Eosinophilic esophagitis-
Diagnosis and Treatment
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The “Atopic poor eater”
• 3 yo Male
• Never been a “good eater” / Chronic regurgitation
• Atopic dermatitis
• Treated with proton pump inhibition / no change
• Mucosal biopsies with dense epithelial eosinophilia

The “Fearful Carnivore”
• 7 year old Hispanic male
• Eating problems—he does not want to eat meat, he experiences chronic intermittent vomiting episodes
The “Cautious Traveler”

• 17 y.o. Caucasian male who got “food stuck” while on cruise last month

• No swallowing problems in past

Eosinophilic esophagitis
Pubmed citations “New Disease”

Eosinophilic Esophagitis:
Consensus recommendations 2007 and 2011

Clinical reviews in allergy and immunology
Series editors: Dennis Y.H. Leung, MD, PhD, and Dennis K. Loefard, MD

Eosinophilic esophagitis: Updated consensus recommendations for children and adults
**Eosinophilic Esophagitis (EoE)**

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

Liacouras C et al, J Allergy Clin Immunol 2011

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**2011 Updated Consensus Report**

- EoE is a clinico-pathologic disease
- Clinically characterized by esophageal dysfunction
- Pathologically 1 or more biopsies show eosinophil predominant inflammation (15+ eos in peak hpf)
- Histopathology is isolated to esophagus
- Other causes need to be excluded
- "**PPI responsive esophageal eosinophilia**"
  - Diagnosis made by clinicians
  - Rarely < 15 eos/hpf (if other clinicopathologic features present)

Liacouras C et al, J Allergy Clin Immunol 2011

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**“PPI responsive esophageal eosinophilia”**

- Gastroesophageal Reflux Disease
- Eosinophilic Esophagitis
- Something else?

Sperelakis S Am J Gastro et al 2007
Chang E et al Gut 2012
Other changes

- “EE” to “EoE”
- Chronic
- Immune / antigen driven

Excluding other causes of esophageal eosinophilia

Clinical point #1

*Esophageal eosinophilia is not pathognomonic of eosinophilic esophagitis*
Epidemiology
• 1-10 in 10,000 prevalence
• Male Predominance
• Geography
  – South America
  – Asia
  – Europe
  – Middle East

Clinical Features- Children
• “GERD” symptoms
• Abdominal pain, vomiting
• Feeding dysfunction
  • Coping mechanisms- avoid highly textured and bulky foods, cut food into small pieces, lubricating foods, extensive chewing / long meals

Clinical Features- Adults
• Chest pain-“with alcohol”
• Food impaction
• Dysphagia
  – 25% with manometric findings

Straumann A et al Allergy 2012
Do patients with EoE complain of heartburn?

<table>
<thead>
<tr>
<th>Percent and number of patients in study</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>29% of 21</td>
<td>Alexander JA et al, 2012</td>
</tr>
<tr>
<td>94% of 50</td>
<td>Gonsalves N et al, 2012</td>
</tr>
<tr>
<td>39% of 169</td>
<td>Spergel J et al, 2012</td>
</tr>
<tr>
<td>54% of 74</td>
<td>Iwanczak B et al, 2011</td>
</tr>
<tr>
<td>20% of 149</td>
<td>Assa’ d et al, 2011</td>
</tr>
</tbody>
</table>

YES!

What is eosinophilic esophagitis? “swallowing problem”

- Children-
  - eating problems (65%), vomiting, pain

- Adults-
  - swallowing problems, food stuck in esophagus (57%)

- Coping mechanisms- avoid highly textured and bulky foods, cut food into small pieces, lubricate foods, lots of chewing and long meals

Straussman et al Allergy 2012
Liacouras et al JACI 2011

Do you have any problems swallowing?

No
Do you have any problems swallowing?

• Do you—
  – cut food in small pieces / chew food a lot?
  – “pocket” food / keep food in your cheek?
  – need liquid / ketchup to eat your meals?
  – avoid “highly textured” foods?

Have you had a food impaction / food stuck in your throat?

No

Have you had a food impaction / food stuck in your throat?

• Do you—
  • jump up and down / raise arms above the head after eating?
  • avoid eating in public?
  • wet your food / need liquid with meals?
Clinical point #2

Ask at least 2 questions!

Diagnostic clues / cautions

- Family history of-
  - Esophageal dilations
  - Connective tissue diseases
  - Recalcitrant GERD

- “Pretreated mucosa”—i.e. use of topical steroids for other atopic diseases may diminish esophageal inflammation

Diagnostic clues / cautions

- Normal endoscopy in past does not rule out EoE.

