First Two Decades of EoE

- Epidemiology: How EoE transitioned from esoterica to common conundrum
- Clinical features: Why we are just scratching the surface
- Pathogenesis: How EoE has transitioned from acid reflux to food allergy
- Therapy: Is diet therapy a practical alternative?

EoE: Emergence from esoterica

- Case reports of EoE in adults
- Initial series characterizing of EoE in adults
- Growing international recognition of EoE
- Esophageal Eosinophilia as biomarker of GERD
- Identification of EoE as diet responsive in children
- First international consensus recommendations on EoE
**Eosinophilic Esophagitis 2011**

EoE is a clinicopathologic disease

- 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, specifically PPI responsive esophageal eosinophilia


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**Prevalence of Eosinophilic Esophagitis in Children and Adults**

Prevalence per 100,000

Epidemiology of EoE in US

Health insurance database 2009-11 of 11.5 million; Prevalence based on ICD9 (530.13) 57/100,000


Noel, Rothenberg N Engl J Med 351;9 2005; 940-1

Straumann J Allergy Clin Immunol. 115(2) 2005. 418-19
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

Symptoms are an inadequate measure of disease activity
Symptoms measured by a validated, disease specific patient reported outcome instrument (EEsAI) only modestly detected histologic remission

ROC Curves for EEsAI in detection of histologic remission

Esophageal Subepithelial Fibrosis
Demonstrated in majority of EoE patients

References:
- Straumann et al., Gastroenterology 2003.
- Aceves J Allergy Clin Immunol 2007
- Chehade J Pediatr Gastro Nutr
- Lucendo J Allergy Clin Immunol 2011
Esophageal subepithelial fibrosis in most adult and pediatric EoE patients

Complications of EoE: Narrow caliber esophagus

Fibrostenotic Complications of Eosinophilic Esophagitis

Slide courtesy of Alain Schoepfer MD
EoE Disease Activity: More than just counting eosinophils!

Activity = Inflammation + Tissue Remodeling

Methods to detect remodeling consequences of EoE

- Endoscopy
- Upper GI radiologic examination
- Esophageal manometry
- Endoscopic ultrasonography (EUS)
- Pathology - subepithelial fibrosis
- Biomarkers of fibrogenesis and remodeling (EMT, TGF B, MBP etc)
- Functional luminal imaging (FLIP)

EoE Endoscopic Reference Score (EREFS)

<table>
<thead>
<tr>
<th>Edema (loss vascular markings)</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0: Distinct vascularity</td>
<td></td>
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<tr>
<td>Grade 1: Decreased</td>
<td></td>
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</tr>
<tr>
<td>Grade 2: Absent</td>
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</tbody>
</table>

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

| Exudate (white plaques)        |         |         |         |         |
| Grade 0: None                  |         |         |         |         |
| Grade 1: Mild (>10% surface area) |     |         |         |         |
| Grade 2: Severe (>10% surface area) |   |         |         |         |

| Furrows (vertical lines)       |         |         |         |         |
| Grade 0: None                  |         |         |         |         |
| Grade 1: Mild                  |         |         |         |         |
| Grade 2: Severe (depth)        |         |         |         |         |

| Stricture                      |         |         |         |         |
| Grade 0: Absent                |         |         |         |         |
| Grade 1: Present               |         |         |         |         |
| Grade 2: Present               |         |         |         |         |

Hirano Gut. 2013
**FLIP in EoE: Esophageal Distensibility**

*33 patients with EoE; 15 controls*

Data shown as medians.

