoE be given a trial of PPI therapy?
- Why the assessment of disease activity involves more than counting eosinophils?
- What are the pros and cons of drug and diet therapies?
Case: Patient MH

- 18 yo M with 5 year h/o progressive dysphagia now occurring on a daily basis with monthly, self limited food impactions
- One ER visit for food impaction
- Denies heartburn, refluxate or chest pain
- PMH Allergic rhinitis

Case: Patient MH

- EGD 3/07: Furrows, edema, exudates, rings.
- Path: Marked eosinophilic infiltrate (77 eos/hpf) with microabscess in both prox and distal esophagus.

- pH study OFF medications: Distal acid exposure 3.7%
- Allergy evaluation. SPT reactive to sweet potato, peas, squash, tomato, corn, chicken, rye, wheat, oat, barley. APT negative to same foods. APT equivocal to milk.
Case: Patient MH

- EGD 3/07: Furrows, edema, exudates, rings.
- Path: Marked eosinophilic infiltrate (77 eos/hpf) with microabscess in both prox and distal esophagus.

**What is the patient’s diagnosis?**

- pH study OFF medications: Distal acid exposure 3.7%
- Allergy evaluation. SPT reactive to sweet potato, peas, squash, tomato, corn, chicken, rye, wheat, oat, barley.
  APT negative to same foods. APT equivocal to milk.

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Case: Patient MH

- EGD 6/08 lansoprazole 30 mg BID. No dysphagia.
  - Rings. No exudates.
  - Path: 6 eos/hpf

- EGD 1/12 lansoprazole 30 mg QD. No dysphagia. 7 eos/hpf
Case: Patient MH

- EGD 6/08 lansoprazole 30 mg BID. No dysphagia.
- Rings. No exudates.
- Path: 6 eos/hpf

**Does this patient have EoE or GERD?**

- EGD 1/12 lansoprazole 30 mg QD. No dysphagia. 7 eos/hpf

GERD vs Eosinophilic Esophagitis (EoE): circa 2005
PPI Responsive Esophageal Eosinophilia

Prospective Study, 712 adults with EGD;
35 pts with > 15 eos/hpf; Rabeprazole 20 mg BID x 2 mos;
PPI response < 5 eos/hpf

Prospective studies have demonstrated a 25-50% histologic response in adults with suspected EoE

Dilated Intercellular Spaces in GERD

*Increased epithelial permeability to antigens?*

Odze Am J Gastro 2009; 104: 485-490
Van Rhijn Clin Gastro Hep 2014

Possible Interaction Between GERD and EoE

Acid-peptic attack weakens cell junctions
leading to a widening of cell gaps
and thus allowing antigen penetration

Adapted from Orlando. Am J Gastroenterol 1996
PPI therapy improves the epithelial barrier in patients with esophageal eosinophilia

16 patients with esophageal eosinophilia treated with omeprazole x 8 weeks

Van Rhijn Brendenoord Clin Gastro Hep 2014

PPI Response = GERD

PPI Response

GERD
GERD vs PPI responsive EoE??

“PPI responsive esophageal eosinophilia (PPIREE)”

PPI response does not rule in GERD or rule out EoE

Why patients with suspected EoE should be given a course of PPI therapy

1. It works. Reduces symptoms and esophageal eosinophilia in 25-50% of patients
2. PPIs are safe
3. pH testing is cumbersome and subject to significant false positive and negative results
4. Experimental evidence that GERD may contribute to allergic inflammation in EoE *(Paterson Am J Physiol 1998; Rhiijn CGH 2014; Sherril Mucosal Immunol 2013)*
5. PPIs may have anti-inflammatory properties beyond acid suppression *(Cheng,Souza Gut 2013)*
Ikuo Hirano, MD, FACG

Diagnosis & Management of EoE

• Why should patients with suspected EoE be given a trial of PPI therapy?
• Why the assessment of disease activity involves more than counting eosinophils?
• What are the pros and cons of drug and diet therapies?

EoE Disease Activity:

Activity = Inflammation

Esophageal eosinophilia
Are we just scratching the surface?

*Do the effects of EoE extend beyond the mucosa?*

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**Esophageal Subepithelial Fibrosis**

*Demonstrated in majority of EoE patients*

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*Straumann et al., Gastroenterology 2003.*

*Aceves J Allergy Clin Immunol 2007 ‡*

*Chehade J Pediatric Gastro Nutr.*

*Lucendo J Allergy Clin Immunol 2011 †*
EoE: A transmural disease?

