Eosinophilic Esophagitis
Practical Management in 2017

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No Disclosers or Conflicts of Interest
Diagnostic Guideline for Eosinophilic Esophagitis

• Symptoms related to esophageal dysfunction: dysphagia, food impaction, GERD

• >15 eosinophils per high powered field

• Eosinophils limited to the esophagus

• Other causes of esophageal eosinophilia eliminated, especially PPI responsive disease

Liacouras CA et al. J Allergy Clin Immunol July 2011
Demographics of Eosinophilic Esophagitis

- 74% males
- 80% white

54% (43%-68%) of patients with food impactions in meta-analysis*

Karpel R et al Gastroenterology 2008

*Hiremath GS et al Dig Dis Sci 2015
Natural History of Eosinophilic Esophagitis

- 1970: Esophageal eosinophilia as biomarker of GERD
- 1980: Case reports of EoE in adults
- 1990: Initial series characterizing of EoE in adults
- 2000: Identification of EoE as diet responsive in children
- 2010: Growing international recognition of EoE
- 2010: First international consensus recommendations on EoE

Hirano I Am J Gastro 2016
New Cases of EoE at University of North Carolina 2000 to 2007

Dellon E, et al. Clinical Gastroenterol and Hepatol 2009
Incidence of EoE Rising more Rapidly than Esophageal Biopsy Rate

Danish Population Based Study 1997-2012

Dellon ES et al. APT 2015
Why is Eosinophilic Esophagitis Increasing?

• Allergen and hygiene hypotheses
  --more sterile –less antigen exposure and tolerance
  --H pylori infection is protective
• Environmental hypotheses
  --aeroallergens
  --cold and arid climate
  --urban vs rural locations
• PPI hypothesis
• Early life factors—breast feeding, antibiotics cesarean sections
Seasonal Variation in Detection of Mucosal Eosinophilia

Cross-sectional US study: 14 524 cases with esophageal eosinophilia and 90 459 normals

Arid Climate Zone

Cold Climate Zone

Jensen ET et al APT 2015
Food Allergy Testing in EoE

• More useful in children than adults
• Prick testing—IgE patch—non-IgE, cell mediated
  No role for serum IgE
• Negative tests more useful that positive
  --exception is milk
• May have cross-reactivity with environmental allergies—wheat cross reacts with grass
• Allergy testing is not substitute for food elimination then reintroduction with EGD fu
Eosinophilic Esophagitis

Furrows

Microabscesses
Furrows with White Light
Furrows with NBI
Eosinophilic Esophagitis - Rings
Food Impaction in EoE Patient
Esophageal Biopsy Tug or Pull Sign

83 EoE and 121 control subjects—single person did all EGDs

Sensitivity 76% and Specificity 98%

Dellon ES et al GI Endoscopy 2016
Histology of Eosinophilic Esophagitis
> 15 eosinophils/hpf

Odze RD. Am J Gastroenterology 2009
Eosinophilic Esophagitis

Number of Biopsies to Make Diagnosis

Gonsalves N, et al. GIE 2006
Patchy Nature of EoE

Pathology

• 12/12/2011
  – Distal -- no eos
  – Proximal -- 8 eos/hpf

• 1/16/2012
  – Maximum of 10 eos/hpf

• 2/6/2012
  – Maximum of 15 eos/hpf

42 yo white male
Eosinophil Peak Counts Vary with Specific Endoscopy Findings

Salek J et al APT 2015
Pathophysiology of Eosinophilic Esophagitis

Inflammatory Phase

Ferguson DD. Diseases of Esophagus 2007
Tissue Remodeling in Eosinophilic Esophagitis

Eosinophilic Esophagitis: Inflammation vs Fibrosis with Remodeling

<table>
<thead>
<tr>
<th>Baseline (inflammation active)</th>
<th>Budesonide (inflammation in remission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White exudates</td>
<td></td>
</tr>
<tr>
<td>Red furrows</td>
<td></td>
</tr>
<tr>
<td>Corrugated rings</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of GERD with Mucosal Eosinophilia

