Eosinophilic Esophagitis (EoE): The Burn that is not GERD
Courtney Hugie, PharmD

Definition and History of EoE

- Definition
  - Allergic inflammatory disease of the esophagus
  - Also called allergic oesophagitis

  - 1960-70s: First probable cases of EoE
  - 1993: First case series of EoE

Early 1990s
Early reports of patients with multiple esophageal rings

Epidemiology

- Prevalence on rise
- Variations in endoscopy practices introduce bias to epidemiology studies
- Children/Adolescents up to 19 years
  - 1-4/10,000 persons
- Overall
  - 56.7/100,000 persons
  - Peak prevalence 114.6/100,000 in men 35-39 years old

Pathophysiology

Eotaxins 1, 2, 3
Mast Cell
Airborne Allergens
Food Allergens
Epithelial cells, smooth muscle cells, fibroblasts
IL-4, IL-13
Eotaxins 1, 2, 3
Bone marrow
Eosinophil production
Esophageal epithelium

Smoke Detector: Clinical Symptoms

- Food Impaction
- Dysphagia
- Regurgitation
- Burning sensation
- Nausea
- Vomiting
- Abdominal pain
- Chest pain
- Difficulty sleeping

Patient Demographics

- Gender
  - Male:Female 3:1
- Age
  - Childhood, 3rd, or 4th decade of life
- Race
  - Present in all ethnic groups
  - Predominant in non-Hispanic white
- Disease States
  - Food allergies, asthma, eczema, chronic rhinitis, environmental allergies, celiac disease
  - Inverse relationship with H. Pylori infection
- Climate
  - Cold and arid zones
- Genetic
  - Single nucleotide polymorphism in eotaxin-3
### Symptoms in Children vs Adults

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Children</th>
<th>Adults/Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food refusal</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting/regurgitation</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GERD refractory to therapy</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Food impaction/foreign body impaction</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

### Common Foods Causing EoE

<table>
<thead>
<tr>
<th></th>
<th>Biopsy n=602 (%)</th>
<th>Symptoms n=726 (%)</th>
<th>IgE-mediated n=269 (%)</th>
<th>Combined n=1597 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>211 (35)</td>
<td>139 (19)</td>
<td>27 (10)</td>
<td>377 (24)</td>
</tr>
<tr>
<td>Egg</td>
<td>78 (13)</td>
<td>81 (11)</td>
<td>47 (17)</td>
<td>206 (13)</td>
</tr>
<tr>
<td>Wheat</td>
<td>72 (12)</td>
<td>65 (9)</td>
<td>2 (1)</td>
<td>139 (9)</td>
</tr>
<tr>
<td>Soy</td>
<td>52 (9)</td>
<td>75 (10)</td>
<td>10 (4)</td>
<td>137 (9)</td>
</tr>
<tr>
<td>Peanut</td>
<td>16 (3)</td>
<td>37 (5)</td>
<td>58 (22)</td>
<td>111 (7)</td>
</tr>
<tr>
<td>Beef</td>
<td>33 (5)</td>
<td>59 (8)</td>
<td>1 (&lt;1)</td>
<td>93 (6)</td>
</tr>
<tr>
<td>Corn</td>
<td>39 (6)</td>
<td>51 (7)</td>
<td>0</td>
<td>90 (6)</td>
</tr>
<tr>
<td>Chicken</td>
<td>32 (5)</td>
<td>52 (7)</td>
<td>2 (&lt;1)</td>
<td>86 (5)</td>
</tr>
</tbody>
</table>

### Case

BH is a 35 year old Caucasian male. He presents to your pharmacy/clinic with “heartburn” 4 days/week. He is unsure of his trigger foods but would like some help in relieving his symptoms. He has no active prescription medications.

- What recommendations do you have for him at this time?
  - A. Food Diary
  - B. OTC PPI trial (max of 2 weeks)
  - C. OTC H2 Receptor Antagonist
  - D. A and B

Upon further questioning, BH states he is having food impaction resulting in difficulty breathing. Does this symptom warrant a referral to a physician?

