Management of Eosinophilic Esophagitis

Management of EoE

- Why we are just scratching the surface with our current clinical assessment?
- Can diet therapy can be a practical alternative to steroids?
- Is there a role for maintenance therapy? (Can a puff a day keep the dilator away?)
Eosinophilic Esophagitis
A clinicopathologic diagnosis

• Clinically, EoE is characterized by symptoms related to esophageal dysfunction

• Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With few exceptions, 15 eos/hpf is considered a minimum threshold for the diagnosis of EoE

• The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded

Furuta et al Eosinophilic esophagitis in children and adults: A systematic review and consensus recommendations. Gastroenterology 2007

EoE is increasing over past 2 decades in both children and adults worldwide

Olmstead County, MN (peds/adults) Olten County, Switzerland

Hamilton County, OH (peds) Denmark

Deberosse J Allergy Clin Immunol 2010; Dellon Aliment Pharm Ther 2015
Etiology of Dysphagia
Retrospective Study 1371 Adults Undergoing EGD for dysphagia

Kidambi World J Gastro 2012
The 2 am “Wake up” Call!

EoE identified in 11-55% of adults with food impaction

Desai Furuta Gastrointest Endosc 2005;61:795
Gonsalves Sanger Zhang Hirano Am J Gastro 2006;101, S66
Kerlin Jones Remedios Campbell J Clin Gastro 2007;41:256
Byrne Peterson Fang Dig Dis Sci 2007; 52: 717
Sengupta Lembo Aliment Pharm Therap 2015; 42; 91

Eosinophilic Esophagitis
Clinical Features in Adults

- Male predominant ~70%
- Age at diagnosis: 35-40
- Atopy (asthma, allergic rhinitis, atopic dermatitis): ~70%
- Primary symptoms: dysphagia, food impaction
- Secondary symptoms: heartburn, chest pain
- Symptom duration prior to diagnosis: 5 years
**Classification and grading of endoscopically detected esophageal features in EoE**

**EoE Endoscopic Reference Score (EREFS)**

- **Edema** (pallor)
- **Rings** (“trachealization”)
- **Exudates** (plaques)
- **Furrows** (vertical lines)
- **Stricture**

- Mucosal fragility
- Narrow caliber esophagus

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**EREFS allows clinicians to “speak the same language” in describing findings and to track improvement with therapy**

### EoE Endoscopic Reference Score (EREFS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edema</strong> (loss vascular markings)</td>
<td><img src="image" alt="Grade 0" /></td>
<td><img src="image" alt="Grade 1" /></td>
<td><img src="image" alt="Grade 2" /></td>
<td><img src="image" alt="Grade 3" /></td>
</tr>
<tr>
<td>Grade 0: Distinct vascularity</td>
<td>Grade 1: Decreased or absent</td>
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</tbody>
</table>

| **Rings** (trachealization) | ![Grade 0](image) | ![Grade 1](image) | ![Grade 2](image) | ![Grade 3](image) |
| Grade 0: None | Grade 1: Mild (ridges) | Grade 2: Moderate (distinct rings) | Grade 3: Severe (not pass scope) |

| **Exudate** (white plaques) | ![Grade 0](image) | ![Grade 1](image) |
| Grade 0: None | Grade 1: Present |

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Limitations of current clinicopathologic assessment of disease activity in EoE

- **Symptoms**
  - Difficult to quantify and are often sporadic
  - May improve as result of changes in eating behavior, mastication, and food avoidance

- **Histology**
  - Limited correlation between degree of esophageal eosinophilia and clinical severity (Safroneeva Gastro 2016; Pentium JPGN 2009; Nicodeme CGH 2013; Martin JACI 2015)

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**Case:** 28 yo man with progressive dysphagia. Admission for esophageal tear post endoscopic food disimpaction

EGD on PPI with severe rings. Unable pass standard endoscope. 94 eos/hpf
Case: 28 yo man with progressive dysphagia. Admission for esophageal tear post endoscopic food disimpaction

EGD on PPI with severe rings. Unable pass standard endoscope. 94 eos/hpf

Post Fluticasone 880 mcg BID x 6 mos. 0 eos/hpf
Continued dysphagia.