- Hard to really identify in literature but **LOW**

<table>
<thead>
<tr>
<th>Center</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>USC</td>
<td>40/3648 (1%)</td>
<td>Surgery series</td>
</tr>
<tr>
<td>Spain</td>
<td>25/712 (4%)</td>
<td>Random EGDs</td>
</tr>
<tr>
<td>Mayo</td>
<td>8/66 (12%)</td>
<td>Dysphagia patients</td>
</tr>
<tr>
<td>Mayo</td>
<td>14/200 (7%)</td>
<td>Barretts</td>
</tr>
<tr>
<td>Walter Reed</td>
<td>8/42 (19%)</td>
<td>Randomized study</td>
</tr>
<tr>
<td>USF</td>
<td>10/101 (10%)</td>
<td>Personal series</td>
</tr>
</tbody>
</table>
Evolution of Eosinophilic Esophagitis

Early
- GERD
- Dietary or Airborne Allergens

Eosinophilic Esophagitis with Chronic Inflammation

Late
- Rings
- Diffuse Scarring

Children
- Early
- Late

Adults
- Early
- Late
Factors Contributing to Dysphagia in Eosinophilic Esophagitis

- **Dysmotility**
  - High Resolution Manometry
  - Esophageal motility disorders
  - Increased intrabolus pressure

- **Inflammation**
  - Biopsies (> 15 eosinophils/hpf)
  - PPIs
  - Steroids
  - Diet

- **Fibrostenosis**
  - Endoscopy (rings/strictures)
  - Esophageal dilation
Predilation and PPIs

- Eosinophil count: 170
- Esophageal diameter: 8mm
- Intrabolus pressure: 25 mmHg

Post-dilation and 2 months PPIs

- Eosinophil count: 200
- Esophageal diameter: 17mm
- Intrabolus pressure: 18 mmHg
Mucosal Eosinophilia (> 15 eos/hpf)

- > 15 eos/hpf
  - BID PPIs for 8 weeks
  - < 15 eos/hpf

- Idiopathic EOE
- PPI Responsive Eosinophilia
  - Dysphagia
  - Rings /furrows
  - - pH tests
- GERD related Eosinophilia
  - HB, regurgitation
  - Erosions/hernia
  - + pH tests

Estimated prevalence of PPI responsive mucosal eosinophilia: 33% to 74%
Comparison of EoE Responsive and Nonresponsive to PPI Therapy

Why EoE May Respond to PPIs

- Healing disrupted epithelial barrier to prevent further immune activation
- Decrease eosinophil longevity
- Inherent anti-inflammatory properties of PPIs
  - Downregulation of IL-4 and IL-13 murine asthma model
  - Block IL-13 stimulated secretion of eotaxin 3 in EoE esophageal cell line

Kedika RR et al. Dig Dis Sciences 2009
Cheng E et al Gut 2013
Long-Term Response in PPI-REE

- Retrospective multicenter cohort study
- 75 PPI responders to high dose PPIs
- Mean follow-up 26 months (12-85)
- 55 (73%) sustained histologic response on low dose PPI therapy
- Predictors of relapse
  - rapid metabolizer (CYP2C19): OR-12.5 (CI:1.3-116)
  - rhinoconjunctivitis: OR 8.6 (CI: 1.5-48.7)
- Relapse limited to distal biopsies in 14/20 (70%)

Practice Patterns of Community Referred Patients

6 Food Elimination Diet (SFED)

- Milk
- Soy
- Eggs
- Wheat
- Peanuts/tree nuts
- Shellfish/fish
Eosinophil Response to Reintroduction of Foods

Common food triggers
Wheat—60%
Milk—50%
Soy—10%
Nuts—10%
Egg—5%

Gonsalves N et al Clin Gastro and Hepatology 2012
Specific Food Triggers Identified in Adult Series of Elimination Diets

Hirano I Am J Gastro 2016
Efficacy of Six Food Elimination Diet in Inducing Histologic Remission

Arias A et al. Gastroenterology 2014
Food Reintroduction after Successful 6 Food Elimination Diet

Doerfler B et al Diseases of the Esophagus 2015
First EoE Study in Adults with Fluticasone vs Placebo

- Fluticasone 220 microgams—4 puffs BID for 6 weeks vs Placebo
- Initially 21 EoE patients in each group

