Eosinophilic Esophagitis
Practical Management in 2017

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No Conflicts of Interest
Points to Discuss

• Review the epidemiology and pathophysiology of eosinophilic esophagitis (EoE)

• Discuss the two phenotypes of EoE

• Emphasize the critical role of the PPI trial in the treatment of EoE

• Review important aspects of treatment with diet, steroids or esophageal dilation

• Close with a practical treatment algorithm
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: Case reports of EoE in adults
1980: Esophageal eosinophilia as biomarker of GERD
1990: Initial series characterizing of EoE in adults
2000: Identification of EoE as diet responsive in children
2010: Growing international recognition of EoE
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 Gastroenterology and Hepatology 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—food allergies
  --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
Eosinophilic Esophagitis

A. Furrows

B. 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

Baseline
(inflammation active)

Budesonide
(inflammation in remission)

White exudates

Red furrows

Corrugated rings

Straumann A Gastroenterology 2010
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

- GERD
- Dietary or Airborne Allergens

Eosinophilic Esophagitis with Chronic Inflammation

Fibrosis

Rings

Diffuse Scarring

Early

Children

Late

Adults
Factors Contributing to Dysphagia in Eosinophilic Esophagitis

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

- **Inflammation**
  - Biopsies (> 15 eosinophils/hpf)

- **Fibrostenosis**
  - Endoscopy (rings/strictures)
  - PPIs
  - Steroids
  - Diet
  - 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
Comparison of EoE Responsive and Nonresponsive to PPI Therapy

Mucosal Eosinophilia
(> 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%
Three Phases of the PPI Trial for EoE

- High dose BID PPI
- At least two months of treatment
- Repeat EGD with multiple biopsies
- Success: less than 15 eosinophils/hpf

PPI trial for EoE not based on symptom relief
Baseline

1 month BID PPI

2 months BID PPI

Lipka S et al Diseases of Esophagus 2014
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%)

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

Aceves S. Clinical Gastroenterology and Hepatology 2014
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

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**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

<table>
<thead>
<tr>
<th>Therapy (no. receiving)</th>
<th>Responded with &lt;15 eosinophils, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary (16)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Increased dose (14)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Changed topical agent (7)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Singular (7)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Prednisone (5)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Ciclesonide (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Compounded budesonide (2)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Ketotifen (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>6-mercaptopurine (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (48)</td>
</tr>
</tbody>
</table>

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

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

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>Table 1 – General Guidelines for Esophageal Dilation In EoE Patients&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>
The EoE Patients No One Wants to Dilate

<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>
<thead>
<tr>
<th>Table 4 – Details of Esophageal Dilation Among the Two Groups at Our USF EoE Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Complication (N=8)</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Initial Esophageal Diameter (mm)</strong></td>
</tr>
<tr>
<td><strong>End Esophageal Diameter (mm)</strong></td>
</tr>
<tr>
<td><strong>Mean Change in Diameter (mm)</strong></td>
</tr>
<tr>
<td><strong>Number of Dilation Sessions</strong></td>
</tr>
<tr>
<td><strong>Achieved 17mm Diameter</strong></td>
</tr>
<tr>
<td><strong>Dilation Sessions to Reach 17mm</strong></td>
</tr>
<tr>
<td><strong>Time to Reach 17mm (Months)</strong></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td><strong>Symptom Resolution</strong></td>
</tr>
<tr>
<td><strong>Follow up time (Months)</strong></td>
</tr>
</tbody>
</table>
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 ↓

< 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