- A. Yes
- B. No

### The Fire Alarm: Associated Complications

- Esophageal Strictures
- Esophageal Rings
- Barrett’s Esophagus
  - Risk factor for Cancer

### Diagnosis

- Radiology Findings
  - Strictures
  - Fixed rings
  - Diffuse corrugation
  - Esophageal intramural diverticulosis (rare)
- Histology Findings
  - Required: absolute eosinophil count
  - Other histologic features should be evaluated and noted in pathology reports

### Endoscopic Features
Diagnostic Criteria

- Symptoms related to esophageal dysfunction
- ≥1 biopsy showing eosinophil predominant inflammation
- ≥15 eos/hpf
- Mucosal Eosinophilia isolated to the esophagus
  - Persists after PPI trial
- Exclusion of other disorders associated with similar clinical, histological, or endoscopic features (mainly GERD)

PPI Trial

- Important to distinguish between EoE and PPI-REE
- Dellon et al 2013
  - 66 patients with ≥15 eos/hpf and dysphagia
    - 40 diagnosed with EoE
    - 24 diagnosed with PPI-REE
- Adequate Trial
  - Omeprazole 20 mg oral twice daily or equivalent for 8 weeks

Case

BH saw a physician based on your referral and states he has eosinophils in his esophagus. He has a prescription in hand for omeprazole and would like it filled.

- You are making a call to Dr. GI to make changes to the prescription. What change(s) would you like him to make?
  A. Strength
  B. Frequency
  C. Drug
  D. Quantity
  E. B and D

- When should BH follow-up with Dr. GI?
  A. 2 weeks
  B. 4 weeks
  C. 8 weeks

Guidelines

- AGA guidelines published in 2007
  - Updated in 2011
- ACG guidelines published February 2013
  - Recommendations
    - Strong: desirable effects outweigh undesirable effects
    - Conditional: trade-offs less certain
  - Quality of Evidence
    - High: further research unlikely to change confidence
    - Moderate: further research likely to change confidence
    - Low: further research very likely to change confidence
    - Very Low: estimate of the effect very uncertain

Treating EoE: Extinguishing the Fire

- AGA guidelines published in 2007
  - Updated in 2011
  - ACG guidelines published February 2013
  - Recommendations
    - Strong: desirable effects outweigh undesirable effects
    - Conditional: trade-offs less certain
  - Quality of Evidence
    - High: further research unlikely to change confidence
    - Moderate: further research likely to change confidence
    - Low: further research very likely to change confidence
    - Very Low: estimate of the effect very uncertain
Goals of Treatment

- Reduce esophageal eosinophilic inflammation
- Reduce Symptoms

Treatment Options

First Line:
- Pharmacologic
  - Evidence: high
- Dietary Therapy
  - Evidence: moderate

Second Line:
- Endoscopic Dilation

Pharmacological

- NO FDA-APPROVED MEDICATION
- Proton Pump Inhibitors-used for diagnostic exclusion
- Corticosteroids
  - Topical
  - Systemic
- Other therapies investigated

Fluticasone

Dose for Asthma
- Initial: 88-220 mcg BID; MAX: 880 mcg BID

Dose for EoE
- Adults: 880-1760 mcg/day in a divided dose
- Children: 88-440 mcg/day in a divided dose

Common Adverse Effects
- Throat irritation (3-22%), upper respiratory tract infection (14-21%), headache (14%), sinusitis (4-10%), candidiasis (<1-9%), bronchitis (8%), cough (1-6%)

Serious Adverse Effects
- Secondary hypocortisolism, anaphylaxis, glaucoma, pneumonia

Alexander 2012 Trial Characteristics

- Swallowed Fluticasone Improves Histologic but Not Symptomatic Response of Adults With Eosinophilic Esophagitis
- Design: Randomized, double-blind, placebo controlled
- Patients: Inclusion: Diagnosed with EoE at Mayo Clinic 2005-2009, age 18-65 years, symptomatic dysphagia, peak eosinophil ≥ 20 eos/hpf
- Intervention: 4 puffs BID of fluticasone 220 mcg/puff (n=21) OR placebo (n=21) for 6 weeks
- Primary Endpoint: Complete symptom response according to Mayo dysphagia questionnaire
- Secondary Endpoint: Partial symptom response, partial and complete histologic response, and EDN staining

Symptom Response

- Complete Response
  - Fluticasone: 42.9%
  - Placebo: 28.6%
  - p = 0.52

- Partial or Complete Response
  - Fluticasone: 57.1%
  - Placebo: 33.3%
  - p = 0.22
**Fluticasone**

- ACG guidelines
  - Recommendation: Strong
  - Evidence: High
- Counseling
  - **NO SPACER**
  - **HOLD BREATH, PUFF, THEN SWALLOW**
  - **NO FOOD OR DRINK FOR 30-60 MINUTES**

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**Budesonide**

**Dose for Asthma**
- Initial: 200-400 mcg BID; MAX: 800 mcg BID

**Dose for EoE**
- Adults: 2 mg/day, typically in a divided dose
- Children: 1 mg/day

**Common Adverse Effects**
- Respiratory tract infection (3-38%), sinusitis (3-16%), candidiasis (1.3-10%), arthralgia (6%), nausea (1.8-6%)