Case: 28 yo man with progressive dysphagia. Admission for esophageal tear post endoscopic food disimpaction

EGD on PPI with severe rings. Unable pass standard endoscope. 94 eos/hpf

Post Fluticasone 880 mcg BID x 6 mos. 0 eos/hpf
Continued dysphagia. EGD scope not traverse.
Are we just scratching the surface?
*Do the effects of EoE extend beyond the mucosa?*

Esophageal Subepithelial Fibrosis
Demonstrated in majority of EoE patients

**Muscularis Propria**

Straumann et al., Gastroenterology 2003.
Chehade J Pediatric Gastro Nutr
Complications of EoE: 
*Narrow caliber esophagus*

Slide courtesy of Alain Schoepfer MD
Schoepfer AM, Safroneeva E, et al., Gastroenterology 2013;145(6):1230-6

Fibrostenotic Complications of Eosinophilic Esophagitis

Risk for stenosis over time

Slide courtesy of Alain Schoepfer MD
Schoepfer AM, Safroneeva E, et al., Gastroenterology 2013;145(6):1230-6
EoE Disease Activity: More than just counting eosinophils!

**Activity = Inflammation + Tissue Remodeling**

- Esophageal Eosinophilia
- Mucosa/submucosa/ muscularis expansion, Subepithelial fibrosis, Increased vascularity, Dysmotility


EoE: A Conceptual Model of Clinical Subtypes Based On Inflammation and Tissue Remodeling

Normal

EoE: A Conceptual Model of Clinical Subtypes
Based On Inflammation and Tissue Remodeling

EoE: A Conceptual Model of Clinical Subtypes Based On Inflammation and Tissue Remodeling

Normal

EoE Inflammation

EoE inflammation + Fibrosis

EoE Fibrosis

Management of EoE

- Why we are just scratching the surface with our current clinical assessment?
- Can diet therapy can be a practical alternative to steroids?
- Is there a role for maintenance therapy? (Can a puff a day keep the dilator away?)

Increasing Incidence of Eosinophilic Esophagitis: Hygiene Hypothesis?

Novel Therapeutic Options for EoE?
Topical steroids

- Swallowed - not inhaled
  - Fluticasone 440-880 mcg BID
  - Budesonide 0.5-2 mg BID
  - Ciclesonide (aerosolized) 80-160 mcg BID
- Liquid formulations are mixed with substance (sucralose, honey) to increase viscosity
- Patients instructed to fast for 30 minutes after administration
- Side effects: esophageal Candidasis (5-25%)

Randomized controlled trials of topical steroids with variable histologic response rates (50-90%)

<table>
<thead>
<tr>
<th>Fluticasone RCTs</th>
<th>Most stringent histologic outcome</th>
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<tbody>
<tr>
<td>Konikoff, 2006</td>
<td>≥ 1 eos/hpf</td>
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<tr>
<td>Alexander, 2012</td>
<td>&gt; 90% decrease in eosinophils</td>
</tr>
<tr>
<td>Butz, 2014</td>
<td>≥ 1 eos/hpf</td>
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</table>

<table>
<thead>
<tr>
<th>Budesonide RCTs</th>
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<tr>
<td>Dohil, 2010</td>
<td>≥ 6 eos/hpf</td>
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<tr>
<td>Straumann, 2010</td>
<td>&lt; 5 eos/hpf</td>
</tr>
<tr>
<td>Gupta, 2011</td>
<td>≤ 1 eos/hpf</td>
</tr>
<tr>
<td>Miehike, 2014</td>
<td>&lt; 16 eos/mm²</td>
</tr>
</tbody>
</table>

Histologic responders (%)
Diet Treatment:

Proof of concept regarding role of food allergens in pathogenesis of EoE

• **Elemental diet:** Amino acid, carbohydrate, lipid, vitamin/mineral based formula *(Kelly Sampson, Gastroenterology 1995)*