- Abnormal endoscopy / histology is not diagnostic of EoE.
Radiological examinations of EoE

![Normal](image1)
![Eosinophilic Esophagitis](image2)

4 year old girl

- EoE
- Repeated episodes of food “impactions”
- Abnormal esophagram
- Endoscopy #1-no stricture identified -no dilation
- Endoscopy #2- no stricture but esophageal dilation performed
Clinical Point #3 - Esophagrams in EoE are beneficial to identify narrowed segments.

Normal
Longitudinal tear
Crepe paper mucosa

White Exudate
Rings

Furrows
Strictures

Aceves et al Sem Immunopathol 2012

Diagnostic dilemma
Aim

• To determine whether eosinophil granule proteins (EDGPs) were detectable in the esophageal lumen in children with EoE

• To utilize a novel application of the Enterotest™ to capture luminal EDGPs

Hypotheses

• Mucosal inflammation could be detected in luminal secretions

• Luminal secretions correlate with mucosal inflammation.

• Luminal measurements could differentiate disease states “active EoE and EoE in remission”

The Enterotest

Developed in 1970’s for analysis of parasitic infections
Methods

- EST was swallowed the night before the endoscopic procedure.
- At endoscopy, EST was removed, adherent cells and secretions eluted, and mucosal biopsies obtained (proximal and distal esophagus, and gastric).

Method - The Esophageal String Test (EST)

Methods

- Prospective study of pediatric patients (>7 yo) at Children’s Hospital Colorado and Children’s Memorial Hospital in Chicago
- Eosinophilic Esophagitis (untreated and treated), Gastroesophageal Reflux Disease and control patients with normal esophageal mucosa
- Exclusions
  - Stricture
  - Gelatin allergy
Methods

• Luminal secretions and biopsy lysates were analyzed by ELISAs
  – Major Basic Protein-1 (MBP-1)
    • in house – University of Illinois at Chicago
  – Eosinophil Peroxidase (EPX)
    • in house – Mayo Scottsdale, AZ
  – Eosinophil Derived Neurotoxin (EDN)
  – Eosinophilic Cationic Protein (ECP)
    • commercial – MBL International Corp.

Results

• Patients- 42 pediatric subjects (7 yrs-21 yrs)
  – EoE (no Rx) n=14
  – EoE (Rx) n=8
  – GERD n=5
  – Normal mucosa n=15

• Side effect- Gagging

Do luminal measurements reflect mucosal inflammation?

Furuta GT et al Gut 2012
Do luminal measurements differentiate between disease states?

![Graph showing EST and Biopsy Lysate MBP Levels]

**EoE (No Rx) n=14**

**EoE (Rx) n=8**

**MBP Level (ng MBP/mg Protein)**

<table>
<thead>
<tr>
<th>EDGP</th>
<th>Sample Source</th>
<th>r-value**</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP1</td>
<td>EST</td>
<td>0.735</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>MBP1</td>
<td>Biopsy</td>
<td>0.808</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EDN</td>
<td>EST</td>
<td>0.758</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EDN</td>
<td>Biopsy</td>
<td>0.830</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>ECP</td>
<td>EST</td>
<td>0.606</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>ECP</td>
<td>Biopsy</td>
<td>0.508</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**Pearson correlations with mean eosinophils/HPF**

EST and mucosal biopsies EDGP concentrations correlate with mucosal eosinophil counts.

Conclusions

- The EST can be used as a novel device to capture luminal inflammation in EoE.
- EDGPs are secreted mediators that may participate in esophageal dysfunction in EoE.
Microenvironment-
Genes and local factors

Macronvironment-
Triggers

Eosinophilic Esophagitis

Treatments

• “Drugs” steroids
  – Topical
  – Systemic

• “Diet” exclusions
  – 6 food elimination
  – “Tailored” diet
  – Elemental diet

• “Dilation”
  – Pre-treatment?
  – Through the scope vs. Bougie
Topical Corticosteroids

- Fluticasone
  - Lawrence AE et al, Allergy Clin Immunol 2011
  - Abu-Ali HA et al, Allergy 2012
  - Prendiville S et al, Allergy Clin Immunol 2010
  - Teitelbaum J et al, Gastroenterology 2003
  - Faubion WA et al, Pediatrics Gastroenterol Nutr 1998

- Budesonide
  - Straumann A et al, Clin Gastroenterol Hepatol 2011
  - Straumann A et al, Gastroenterology 2010
  - Goldner JF et al, Gastroenterology 2010
  - Aran SS et al, Acta Gastroenterol 2007

- Ciclesonide
  - Schroeder S et al, J Allergy Clin Immunol 2012

Fluticasone impacts EoE

- Pre-treatment
- Post-treatment
- ***p<0.001

- Proximal
- Distal
- 10
- 20
- 30
- Eosinophils / hpf

- Flu.casone
- 21 FP treated subjects compared to 21 placebo
- 6 week trial
- Histology significantly improved
- Symptoms improved (not significantly) in both groups
- Thrush developed in 26%