**Serious Adverse Effects**
- Cushing’s Syndrome, syncope, secondary hypocortisolism, immune hypersensitivity reaction, cataracts, glaucoma

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**Straumann 2010 Trial Characteristics**

| Budesonide Is Effective in Adolescent and Adult Patients With Active Eosinophilic Esophagitis |
|---|---|---|---|
| **Design** | Randomized, double-blind, placebo controlled |
| **Patients** | Inclusion: Age >14 years, with clinically, endoscopically, and histologically confirmed EoE; patients had dysphagia almost always occurring with intake of solids and ≥20 eos/hpf |
| **Intervention** | NEB 1 mg twice daily via (n=18) OR placebo (n=18) for 15 days |
| **Primary Endpoint** | Reduction in the esophageal eosinophil load |
| **Secondary Endpoint** | Reduction of EoE-associated symptoms, changes in EoE-relevant biomarkers in the esophagus and peripheral blood |

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**Histologic Response**

- **Histologic Response**
  - *p < 0.001

- **Safety**
  - **Side Effect**
    - **Fluticasone**
    - **Placebo**
    - **p-value**
  - **Sore throat**
    - 2/19 (11%)
    - 3/15 (20%)
    - 0.63
  - **Hoarseness**
    - 0
    - 3/15 (20%)
    - 0.08
  - **Esophageal candidiasis**
    - 5/19 (26%)
    - 0
    - 0.05

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**Histologic Response**

- **Baseline**
  - 68.2
  - 62.3
  - 56.5

- **Posttreatment**
  - 68.2
  - 62.3
  - 56.5

- *p < 0.0001
Extended Use Budesonide
- 28 patients previously brought into remission
  - Randomized to continue budesonide 250 mcg BID or receive placebo for 50 weeks
- All patients had ↑ in eosinophil count
  - Significantly higher ↑ in placebo group
- Symptom score ↑ in placebo group
- No adverse effects

Budesonide Formulation
- OVB vs. NEB

<table>
<thead>
<tr>
<th></th>
<th>Baseline eos count (max)</th>
<th>Post-treatment eos count (max)</th>
<th>Baseline eos count (mean)</th>
<th>Post-treatment eos count (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVB</td>
<td>83±89</td>
<td>11±23</td>
<td>20±24</td>
<td>3±7</td>
</tr>
<tr>
<td>NEB</td>
<td>101±85</td>
<td>89±194</td>
<td>23±20</td>
<td>31±37</td>
</tr>
<tr>
<td>p value</td>
<td>0.62</td>
<td>0.02</td>
<td>0.30</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Mucosal medication contact time was higher for the OVB group and inversely correlated to eosinophil count

Budesonide
- ACG guidelines
  - Recommendation: Strong
  - Evidence: High
- Counseling

- NO SPACER
- OVB: SWALLOW SLURRY
- NEB: SWALLOW ACCUMULATED LIQUID

- NO FOOD OR DRINK FOR 30-60 MINUTES

Case
BH sees Dr. GI after 8 weeks of PPI therapy. He reports no change in symptoms. Repeat endoscopy and biopsy show no histologic changes. BH is officially diagnosed with EoE and has a stricture present in his esophagus. Patient would like counseling on using his inhaled corticosteroid for topical use.

- What counseling would you provide if the patient received nebulized budesonide?
  A. Do not use a spacer, swallow the liquid
  B. No food or drink for 30 minutes following administration
  C. Rinse mouth after administration
  D. A and B
  E. All of the above
Prednisone

**Common Dose**  5-60 mg/day

**Dose for EoE**  Not specified

**Common Adverse Effects**  Hypertension, body fluid retention, impaired glucose tolerance, increased appetite, weight gain, osteoporosis, mood disturbance

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Schaefer 2008 Trial Characteristics

<table>
<thead>
<tr>
<th>Comparison of Oral Prednisone and Topical Fluticasone in the Treatment of Eosinophilic Esophagitis: A Randomized Trial in Children</th>
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</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
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<tr>
<td><strong>Patients</strong></td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td><strong>Primary Endpoint</strong></td>
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<tr>
<td><strong>Secondary Endpoint</strong></td>
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</tbody>
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**Histologic Response**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Histologic Grade Change ≥ 1</th>
<th>Histologic Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>93.8</td>
<td>81.3</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>94.4</td>
<td>50</td>
</tr>
</tbody>
</table>

*p = 0.04

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**Symptom Persistence/Recurrence**