• **Directed elimination diet:** Exclusion of specific food allergens based on the results of allergy testing (skin prick & patch) *(Spergel, Liacouras, Ann Allergy Asthma Immunol 2005)*

• **Non-directed elimination diet:** Empiric exclusion of common food allergens *(Kagalwalla, Li, Clin Gastro Hep 2006)*

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Six Food Elimination Diet (SFED)

6 wk elimination (milk, soy, nuts, eggs, wheat, seafood/shellfish)

*Before Diet*  
*After Diet*

*Kagalwalla, Clin Gastro Hep 2006; Gonsalves, Gastroenterology 2012*
SFED: Not Just for Kids Anymore
73% response in children; 72% response in adults

Arias Diet Interventions for EoE: Systematic review and meta-analysis. Gastroenterology 2014

Endoscopic improvement with SFED

Pre Diet

Post Diet

Reintro

Patient 1

Patient 2

Patient 3
Six Food Elimination Diet (SFED) Protocol:  
*Induction-Reintroduction-Maintenance*

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**Baseline Diet**

- All table foods

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**Induction**

- Allowed table foods (e.g., fruit, vegetable, rice, chicken, beef, pork, beans, corn, quinoa, etc.)

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**Resolution with SFED diet**

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*Hirano Am J Gastro 2016; Doerfler Practical approach to implementing diet therapy in adults with EoE, Dis Esophagus 2015*
Six Food Elimination Diet (SFED) Protocol:
*Induction-Reintroduction-Maintenance*

**Induction**
- Resolution with SFED diet

**Reintroduction**
- Identification of specific food trigger(s) with serial monitoring of disease activity

**Maintenance**
- Avoidance of identified food trigger(s)

Allowed table foods (eg. fruit, vegetable, rice, chicken, beef, pork, beans, corn, quinoa et al)

- Fish
- Soy
- Egg
- Wheat
- Milk
- + Food trigger

Allowed table foods

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Diet therapy in EoE: PROS

- No medical therapies approved by US or European regulatory authorities for EoE
- Many patients would prefer a dietary alternative rather than chronic steroids
- Conceptual appeal of removing disease trigger rather than suppress inflammatory consequences
- Goal of diet therapy is the identification of specific food trigger(s), not elimination of all potential food groups.

Management of EoE

- Why we are just scratching the surface with our current clinical assessment?
- Can diet therapy can be a practical alternative to steroids?
- Is there a role for maintenance therapy?  
  *(Can a puff a day keep the dilator away?)*
Randomized, Double-Blind Placebo Controlled Maintenance Trial Budesonide

Initial induction with budesonide 1 mg BID
50 week follow up on budesonide 0.25 mg BID vs placebo

At week 50, 64% of budesonide vs 36% of placebo patients in symptomatic remission

Straumann Simon Clin Gastro Hepatology 2011
Maintenance Therapy for EoE

- Rationale and options for maintenance therapy should be discussed with all patients with EoE.
- Maintenance therapy should be strongly considered in the following patient subgroups:
  - Severe dysphagia or frequent food impactions
  - High grade esophageal stricture including narrow caliber esophagus
  - Rapid symptom or endoscopic progression after stopping initial therapy
  - Patients requiring repeated esophageal dilations
  - Patients with previous complication of disease (esophageal perforation, bleeding)
- Maintenance steroid therapy options include continued induction dose, reduced dose of topical steroids or on demand therapy.

Treat to target:

*My goals in the management of EoE patients (while awaiting more definitive endpoint studies)*

1. **Symptoms**: Resolution of dysphagia
2. **Pathology**: Improvement in eosinophilia (<15 eos/hpf)
3. **Endoscopy**: Improvement in inflammatory features (edema, furrows, exudate) and esophageal diameter ≥16 mm
**Suggested Algorithm for Management Of Eosinophilic Esophagitis**

**Suspected EoE**

Symptom relief & Normal histology → EGD with Bx → "PPI Responsive Esophageal Eosinophilia" (EoE vs GERD)

→ PPI x 8 wks

→ > 15 Eos/hpf

**EoE**

Topical steroid

Dietary therapy

**Persisting Symptoms and Pathology**

Elimination diet

↑ Dose topical Systemic steroid

Biologic therapy ?

