Eosinophilic Esophagitis: From Acid to Allergy

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Eosinophilic Esophagitis (EoE)

- What is EoE?
- What are the clinical features of EoE?
- Is EoE “Asthma of the esophagus”
- What are the complications of EoE?
- What is the best treatment for 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 a diagnosis of EoE
- The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically PPI-responsive esophageal eosinophilia
- The disease should remit with treatments of dietary exclusion, topical corticosteroids, or both
- EoE should be diagnosed by clinicians, taking into consideration all clinical and pathologic information; neither of these parameters should be interpreted in isolation

Historical Notes

1970
3 case reports of EoE in adults

1980
EoE=GERD
Winter 1982, Brown 1984

1990
2 case series of EoE in adults
Attwood 1993, Straumann 1994

1995
EoE as food allergy
Kelly Sampson 1995

2000
New Diagnoses of Eosinophilic Esophagitis Increasing in Both Children and Adults

Gonzalvez Pili, capio, Zhao Rui Hirano, Gastrin and Endoscopy, 2006
Prevalence of Eosinophilic Esophagitis in Children and Adults

Prevalence EoE:
- 4.3/10,000 Olten County, Switzerland (2009)
- 5.5/10,000 Olmsted County, MN
- 10.4/10,000 Hamilton County, Ohio (Peds)

Clinical Features in Adults

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>37 (14-81)</td>
</tr>
<tr>
<td>Male</td>
<td>72%</td>
</tr>
<tr>
<td>Mean Duration</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Atopic History</td>
<td>74%</td>
</tr>
<tr>
<td>Food Allergy History</td>
<td>19%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>82%</td>
</tr>
<tr>
<td>Frequency</td>
<td>1x/week</td>
</tr>
<tr>
<td>Food Impaction</td>
<td>76%</td>
</tr>
<tr>
<td>Heartburn</td>
<td>29%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8%</td>
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Etiology of Dysphagia

Retrospective Study 1371 Adults Undergoing EGD for Dysphagia

Presentation of EoE in Children is Distinct from Adults

Histology in EoE:
* Increased Esophageal Eosinophils (>15 Eos/hpf)

Histology in EoE
* EoE is a patchy disease
Differential Diagnosis for Esophageal Eosinophilic Infiltration (EEI ≠ EoE)

- Eosinophilic esophagitis
- Gastroesophageal reflux disease
- Eosinophilic gastroenteritis
- Crohn’s disease
- Achalasia
- Hypereosinophilic syndrome
- Infectious esophagitis
- Drug hypersensitivity
- Neoplasia
- Immunosuppression
- Pemphigoid vegetans

Classification and grading of endoscopically detected esophageal features in EoE

**EoE Endoscopic Reference Score (EREFS)**

- **Exudates** (plaques)
- **Rings** (“trachealization”)
- **Edema** (pallor)
- **Furrows** (vertical lines)
- **Stricture**
- Mucosal fragility
- Narrow caliber esophagus

**Exudates (Also referred to as white exudates, plaques or punctate white spots)**

Mild (Grade 1): White lesions involving < 10% of the surface area of the esophagus

Severe (Grade 2): White lesions involving ≥ 10% of the surface area of the esophagus

**Rings (Also referred to as esophageal rings, corrugated esophagus or trachealization)**

Mild (Grade 1): Subtle circumferential ridges seen on esophageal distension

Moderate (Grade 2): Distinct rings that do not occlude passage of diagnostic (8-10 mm) endoscope

Severe (Grade 3): Distinct rings that do not permit passage of diagnostic (8-10 mm) endoscope

Number of Biopsies to Diagnose EoE in Adults

- Bx 1
- Bx 2
- Bx 3
- Bx 4
- Bx 5

≥15 eos/hpf

% Positive Diagnosis
EoE Reference Score for Endoscopic Abnormalities (EoE-EREFs)

**Edema** (Also referred to as decreased vascular markings, pallor or edema)

- Normal (Grade 0): Distinct vascular markings
- Decreased (Grade 1): Loss of clarity or absence of vascular markings
- Severe (Grade 2): Edema

**Furrows** (Also referred to as vertical lines or longitudinal furrowing)

- Mild (Grade 1): Vertical lines without visible depth (indentation of the esophageal mucosa)
- Severe (Grade 2): Vertical lines with clear depth (indentation of the esophageal mucosa)

**Stricture** (Estimate luminal diameter)

- Allows for uniform characterization of esophageal abnormalities that are present in most EoE patients
- Facilitates comparisons of endoscopic severity amongst clinicians and investigators
- Complements assessment of therapeutic outcomes in EoE that is currently based on symptoms and pathology
- Provides important information regarding fibrostenosis that is a major determinant of symptoms in EoE

**Eosinophilic Esophagitis (EoE)**

- Is EoE an emerging entity or misdiagnosed malady?
- What are the clinical features of EoE?
- Is EoE “asthma of the esophagus”?
- What are the complications of EoE?
- What is the best treatment for EoE: dilation, drugs or diet?

