Eosinophilic Esophagitis: Update 2012

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Objectives

• Describe the clinical presentation and epidemiology of eosinophilic esophagitis
• Know when to include EoE on the DDx for common GI complaints
• Understand how the diagnostic criteria for EoE
• State the current treatment options and their efficacy
Overview

• Diagnosis
• Epidemiology
• Pathogenesis
• Treatment
• Recommendations
What is eosinophilic esophagitis?

- Clinicopathologic condition:
  - Correct symptoms
  - Correct endoscopic appearance
  - Correct pathologic findings
    - Esophageal eosinophilia (of some degree)
Clinical presentation

• Symptoms:
  • Dysphagia is thought to be the hallmark
    • EoE now seen in > 50% of food impactions*
    • Ask about dietary modification, speed of eating, chewing, drinking to clear food, eating out, etc…
  • Heartburn
    • “Refractory reflux”
  • Chest pain, abdominal pain, nausea, vomiting
  • Children: failure to thrive, feeding intolerance, reflux, abdominal pain, nausea, vomiting

Endoscopic findings
Histopathologic findings

Intense mucosal eosinophilic infiltrate

Eosinophilic microabscess
How to find EoE?
<table>
<thead>
<tr>
<th>Conceptual framework</th>
<th>2007(^1)</th>
<th>2011(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinicopathologic disorder</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Esophageal dysfunction</td>
<td>Esophageal dysfunction</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>≥ 15 eos/hpf</td>
<td>≥ 15 eos/hpf (with few exceptions)</td>
</tr>
<tr>
<td>Other histology</td>
<td>--</td>
<td>Report associated findings</td>
</tr>
<tr>
<td>Exclude GERD?</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>Exclude other causes of eosinophilia?</td>
<td>Implied</td>
<td>Yes, including PPI-responsive</td>
</tr>
</tbody>
</table>

\(^1\)Furuta et al, Gastro, 2007; \(^2\)Liacouras et al, JACI, 2011
Biopsy yield by diagnostic cut-point

Gonsalves et al, GIE, 2006
DDx of esophageal eosinophilia

- EoE
- Eosinophilic gastroenteritis
- GERD
- Crohn’s disease
- Connective tissue diseases
- Hypereosinophilic syndrome
- Infections
- Drug hypersensitivity response

- Common
- Frequent EGDs
- Clinical overlap
- Diagnostic overlap

Furuta et al, Gastro, 2007
EoE vs GERD – UNC experience

Clinical, Endoscopic, and Histologic Findings Distinguish Eosinophilic Esophagitis From Gastroesophageal Reflux Disease

Evan S. Dellen, Wood B. Gibbs, Karen J. Fritchie, Tara C. Rubinas, Lindsay A. Wilson, John T. Woosley, and Nicholas J. Shaheen

*Center for Esophageal Diseases and Swallowing and †Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine; and ‡Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

- Retrospective case-control study (UNC, 2000-2007) of EoE (n = 151) vs GERD (n = 226)
- Aimed to characterize clinical, endoscopic, and histologic features of EoE and GERD, and to identify factors that could differentiate them
- Study population included adults and children
### Predicting EoE – multivariate model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Age at biopsy*</td>
<td>0.98</td>
<td>0.95-1.00</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11.8</td>
<td>3.77-36.8</td>
</tr>
<tr>
<td>Food allergy</td>
<td>11.2</td>
<td>2.79-45.0</td>
</tr>
<tr>
<td>Rings on EGD</td>
<td>9.9</td>
<td>1.93-51.1</td>
</tr>
<tr>
<td>Linear furrows on EGD</td>
<td>6.4</td>
<td>0.62-65.5</td>
</tr>
<tr>
<td>White plaques on EGD</td>
<td>5.4</td>
<td>0.49-58.5</td>
</tr>
<tr>
<td>Hiatal hernia present on EGD</td>
<td>0.21</td>
<td>0.04-1.00</td>
</tr>
<tr>
<td>Maximum eosinophil count**</td>
<td>1.01</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Degranulating eosinophils</td>
<td>4.81</td>
<td>1.52-15.2</td>
</tr>
</tbody>
</table>

* OR for a 1 year increase in age; ** OR for a 1 cell increase in eosinophil count
Predicting EoE – ROC curve

\[ \text{AUC} = 0.934 \]

Dellon et al, CGH, 2009
Conclusions about diagnosis

• A suggestive clinical picture is needed
• A supportive endoscopic exam is helpful, though in some cases, the esophagus may appear normal
• Esophageal eosinophilia must be demonstrated on biopsy
  • At least 15 eos/hpf are needed for diagnosis*
  • Know how your pathologist makes the count
  • At least 5 biopsies, preferably from at least 2 locations, give the best diagnostic sensitivity
• Exclude competing causes of esophageal eosinophilia
EoE Diagnosis: The Future?