<table>
<thead>
<tr>
<th>Patients with persistent/recurring symptoms (%)</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 18</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>2.8</td>
<td>1.6</td>
<td>21.7</td>
<td>44.4</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>45.8</td>
<td>21.7</td>
<td>35.7</td>
<td>45.8</td>
</tr>
</tbody>
</table>

*p = 0.34 | *p = 0.28 | *p = 0.28 | *p = 0.92

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**Safety**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Prednisone</th>
<th>Fluticasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperphagia, weight gain, and/or cushingoid features</td>
<td>16/40 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>0</td>
<td>6/40 (15%)</td>
</tr>
</tbody>
</table>

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**Prednisone**

- **ACG Guidelines:**
  - Recommendation: Conditional
  - Evidence: Low
- **Place in Therapy**
  - Reserved for patients in which topical corticosteroids are not effective
  - Need rapid improvement in symptoms
- **Counseling**
  - Immunosuppression
  - Adverse effects
  - Advise against sudden discontinuation
Addional Therapies Investigated

• Leukotriene Inhibitors (montelukast)
  — Case series of 12 adult patients
  • Symptomatic response but no histologic response
  — Study of 11 adult patients
  • Not effective for maintaining a steroid-induced remission
• Mast Cell Inhibitors (cromolyn sodium)
  — Case series in 14 children for 4 weeks
  • No symptomatic or histologic improvement

• Anti-IgE Antibody (omalizumab)
  — Case series with 2 patients
  • Not effective
• Immunomodulators (6-MP & azathioprine)
  — 3 case reports in steroid-dependent adults
  • Symptomatic and histologic remission
  • Not recommended due to potential side effects and little data

Case

After 2 years of topical corticosteroids, BH presents with a recurrence of his symptoms and endoscopic findings. Dr. GI does not want him to be on long-term prednisone due to risk of adverse effects. He would like your recommendation regarding other medications studied for EoE.

• What to tell Dr. GI about studied drugs?
  A. Omalizumab has been effective in case studies
  B. Montelukast is improve symptoms and histology findings
  C. Anti-Interleukin 5 agents decrease symptoms with no histologic improvement
  D. The guidelines do not recommend other agents because efficacy has not been established

Dietary Therapy

• Goal: Use diet for 4-8 weeks and then slowly reintroduce foods
• Dietary Management
  – Elemental Diet
  – Elimination Diet
    • 6 food Empiric Elimination Diet
    • Specific Food Elimination Diet
• Disadvantages: labor, cost, time-intensive

Elemental Diet

• Formula is made from amino acids and is free of milk and soy proteins
• Nutritionally complete
• Advantage: most effective in pediatric patients
• Disadvantages: expensive, may require feeding tube placement, impact quality of life, many adults find unpalatable
6 Food Empiric Elimination Diet

- Avoid milk, eggs, seafood, soy, legumes/peanuts, and wheat for 6 weeks
- Children: Effective but more patients respond to elemental diet
- Advantages: cost-effective, long-term management
- Disadvantage: vitamin and micronutrient deficiencies

Specific Food Elimination Diet

- Skin prick testing (SPT) and atopy patch testing (APT) to determine which food should be avoided
- Advantages: specific elimination
- Disadvantages: skin irritation, less effective compared to elemental diet and 6 food empiric elimination diet

Procedures

- Esophageal dilation may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy
- Can be used initially in patients with severely symptomatic esophageal stenosis
- Patients should be well informed of the risks

Endoscopic Dilation

- Improves dysphagia and increases esophageal diameter
- Dysphagia recurs after an average of 20-23 months
- No impact on eosinophil peak infiltration, eosinophil load, or EoE-associated histological signs
- Concerns: post-dilation chest pain, bleeding, mucosal tears, and perforations

Self-Dilation

- Used in resistant, benign esophageal strictures including EoE
- Successful in treating 90% of patients
- May cause increase in acid-reflux symptoms

Case

BH does not want to try any other medications.
- What are his options for therapy?
  A. Dilation/Self-Dilation
  B. Elimination Diet
  C. Specific Food Elimination Diet
  D. B & C
  E. All of the above
Emerging Therapies

- Improved steroid vehicles for topical delivery
- Novel anti-interleukin-5 and anti-interleukin-13
- Prostaglandin D2 inhibitors

Summary

- Common symptoms of EoE in adults include: food impaction, dysphagia, and regurgitation
- EoE is different from GERD and PPI-REE as EoE is nonresponsive to PPIs
- Goals of treatment include histologic and symptom improvement
- Patients taking inhaled topical corticosteroids should be counseled
- Patients may benefit from dietary therapy