EGD with Bx

Persistent dysphagia with stricture → Esophageal dilation → Consider Maintenance Therapy


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**EoE: Interdisciplinary Approach**

- **Gastroenterology**
  Nirmala Gonsalves MD, Ikuo Hirano MD, John Pandolfino MD, Peter Kahrilas MD, Christine Ebert BS, Rose Arrieta RN, Paulina Pacheco RN, Gwen Cassidy NP, Angelika Zalewski BS

- **Allergy & Immunology**
  Paul Bryce PhD, Bruce Bochner MD, Anne Ditto MD, Carol Saltoun MD, Anju Peters MD, Paul Greenberger MD, Robert Schleimer PhD

- **Pathology**
  Guang-Yu Yang MD, Sam Rao MD

- **Nutrition**
  Bethany Doerfler RD, Sally Ritz RD

- **Behavioral Medicine**
  Laurie Keefer PhD, Tiffany Taft PhD

- **Collaborators**
  TIGERS, Alex Straumann (Bern), Alain Schoepfer (Lucerne), David Katzka, Sami Achem (Mayo), Steve Ackerman (UIC), Glenn Furuta (Denver), Amir Kagalwalla & Barry Wershil MD (Lurie Childrens), Evan Dellon (UNC), Rothenberg MD, Pablo Abonia (Cincinnati Childrens)

- **Research Support:** CURED, Denise and David Bunning, NIH, FDA, ASGE, CEGiR

- **Medical students, residents, GI fellows**

- **Patients**
Management of EoE

- **Clinical features:**
  - Symptom intensity has limited correlation with histologic severity.
  - Disease complications related to sub-epithelial remodeling

- **Therapy:**
  - Elimination diet is an effective alternative to steroids for motivated patients.
  - Maintenance therapy seeks to suppress inflammation that leads to fibrostenosis

Increased steroid use is associated with lower risk of food impaction
Retrospective study of 265 adults with EoE

![Graph showing decreased food impaction with increased steroid use]
Epidemiology of EoE in US

Health insurance database 2009-11 of 11.5 million (ICD9): 57/100,000¹
Cloud-based database 2011-2014 of 9.5 million (“EoE”): 51/100,000²

Management of EoE

• **Epidemiology**: One of most common etiologies of dysphagia and food impaction. Prevalence 1/2000 in US

• **Clinical features**: Symptom intensity has limited correlation with histologic severity. Disease complications related to sub-epithelial remodeling

• **Therapy**: Elimination diet is an effective alternative to steroids for motivated patients. Maintenance therapy seeks to suppress inflammation that leads to fibrostenosis
## Epidemiology of EoE in US

*Health insurance database 2009-11 of 11.5 million (ICD9): 57/100,000*

*Cloud-based database 2011-2014 of 9.5 million ("EoE"): 51/100,000*  

![US Prevalence EoE: 1/2000 and rising](image)

1^Deillon Clin Gastro Hep 2014; 12 (4): 589;  
2^Maradey-Romero Fass Aliment Pharm Ther 2015; 41: 1016

## Emerging Pharmaceutical Therapies for EoE

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td><strong>TOPICAL STEROID</strong></td>
<td></td>
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<tr>
<td>Budesonide tablet</td>
<td>Falk</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>Budesonide liquid</td>
<td>Shire (Meritage)</td>
<td>Corticosteroid</td>
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<tr>
<td><strong>BIOLOGIC</strong></td>
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<td>Mepolizumab</td>
<td>Glaxo Smith Kline</td>
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<td>Cromolyn sodium</td>
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<td>Mast cell stabilizer</td>
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<td>CRTH2 antagonist</td>
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<td>Leukotriene receptor antag</td>
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<td>Losartan</td>
<td>Investigator initiated</td>
<td>ACE inhibitor</td>
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<tr>
<td>Sulcralfate</td>
<td>Investigator initiated</td>
<td>Mucosal protectant</td>
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*Updated from Kern Expert Opinion Emerging Drugs 2013*