![Graph showing Narrowest CSA vs. Intra-bag pressure](image)

**FLIP parameters associated with clinically significant outcomes**

EoE patients with food impaction (confirmed by endoscopy) had significantly lower distensibility

![Graph showing Narrowest CSA vs. Intra-bag pressure](image)

**GERD vs EoE**

*How hard can it be?*

<table>
<thead>
<tr>
<th>GERD</th>
<th>EoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Sx</td>
<td>Heartburn</td>
</tr>
<tr>
<td>Food impaction</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gender</td>
<td>Normal</td>
</tr>
<tr>
<td>Atopic history</td>
<td>NERD</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Erosions</td>
</tr>
<tr>
<td></td>
<td>Barrett's</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>&lt;7 Eos/hpf</td>
</tr>
<tr>
<td>1st Treatment</td>
<td>Antacid, H2RA, PPI</td>
</tr>
</tbody>
</table>

![Images of GERD and EoE endoscopy](image)
PPI Responsive Esophageal Eosinophilia
Prospective Study, 712 adults with EGD;
35 pts with > 15 eos/hpf; Rabeprazole 20 mg BID x 2 mos;
PPI response (< 5 eos/hpf) in 50% with EoE profile

Problems with utilization of PPI response in the diagnosis of EoE
1. Conceptual concern of using a response to therapy to define a disease
2. Entails costly repeat endoscopy with biopsy to establish the diagnosis of EoE
3. Clinical, endoscopic, histologic and genetic features cannot distinguish PPIREE from EoE
4. **PPI response does not rule in GERD**
5. **PPI response does not rule out EoE**

Why patients with suspected EoE should be given a course of PPI therapy
1. It works. Reduces symptoms and esophageal eosinophilia in 25-50% of patients
2. PPIs are safe
3. pH testing is cumbersome and subject to significant false positive and negative results
4. Experimental evidence that GERD may contribute to allergic inflammation in EoE (Paterson Am J Physiol 1998; Rhijn CGH 2014; Sherril Mucosal Immunol 2013)
5. PPIs may have anti-inflammatory properties beyond acid suppression (Cheng,Souza Gut 2013)
Is EoE Allergic?
Is EoE “Asthma of the Esophagus?”

1. High prevalence of atopic disorders in EoE
2. Seasonal variation in EoE incidence
3. Murine model of EoE demonstrating esophageal eosinophilia with allergen exposure
4. Esophageal expression of allergic type inflammation and cell mediators in EoE
5. Genetic studies identifying allergic mechanisms in EoE
6. Effectiveness of dietary allergen removal in treating EoE
7. Therapeutic response of EoE to steroids and anti-IL5/anti-IL13

Gene Expression Profile of Esophageal Tissue by Microarray

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Candidate Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5p22</td>
<td>TSLP</td>
<td>Cytokine linked to asthma, atopic dermatitis</td>
</tr>
<tr>
<td>2p23</td>
<td>CAPN14</td>
<td>Protease expressed in esophageal epithelia; induced by IL-13</td>
</tr>
<tr>
<td>8q23</td>
<td>X0RE</td>
<td>?</td>
</tr>
<tr>
<td>15q13</td>
<td>Gene desert</td>
<td>?</td>
</tr>
</tbody>
</table>

EoE patients have a unique gene expression profile
Blanchard, et al; J Clin Invest 2006;116(2) 536-537

Putative gene associations in EoE
Elemental diet in EoE

**Overall 91% histologic remission rate; 429 patients**

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

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**EoE Pathogenesis**

**Mucosal Response**

Allergen Challenge → Active EoE

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**Topical steroids significantly improve histopathology in EoE: Meta-analysis**

Sawas et al Aliment Pharm Ther 2015
Symptom relief with topical steroids in EoE is variable: Meta-analysis

<table>
<thead>
<tr>
<th>Study and subgroup</th>
<th>Topical steroids</th>
<th>Control</th>
<th>Skin side</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.2 Topical steroid vs. placebo</td>
<td></td>
<td></td>
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<tr>
<td>Kardakov MR 2006</td>
<td>12</td>
<td>11</td>
<td>23</td>
<td>1.84</td>
<td>0.37, 9.36</td>
<td>2006</td>
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<tr>
<td>Kadi 2010</td>
<td>15</td>
<td>14</td>
<td>29</td>
<td>1.82</td>
<td>0.35, 9.02</td>
<td>2010</td>
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<tr>
<td>Kadi 2012</td>
<td>15</td>
<td>14</td>
<td>29</td>
<td>1.70</td>
<td>0.33, 9.18</td>
<td>2010</td>
</tr>
<tr>
<td>Alexander 2012</td>
<td>12</td>
<td>11</td>
<td>23</td>
<td>1.77</td>
<td>0.37, 9.36</td>
<td>2012</td>
</tr>
<tr>
<td>Altay 2014</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td>1.93</td>
<td>0.38, 9.65</td>
<td>2014</td>
</tr>
<tr>
<td>Spain 2016</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td>1.79</td>
<td>0.38, 9.65</td>
<td>2016</td>
</tr>
<tr>
<td>Spain 2017</td>
<td>102</td>
<td>89</td>
<td>191</td>
<td>1.77</td>
<td>0.37, 9.36</td>
<td>2017</td>
</tr>
<tr>
<td>P= NS; I²= 63%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z= 1.78 (P=0.08)</td>
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</tbody>
</table>