Tryptase:

Eotaxin-3:

Normal | GERD | EoE

Dellon et al, AJG 2011
A possible biopsy protocol

Proximal: 13-15 cm → x x x x

Mid: 8-10 cm → x x x x

Distal: 3-5 cm → x x x x
Epidemiology of EoE

• Demographics:
  • Age range of reported cases: 6 mos to 89 yrs
  • Males > females (~ 3-4 : 1)
    • the reasons for this are unclear
  • Described in many racial/ethnic backgrounds, but appears to be more common in whites
    • the reasons for this are unclear
  • Association with atopic disease
  • Familial clusters have been reported
EoE in the literature

Number of citations vs. Year

Year:
- 1978
- 1984
- 1990
- 1996
- 2002
- 2008

Number of citations:
- 0
- 30
- 60
- 90
- 120
- 150
Increasing incidence of EoE

Extrapolating to the US: 18,000 – 60,000 new cases/yr?

Noel, NEJM, 2004; Straumann, J All Clin Immunol, 2005; Buckmeier, TIGERS, 2008; Williams, DDW, 2008
Extrapolating to the US: 300,000 – 1.2 mil cases (gen pop), with a high prevalence in symptomatic patients

Straumann, J All Clin Imm, 20005; Ronkainen, Gut, 2006; Prasad, AJG, 2007; Buckmeier, TIGERS, 2008; Veerappan, CGH, 2009
Pathogenesis of EoE

Environment

Genetics

Question marks represent areas of uncertainty or investigation in the relationship between environment and genetics in the context of EoE.
Role of allergy

• Clinical observations
  • Many patients with EoE have associated atopic conditions:
    • Asthma, atopic dermatitis, allergic rhinitis
    • Food allergies (sensitivity or anaphylaxis)
  • Symptoms and eosinophil counts can have seasonal variation
  • Symptoms improve rapidly on allergen free diets
• $T_H^2$ response to allergens demonstrated as a likely pathogenic mechanism of EoE

Liacouras, CGH, 2005; Roy-Ghanta, GCH, 2008; Fogg, J Allergy Clin Immunol, 2003
## Role of Allergy

<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Age</th>
<th>Asthma</th>
<th>Allergic Rhinitis</th>
<th>Atopic Dermatitis</th>
<th>Food allergy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spergel, 2009</td>
<td>620</td>
<td>9 ± 3</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
<td>6%</td>
</tr>
<tr>
<td>Assa’ad, 2007</td>
<td>89</td>
<td>6 ± 5</td>
<td>39</td>
<td>30</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Sugnanam, 2007</td>
<td>45</td>
<td>0 – 16 yr</td>
<td>66</td>
<td>93</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>Guajardo, 2002</td>
<td>39</td>
<td>8 ± 12</td>
<td>38</td>
<td>64</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Roy-Ghanta, 2008</td>
<td>23</td>
<td>18 – 57 yr</td>
<td>26</td>
<td>78</td>
<td>4</td>
<td>--</td>
</tr>
<tr>
<td>Penfield, 2009</td>
<td>26</td>
<td>20-74 yr</td>
<td>35</td>
<td>92</td>
<td>12</td>
<td>--**</td>
</tr>
</tbody>
</table>

* Anaphylactic reaction; **50% were skin prick test positive for food allergies

Adapted from Jyonouchi, Immunol Allergy Clin N Am, 2009
EoE treatment options

- Pharmacologic therapy
  - Acid suppression
  - Corticosteroids (systemic; topical)
  - Leukotriene antagonists (montelukast)
  - Mast cell stabilizers (cromolyn)
  - Immunomodulators (6-MP; azathioprine)
  - Biologics (anti-IL-5; anti-IgE; anti-TNF)

- Dietary therapy

- Endoscopic therapy (dilation)

No FDA-approved medications for EoE!
Acid suppression in EoE

CASE REPORT

Eosinophils in the Esophagus—Peptic or Allergic Eosinophilic Esophagitis? Case Series of Three Patients with Esophageal Eosinophilia

Peter Ngo, M.D.,1 Glenn T. Furuta, M.D.,1 Donald A. Antonioli, M.D.,2 and Victor L. Fox, M.D.1

1Division of Pediatric Gastroenterology, Children's Hospital, Boston, Massachusetts; 2Department of Pathology, Beth Israel Deaconess Hospital, Boston, Massachusetts

- 3 cases of patients with dysphagia, food impaction, and vomiting and with marked esophageal eosinophilia, resolving on AST.
- All subjects with esophageal eosinophilia need assessment of reflux status or empiric trial of AST.
Topical steroids – eosinophil counts