Straumann et al., Gastro 2003.
Aceves J Allergy Clin Immunol 2007
Chehade J Ped Gastro Nutr 2007
Straumann Clin Gastro Hepatol 2011
Lucendo J Allergy Clin Immunol 2012

Complications of EoE:
Narrow caliber esophagus

EoE Disease Activity: More than just counting eosinophils!

Activity = Inflammation + Tissue Remodeling

Esophageal Eosinophilia

Mucosa/submucosa/muscularis expansion,
Subepithelial fibrosis,
Increased vascularity,
Dysmotility

Classification and grading of endoscopically detected esophageal features in EoE

EoE Endoscopic Reference Score (EREFS)

- **Edema** (pallor)
- **Rings** (“trachealization”)
- **Exudates** (plaques)
- **Furrows** (vertical lines)
- **Stricture**

- Mucosal fragility
- Narrow caliber esophagus

Classification and grading of endoscopically detected esophageal features in EoE

EoE Endoscopic Reference Score (EREFS)

- **Edema** (pallor)
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**Inflammatory**

- Mucosal fragility
- Narrow caliber esophagus

**Fibrostenotic**

**Mild (Grade 1):** Subtle circumferential ridges seen on esophageal distension
<table>
<thead>
<tr>
<th>Mild (Grade 1): Subtle circumferential ridges seen on esophageal distension</th>
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<tbody>
<tr>
<td>Moderate (Grade 2): Distinct rings that do not occlude passage of diagnostic (8-10 mm) endoscope</td>
</tr>
<tr>
<td>Severe (Grade 3): Distinct rings that do not permit passage of diagnostic (8-10 mm) endoscope</td>
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**EoE Reference Score for Endoscopic Abnormalities (EoE-EREFs)**

**Rings** *(Also referred to as esophageal rings, corrugated esophagus or trachealization)*

- **Mild (Grade 1):** Subtle circumferential ridges seen on esophageal distension
- **Moderate (Grade 2):** Distinct rings that do not occlude passage of diagnostic (8-10 mm) endoscope
- **Severe (Grade 3):** Distinct rings that do not permit passage of diagnostic (8-10 mm) endoscope
Risk of food impaction correlated with endoscopic ring severity score

Fibrostenotic Complications of Eosinophilic Esophagitis
Fibrostenotic Complications of Eosinophilic Esophagitis

Risk of esophageal stricture doubled with each decade of untreated disease

EGD

EoE: A Conceptual Model of Clinical Subtypes Based On Inflammation and Tissue Remodeling

EoE: A Conceptual Model of Clinical Subtypes Based On Inflammation and Tissue Remodeling

EoE: A Conceptual Model of Clinical Subtypes Based On Inflammation and Tissue Remodeling

Normal  EoE inflammation  EoE inflammation + Fibrosis  EoE Fibrosis

Diagnosis & Management of EoE

• Why should patients with suspected EoE be given a trial of PPI therapy?
• Why the assessment of disease activity involves more than counting eosinophils?
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Treatment Options for EoE

• Endoscopic Therapy
• Medical Therapy
  – Topical steroids
  – Systemic steroids
  – Leukotriene antagonists (montelukast)
  – Mast cell stabilizers (cromolyn sodium)
  – Immunomodulators (CRTH2 antagonist, azathioprine)
  – Biologics (anti IL5, anti IL13, anti TNF, anti IgE)
• Dietary Therapy
  – Empiric elimination diet
  – Allergy testing directed elimination diet
  – Elemental diet
Topical steroids

- Swallowed - not inhaled
  - Fluticasone 220 mcg 2-4 puffs BID
  - Budesonide 0.5-1 mg BID
  - Ciclesonide (aerosolized) 80-160 mcg BID
- Liquid formulations are mixed with substance (sucralose, honey, syrup) to increase viscosity
- Patients instructed to fast for 30 minutes after administration
- Mouth rinse after administration to reduce risk of thrush may reduce drug delivery

Randomized, Double-Blind Placebo Controlled Trials Budesonide
36 Adults with EoE: Placebo or budesonide 1 mg BID x 15 days
24 Children with EoE: Placebo or budesonide 0.5-1 mg BID x 3 months

![Graphs showing eosinophils per hpf for adults and children before and after treatment with placebo and budesonide.](image-url)
Steroid therapy in EoE: CONS