**Table 2. Dysphagia Response**

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT complete</td>
<td>42.9% (9/21)</td>
<td>28.6% (6/21)</td>
<td>.52</td>
</tr>
<tr>
<td>PP complete</td>
<td>47.4% (9/19)</td>
<td>40.0% (6/15)</td>
<td>.74</td>
</tr>
<tr>
<td>ITT partial or complete</td>
<td>57.1% (12/21)</td>
<td>33.3% (7/21)</td>
<td>.22</td>
</tr>
<tr>
<td>PP partial or complete</td>
<td>63.2% (12/19)</td>
<td>46.7% (7/15)</td>
<td>.49</td>
</tr>
<tr>
<td>PP complete 2 weeks</td>
<td>42.1% (8/19)</td>
<td>26.7% (4/15)</td>
<td>.47</td>
</tr>
<tr>
<td>PP complete 4 weeks</td>
<td>47.4% (9/19)</td>
<td>26.7% (4/15)</td>
<td>.30</td>
</tr>
</tbody>
</table>

**Table 3. Histologic Response**

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT complete</td>
<td>61.9% (13/21)</td>
<td>0% (0/21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PP complete</td>
<td>68.4% (13/19)</td>
<td>0% (0/15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ITT partial or complete</td>
<td>81.0% (17/21)</td>
<td>4.8% (1/21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PP partial or complete</td>
<td>89.5% (17/19)</td>
<td>6.7% (1/15)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Despite nearly eliminating eosinophils, symptom relief no better than placebo*

Alexander JA et al. Clinical GI and Hepatology 2012
Large Clinical Experience with Steroids in Adult EoE Patients

- 221 EoE received steroids
- Only 57% had histologic remission
- Only 48% responded to second line therapies
- Need for esophageal dilation was predictor of poor outcome

Wolf WA et al. Clinical GI and Hepatology 2015
Systematic Review with Network Meta-Analysis: Topical Steroids vs PPIs

• 10 randomized controlled trials—437 patients

• Topical steroids vs placebo:
  --histologic improvement: OR 12.03 (5.64-25.63)
  --clinical response: OR 1.59 (1.15-2.22)
  --similar for children and adults
  --highest response if definitive a priori PPI trial

• Topical steroids vs PPIs-2 trials
  --no difference in histologic or clinical response
  --however, neither had prior PPI trial

• Network analysis:
  --no difference between fluticasone vs budesonide

Distribution of Nebulized vs Viscous Budesonide in Eosinophilic Esophagitis

Swallowed viscous budesonide

Nebulized budesonide

Dellon ES et al. Gastroenterology 2012
Duration of Symptoms Predict Stricture Disease In EoE Patients—USF Experience

Esophageal Dilation for Eosinophilic Esophagitis

- 6 studies with 170 adult EoE patients
- Types of dilators: 2:1 between bougies and TTS balloons
- Mean # of sessions: 1.2 to 2 to get to 16-17 mm diameter
- Clinical improvement: 91%
- Average symptom relief: 22-23 months
- Mucosal eosinophil count did not change
- Complications: 4 mucosal tears, no perforations

Richter JE Best Practice & Research Clinical Gastroenterology 2015
Esophageal Dilation in EoE
Pain Frequency and Patient Acceptance

74% of patients

Comparison of Eosinophilic Infiltration Distal Biopsies Baseline and Follow-up

Bohm M et al Diseases of the Esophagus 2010
Natural History of EoE Treated with Esophageal Dilation over 13 Years

Lipka S, Richter JE et al. GI Endoscopy 2014

14 patients (11 men)—average age 32
Average followup-13 yrs (5-24 yrs)
<table>
<thead>
<tr>
<th><strong>Table 1 – General Guidelines for Esophageal Dilation In EoE Patients</strong>&lt;sup&gt;27&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forewarn the patient that some degree of post-dilation pain is to be expected.</td>
</tr>
<tr>
<td>Careful endoscopy prior to dilation to assess the location of strictures and estimate esophageal diameter.</td>
</tr>
<tr>
<td>Start low with small diameter bougies and gradually dilate to 16-18mm, if possible.</td>
</tr>
<tr>
<td>Gradual slow dilation is key with sessions separated by 3-4 weeks.</td>
</tr>
<tr>
<td>Limit the progression of dilation per sessions to &lt;3mm after resistance is noted. Stop with moderate resistance or blood on the dilator.</td>
</tr>
<tr>
<td>Look for tears if you must—but they only represent an adequate dilation.</td>
</tr>
<tr>
<td>For post-procedure chest pain, mild analgesia is recommended and rarely narcotics. Expected chest pain is monitored during recovery period and by telephone, if necessary.</td>
</tr>
<tr>
<td>After induction dilation sessions to 16-18mm, repeat dilations are triggered by recurrence of dysphagia symptoms.</td>
</tr>
</tbody>
</table>
Table 2 – Characteristics of Patients with Prior Complications