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<th>Design</th>
<th>Subjects</th>
<th>Med</th>
<th>Rx time</th>
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</thead>
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<tr>
<td>Konikoff</td>
<td>2006</td>
<td>36 children</td>
<td>FP 880/d</td>
<td>3 mos</td>
</tr>
<tr>
<td>Schaefer</td>
<td>2008</td>
<td>80 children</td>
<td>FP 440-880/d*</td>
<td>12 wks</td>
</tr>
<tr>
<td>Straumann</td>
<td>2010</td>
<td>36 adults</td>
<td>Bud 2mg/d**</td>
<td>15 days</td>
</tr>
<tr>
<td>Dohil</td>
<td>2010</td>
<td>24 children</td>
<td>Bud 1-2mg/d***</td>
<td>3 mos</td>
</tr>
<tr>
<td>Alexander</td>
<td>2011 (abs)</td>
<td>34 adults</td>
<td>FP 1560/d</td>
<td>6 wks</td>
</tr>
<tr>
<td>Gupta</td>
<td>2011 (abs)</td>
<td>81 children</td>
<td>Bud 0.35 - 4mg/d***</td>
<td>12 wks</td>
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“71% histologic response”

*Compared to prednisone; **Swallowed nebulized budesonide; ***oral viscous budesonide
Topical steroids – symptoms

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*Compared to prednisone; **Swallowed nebulized budesonide; ***oral viscous budesonide
• 28 adult budesonide responders randomized to maintenance (0.5 mg/d) vs placebo x 1 yr
• Histologic recurrence was more common in the placebo group (100%) vs budesonide (50%)
• Symptom recurrence was more common in the placebo group (64%) vs budesonide (36%)
Topical steroids – side effects

- Lessons from long-term use in asthma:
  - Local (deposition) effects: hoarse voice, cough, throat irritation
  - Systemic effects:
    - High first pass hepatic metabolism
    - Minimal, if any, effect on growth rates (in children), bone mineral density (in adults)
    - Dose dependent mild suppression of the HPA axis with prolonged use
- Oral and esophageal candidiasis: Package insert: 1-10%

References:
Johnson, J All Clin Imm, 1996; Agertoft, NJEM, 2000; Jones, Cochrane, 2002; Lipworth, Arch Int Med, 1999
Corticosteroids in EoE - Recs

• Current practice recommendations:
  • Fluticasone 220 μg inhaler, 4 puffs BID, or…
  • Budesonide 1 mg BID mixed with sugar substitute
• Tips for most effective use:
  • for MDI, swallow medication during breath hold
  • NPO x 30-60 minutes after administration
  • 8 weeks of treatment followed by endoscopy
• Unknowns: Best duration of therapy; best type of topical preparation; indications for chronic use; true reasons for “steroid-refractory” cases…
Dietary therapy in EoE

• The best therapy (particularly in children)?
• Rationale: food allergens may contribute to the pathogenesis of EoE
• Downsides:
  • reliability of detecting food allergy
  • difficulty with dietary compliance
  • most research to date is in children
Dietary therapy in EoE

- Elemental diet: Markowitz et al, AJG, 2003
  - 51 children with EoE
  - Commercial formula (free AAs, corn syrup solids, and medium chain triglycerides); patients also allowed either grapes or apples; 4 week rx period

<table>
<thead>
<tr>
<th></th>
<th>Pre-diet</th>
<th>Post-diet</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eos/hpf</td>
<td>34 ± 10</td>
<td>1 ± 0.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Heartburn</td>
<td>27</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Waterbrash</td>
<td>11</td>
<td>1</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

- Average time to improvement: 9 days
Dietary therapy in adults

• Six food elimination diet (n = 27)*
  • Empirically eliminated milk, soy, egg, wheat, nuts, seafood/shellfish
  • Also eliminated other allergens identified on skin prick testing
  • 1 food added back q 2 wks, w/ EGD q 2 foods
• Outcomes:
  • Improved tissue eosinophilia
  • Improved average symptom scores
  • Reintroduction of foods: recurrence within 5 days

* Gonsalves et al, DDW, 2008
Endoscopic therapy (dilation)
Less risk in the “modern” era?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n*</th>
<th>Perfs</th>
<th>Boerhaave’s (spontaneous)</th>
<th>Tears/rents</th>
<th>Chest pain (hospitalized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonsalves</td>
<td>2007</td>
<td>152</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Schoepfer</td>
<td>2008</td>
<td>106</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Straumann</td>
<td>2008</td>
<td>124*</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dellon</td>
<td>2009</td>
<td>70</td>
<td>0 (0)</td>
<td>--</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Shepherd</td>
<td>2009</td>
<td>34</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Schoepfer</td>
<td>2010</td>
<td>207*</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
<td>**</td>
</tr>
<tr>
<td>Bohm</td>
<td>2010</td>
<td>10</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Jung</td>
<td>2010</td>
<td>293</td>
<td>3 (1)</td>
<td>--</td>
<td>27 (9)</td>
<td>--</td>
</tr>
</tbody>
</table>

* number of dilations reported, except Straumann (EGDs), Schoepfer (patients), and Bohm (patients)

** 74% of patients (n=42) had some complaint of post-procedural chest pain; in 17% it was severe; however, there was a high degree of patient acceptance of this procedure
Summary algorithm

Suspected EoE (≥ 15 eos/hpf)

PPI trial (2-3 mos)

Monitor

Response?

Topical steroids (8 wks)

Response?

Dilation
Repeat topical steroids
Systemic steroids
Montelukast
Immunomodulators
Biologics (trials)

Dietary therapy