- Recurrent disease in almost all patients after steroid cessation
- Efficacy for symptom relief has been variable
- Benefits for reversal of esophageal fibrostenosis remain unproven
- Local side effects (oral and esophageal candidiasis) reported
- Long term safety regarding potential systemic side effects has not been established with higher doses of swallowed topical steroids.
Eosinophilic Esophagitis: Dietary Treatment

Six Food Elimination Diet (SFED)
Prospective Study in Adults (n=50)
6 wk elimination (milk, soy, nuts, eggs, wheat, seafood/shellfish)

Before Diet

After Diet

Gonsalves. Gastroenterology 2012; 142(7):1451-9
Effect of SFED on Esophageal Eosinophilia

Proximal Esophagus

Distal Esophagus

Gonsalves. Gastroenterology 2012; 142(7):1451-9

Effect of SFED on Esophageal Eosinophilia

Proximal Esophagus

Distal Esophagus

Gonsalves. Gastroenterology 2012; 142(7):1451-9
Effect of SFED on Esophageal Eosinophilia

Proximal Esophagus  Distal Esophagus

64% achieved histologic response defined by < 5 eos/hpf

<table>
<thead>
<tr>
<th>Median</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagi hpf</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>48</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

* P <0.05

Gonsalves. Gastroenterology 2012; 142(7):1451-9

Effect of SFED on Dysphagia Score

<table>
<thead>
<tr>
<th>Median Score</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>12</td>
<td>3.5</td>
</tr>
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</table>

* P <0.01

Gonsalves. Gastroenterology 2012; 142(7):1451-9
Effect of Reintroduction of Foods on Esophageal Eosinophilia

Proximal Esophagus  Distal Esophagus

Pre  Post  Reintro

Gonsalves. Gastroenterology 2012; 142(7):1451-9

Effect of Reintroduction of Foods on Esophageal Eosinophilia

Proximal Esophagus  Distal Esophagus

Pre  Post  Pre  Post

Gonsalves. Gastroenterology 2012; 142(7):1451-9
Effect of Reintroduction of Foods on Esophageal Eosinophilia

Food triggers identified by reintroduction:
Wheat (60%), milk (50%), soy (10%), egg (5%)

15% of patients with more than one food trigger

SPT accurately predicted 13% of food triggers.
67% of patients with food trigger had negative SPT

Gonsalves. Gastroenterology 2012; 142(7):1451-9
Ikuo Hirano, MD, FACG

Endoscopic improvement with SFED

<table>
<thead>
<tr>
<th>Pre Diet</th>
<th>Post Diet</th>
<th>Reintro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>E1R1E2F2</td>
<td>E1R0E0F1</td>
</tr>
<tr>
<td>Patient 2</td>
<td>E0R1E1F1</td>
<td>E0R0E0F0</td>
</tr>
<tr>
<td>Patient 3</td>
<td>E1R2E1F1</td>
<td>E0R0E0F1</td>
</tr>
</tbody>
</table>

SFED: Not Just for Kids Anymore
73% response in children; 72% response in adults

Arias Diet Interventions for EoE: Systematic review and meta-analysis. Gastroenterology 2014
Diet therapy in EoE: PROS

- No FDA approved medical therapies for EoE
- Many patients would prefer a dietary alternative rather than chronic steroids
- Conceptual appeal of removing disease trigger rather than suppress inflammatory consequences
- Goal of diet therapy is the identification of specific food trigger(s), not elimination of all potential food groups.

Suggested Algorithm for Management Of Eosinophilic Esophagitis

1. Suspected EoE
   - PPI x 8 wks
   - Symptom relief & Normal histology
   - EGD with Bx
2. "PPI Responsive Esophageal Eosinophilia" (EoE vs GERD)
   - > 15 Eos/hpf
   - Topical steroid
   - Dietary therapy
3. Persistent Symptoms and Pathology
   - Elimination diet
   - Persistent dysphagia with stricture
   - Esophageal dilation
   - Biologic therapy
   - Systemic steroid
4. Consider Maintenance Therapy
   - Symptom relief & Normal histology
   - EGD with Bx

• Why should patients with suspected EoE receive PPIs?  
  *PPI therapy is a safe and an effective (25-50%) means of recognizing the potential contribution of acid reflux in suspected EoE.*  
  *PPI response does not rule in GERD or rule out EoE.*

• Why disease activity involves more than just counting eos?  
  *Esophageal subepithelial remodeling is an important determinant of symptoms and complications of EoE*

• What are the pros and cons of drug and diet therapies?  
  *Elimination diets are an effective alternative for motivated children and adults*