<table>
<thead>
<tr>
<th></th>
<th>Age/ Sex</th>
<th>Initial Diameter Perforation</th>
<th>Dilator Used</th>
<th>Multiple Dilations Prior</th>
<th>Complication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64/m</td>
<td>11.5mm</td>
<td>TTS</td>
<td>Yes</td>
<td>Perforation</td>
<td>7 day hospitalization/Surgery/TPN 17 days</td>
</tr>
<tr>
<td>2</td>
<td>41/m</td>
<td>N/A</td>
<td>Unknown Dilator</td>
<td>Yes</td>
<td>Perforation</td>
<td>5 day hospitalization</td>
</tr>
<tr>
<td>3</td>
<td>44/f</td>
<td>N/A</td>
<td>Maloney</td>
<td>No</td>
<td>Severe Chest Pain</td>
<td>2 day hospitalization</td>
</tr>
<tr>
<td>4</td>
<td>34/f</td>
<td>18mm</td>
<td>Maloney</td>
<td>No</td>
<td>Perforation</td>
<td>5 day hospitalization</td>
</tr>
<tr>
<td>5</td>
<td>27/m</td>
<td>10mm</td>
<td>EGD</td>
<td>No</td>
<td>Perforation</td>
<td>8 day hospitalization</td>
</tr>
<tr>
<td>6</td>
<td>29/m</td>
<td>12mm</td>
<td>Savory</td>
<td>No</td>
<td>Severe Pain/Tear</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>7</td>
<td>23/f</td>
<td>12mm</td>
<td>TTS</td>
<td>No</td>
<td>Perforation</td>
<td>1 day hospitalization</td>
</tr>
<tr>
<td>8</td>
<td>21/f</td>
<td>N/A</td>
<td>Unknown Dilator</td>
<td>No</td>
<td>Severe Pain/Eosophageal Tear</td>
<td>7 day hospitalization</td>
</tr>
</tbody>
</table>

Fr – French, TTS – Through The Scope, Information not available
# Start Low and Go Slow to Keep Out of Trouble

| Table 4 – Details of Esophageal Dilation Among the Two Groups at Our USF EoE Center |
|-------------------------------------------------|------------------|------------------|------------------|
|                                             | Prior Complication (N=8) | No Complication (N=22) | MD/OR 95% CI; p-value |
| Initial Esophageal Diameter (mm)             | 9.0+/−1.51           | 11.73+/−2.98        | -2.73(-4.44,-1.02); p-0.003 |
| End Esophageal Diameter (mm)                 | 15.75+/−1.83         | 16.09+/−1.97        | -0.34(-2.01,1.32); p-0.67 |
| Mean Change in Diameter (mm)                 | 6.75+/−1.98          | 4.36+/−2.80         | 2.39(0.45, 4.32); p-0.019 |
| Number of Dilation Sessions                  | 4.00+/−1.77          | 2.32+/−1.04         | 1.68(0.17,3.19); p-0.033 |
| Achieved 17mm Diameter                       | 4/8 (50%)            | 15/22 (68.2%)       | 0.47(0.09, 2.43); p-0.37 |
| Dilation Sessions to Reach 17mm               | 3.75+/−0.96          | 2.27+/−0.96         | 1.48(0.08, 2.89); p-0.042 |
| Time to Reach 17mm (Months)                  | 3.50+/−0.58          | 2.33 +/−2.29        | 1.17(-0.22, 2.55); p-0.09 |
| Complications                                | 0/8                 | 0/22               | N/A               |
| Symptom Resolution                           | 8/8                 | 22/22              | N/A               |
| Follow up time (Months)                      | 7.63+/−6.41          | 4.59+/−6.12         | 3.03(-2.67, 8.74); p-0.27 |
EoE Algorithm 2015

Mucosal Eosinophilia > 15 eos/hpf

Esophageal dilation to 17-18 mm

BID PPIs for 2 months

> 15 eos/hpf

Idiopathic EoE

Allergy testing

Negative

Fluticasone

Budesonide

Positive

Food elimination diet

< 15 eos/hpf

PPI Responsive EoE/GERD

Continue or decrease PPIs

Richter JE J Clin Gastro 2015
Recommended Readings

1. Eosinophilic esophagitis: Updated consensus recommendations for children and adults
   J Allergy Clin Immunol 2011

2. Richter JE Current management of EoE 2015
   J Clinical Gastroenterology 2016