Eosinophilic Esophagitis: Dietary Treatment

- **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, Liacostras Ann Allergy Asthma Immunol 2003)

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

**Six Food Elimination Diet (SFED)**

Six week elimination of milk, wheat, soy, egg, nuts, seafood

Prospective studies in adults with EoE

**US Study** (Gonsalves 2012)
- 50 EoE adults
  - 74% histologic response (<15 eos/hpf)
  - 15% more than 1 food trigger
  - Skin prick testing (SPT) sensitivity 33%

**Spain Study** (Lucendo 2013)
- 67 EoE adults
  - Elimination of SFED + rice/legumes/com)
  - 73% histologic response (<15 eos/hpf)
  - 64% more than 1 food trigger
  - Skin prick testing (SPT) sensitivity 23%
  - Sustained response at 2 years in 15 patients

Induction
Reintroduction
Maintenance

Resolution of SFED diet
Identification of specific food trigger(s) with serial monitoring of disease activity
Avoidance of identified food trigger(s)

SFED

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

Allowed table foods
+ fish
+ nuts
+ soy
+ egg
+ wheat
+ milk

Office based testing for EoE Activity
- Esophageal string test
  (Furuta Ackerman Gut 2012)
- Cytosponge
  (Katzka Clin Gastro Hep 2015)
- Brush cytology
  (Kern Dis Esophagusa 2016)
- Mucosal impedance
  (van Rhijn Clin Gastro Hep 2014; Aaes Vaazl Gastro 2015)
- Transnasal endoscopy
  (Philpott J Gastro Hepatol 2016; Friedlander Gastroint Endosc 2016)

Emerging Pharmaceutical Therapies for EoE

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPICAL STEROID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide tablet</td>
<td>Falk</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>Budesonide liquid</td>
<td>Shire (Mentage)</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>BIOLOGIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Glaxo Smith Kline</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Teva</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Novartis</td>
<td>Anti-IgE</td>
</tr>
<tr>
<td>QAXISi76</td>
<td>Novartis</td>
<td>Anti-IL-13</td>
</tr>
<tr>
<td>RPC4046</td>
<td>Regeneron</td>
<td>Anti-IL-4/IL-13</td>
</tr>
<tr>
<td>MisCELLANEOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>Investigator initiated</td>
<td>Mast cell stabilizer</td>
</tr>
<tr>
<td>OCS00459</td>
<td>Oxyjen</td>
<td>CRTH2 antagonist</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Merck</td>
<td>Leukotriene receptor antag</td>
</tr>
<tr>
<td>Lomalizumab</td>
<td>Investigator initiated</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Sulcratefate</td>
<td>Investigator initiated</td>
<td>Mucosal protectant</td>
</tr>
</tbody>
</table>
EoE: Interdisciplinary Approach

- **Gastroenterology**
  - Nimai Santos MD, Bao Hirano MD, John Pandolfino MD, Peter Kahrilas MD, Christine Ebert BS, Rose Arrieta RN, Paulina Pazeco RN, Gwen Cassidy NP, Angelika Zalewski BS
- **Allergy & Immunology**
  - Paul Bryce PhD, Bruce Bochner MD, Anna 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**
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- **Research Support**: CURED, Denise and David Bunning, NIH, FDA, ASGE
- **Medical students, residents, GI fellows**
- **Patients**