Oral Viscous Budesonide

• Developed in 2005 to provide alternative administration of topical steroid

• Meritage Pharma has developed product that is currently under investigation

Oral Viscous Budesonide

• Randomized placebo controlled study

• OVB-15, placebo-9

• OVB-1-2 mg QD for 3 months

Dohil R et al Gastroenterol 2010

OVB improves symptoms

Dohil R et al Gastroenterol 2010
OVB improves histopathology

Dohil R et al Gastroenterol 2010

Ciclesonide

- Converted by epithelial esterases to form the biologically potent desisobutryl-ciclesonide (des-CIC)
- Less absorption than other topical steroids

Esterases are expressed by esophageal epithelia


- 4 children-(4-16 years)
- 8 week treatment
- Clinicopathological response in all
Topical Steroids

- Administer product twice a day
- MDI-2 puffs without a spacer, no inhaling
- OVB- 1-2 respules mixed with Splenda to make thick paste
- No eating or drinking for 30 minutes after

Proton pump inhibitors?

- Concominant GERD
- “Proton Pump Inhibitor Responsive Esophageal Eosinophilia”
  - No evidence of GERD and clinicopathological response to PPI
    - Melaka Infants Cla Centre Hospital 2016
- “Transient Proton Pump Inhibitor Responsiveness”
  - Children who respond to PPIs but then have clinic-pathologic recurrence of months later
    - Dheiti R et al Dig Dis Sci 2012
    - Schroeder et al JPGN in press
PPI impacts more than acid production
Omeprazole decreases cytokine production from EoE cells

Diet exclusions—adults and children
• “6” food elimination
  - Gonsalves N et al Gastroenterology 2012
  - Kagalwalla AF et al J Pediatr Gastroenterol Nutr 2011
  - Kagalwalla AF et al Clin Gastroenterol Hepatol 2006

• “Tailored” diet
  - Spergel J et al Gastrointest Endosc Clin NA 2008

• Elemental diet
  - Markowitz JE et al Am J Gastroenterol 2003
  - Kelly K et al Gastroenterology 1995

Dietary Restriction vs. Elimination

Six food elimination diet (SFED)
- 50 adults
- 6 weeks
- Clinicopathological remission with SFED
- Eosinophilia returned when diet liberalized

Treatments
- Dilation considerations
  - Medical / nutritional pre-treatment?
  - Through the scope or bougie?
    - Madanick RD et al Gastrointest Endosc 2011
    - Jung KW et al Gastrointest Endosc 2011
    - Bohn M et al Dis Esophagus 2010
    - Dellon ES et al Gastrointest Endosc 2011
    - Schoepfer AM et al Am J Gastroenterol 2010

Esophageal Dilation in EoE Prior to 2008
High risk of Esophageal Complications
Esophageal Dilation in EoE 2012
Low risk of Esophageal Complications

| 474 dilations | 0 perforations |
| 70 dilations  | 0 perforations |
| 15 dilations  | 0 perforations |
| 293 dilations | 3 perforations |

Esophageal Dilation as Primary Therapy in EoE
- Retrospective study of 474 dilations in 207 adults with EoE
- 63 patients treated with dilation alone
- Post dilation, 93% of patients reported slight or no dysphagia
- Esophageal diameter increased from 11 mm pre to 16 mm post dilation
- 3 mm incremental dilation per session; median 2 sessions per patient (range 1-13)
- Median duration symptom improvement: 15 months

Esophageal Dilation in EoE:
To Do or Not to Do

<table>
<thead>
<tr>
<th>Not to Do</th>
<th>To Do</th>
</tr>
</thead>
<tbody>
<tr>
<td>No influence on underlying inflammation</td>
<td>Provides long lasting relief of dysphagia</td>
</tr>
<tr>
<td>Significant risk of mucosal laceration with associated chest pain</td>
<td>Pain is transient. Dilation has high patient acceptance</td>
</tr>
<tr>
<td>Risk of esophageal perforation</td>
<td>Risk is low. All perforations reported have been partial ruptures</td>
</tr>
</tbody>
</table>

Schoepfer AM et al Am J Gastroenterol 2010

Courtesy of Ikuo Hirano
Biologicals
Reslizumab

- 226 children (mean age 12 ± 1.4)
- 3 doses and placebo
- 12 weeks
- Histological response with treatment
- Treatment and placebo symptom response


Treatment complications

- Topical and systemic steroids
- Diet / nutritional exclusions
  - Malnutrition
  - Diminished quality of life
- Dilation
  - Perforation
  - Pain

Tak TH et al Aliment Pharmacol Ther 2011

Treatment Strategies

- Induce clinical remission-yes
- Induce histological remission-
  - In our experience-yes
  - What defines histological remission-?
  - Does this prevent complications-?
- Balance benefits of treatment (disease complications) with treatment complications and impact of treatment on quality of life.