**Is EoE Allergic?**

*Is EoE “Asthma of the Esophagus”?

1. High prevalence of atopic disorders in adults with EoE
2. Murine model of EoE demonstrating esophageal eosinophilia with allergen exposure (Mishra Hogan Brandt Rothenberg J Clin Invest 2001)
3. Evidence of allergic type inflammation and cell mediators in EoE
4. Effectiveness of dietary allergen removal in treating EoE
Elemental Diet in Pediatric EoE

- 10 pediatric pts with GERD symptoms and esophageal eosinophils
  - Unresponsive to antireflux medications
  - 6 with fundoplication
- After elemental diet:
  - Symptom resolution in 8 patients, improvement in 2
- Symptoms returned when food reintroduced
- Conclusion
  - EoE is an allergic phenomenon

Kelly Sampson Gastroenterology 1995

Elemental Diet in Pediatric EoE

Liacouras (n=164)
95% (160/164) Clinical Improvement
39 → 1 Eos/hpf p < 0.001

Kagalwalla (n=25)
100% (25/25) Clinical Improvement
59 → 4 p < 0.001

Rothenberg Spergel Hakaonarson Nature Genetics 2010

Genome-wide association study identified association of EoE with variants at chromosome 5q22 encompassing the gene for TSLP (Thymic stromal lymphopoetin: cytokine linked to asthma and atopic dermatitis)

Rothenberg Gastroenterology 2009

EoE Pathogenesis

Allergen initiation in genetically susceptible individuals
- Inflammatory cascade involving increased IL-5, IL-13, IgE, and Eotaxin-3 expression
- Squamous epithelium, mast cells, Dendritic cells, lymphocytes as well as eosinophils
- Acid as a potential cofactor

Why the Increase in Food Allergy?

- Hygiene hypothesis
- Vitamin D hypothesis
- Allergen exposure to infants or mothers
- Non ingested routes of sensitization
  - (eg Skin products containing food allergens)
- Bacterial flora
- Environmental toxins or food additives
- Epithelial barrier dysfunction
- Gastroesophageal reflux disease
- Proton pump inhibitor therapy

Increasing Incidence of Eosinophilic Esophagitis: Hygiene Hypothesis?

Complications of EoE in Adults

- Impaired quality of life
- Food impaction
- Esophageal stricture
- Esophageal perforation
- Malnutrition

- No reports of progression to cancer or eosinophilic gastroenteritis

Quality of Life in Eosinophilic Esophagitis: Common Themes

- Concern of Medications for Life
- Concern of Disease Progression
- Fear or Panic During Dysphagia
- Embarrassment or Social Distress
- Changes in Eating Habits

Complications of EoE:

Esophageal Stricture

Narrow caliber esophagus

Management of Food Impaction in EoE

- Diagnosis of EoE should be considered in all patients presenting with food impaction
- Awareness of the risk of esophageal perforation in food impaction in EoE
- No guidelines exist regarding the technique of food disimpaction in EoE
- Reports of esophageal perforation using rigid endoscopy
- When using push technique for proximal foreign body, appreciation for possible long strictures in EoE
- Caution with overtube placement given predilection for proximal strictures (Overtube diameter 19-20 mm)
- Esophageal biopsy following food disimpaction
Complications of EoE:
*Increased risk of esophageal perforation*

- Eosinophilic infiltration
  - Hyperplasia of Squamous Cell Epithelium
  - Subepithelial fibrosis
- Loss of elasticity - Low compliance
- Increase risk for tearing

Esophageal Subepithelial Fibrosis
Demonstrated in 90% of EoE patients

Treatment Options for EoE
- **Medical Therapy**
  - Topical steroids*
  - Systemic steroids
  - Leukotriene antagonists
  - Mast cell stabilizers
  - Immunomodulators (6MP, Azathioprine)
  - Biologics (anti IL5, anti IL13*, anti TNF, anti IgE)
- **Dietary Therapy**
  - Empiric elimination diet*
  - Allergy testing directed elimination diet
  - Elemental diet*
- **Endoscopic Therapy**  *Clinical trials at Northwestern

Esophageal Dilation:
*First Effective Therapy for Adult EoE*

- Retrospective studies reported relief of dysphagia for over a year in most patients following esophageal dilation

Esophageal Dilation in EoE:
*High risk of Esophageal Complications*

- 8 cases; 3 dilations
  - 1 perforation with EGD
- 5 dilations
  - 5 large lacerations with EGD or dilation
- 1 dilation
  - 1 perforation
- 6 dilations
  - 3 perforations

Esophageal Dilation in EoE:
*Low risk of Esophageal Complications*

- 674 dilations
  - 0 perforations
- 70 dilations
  - 0 perforations
- 15 dilations
  - 0 perforations
- 293 dilations
  - 3 perforations
Esophageal Dilation as Primary Therapy in EoE

- Retrospective study of 474 dilations in 207 adults with EoE
- 63 patients treated with dilation alone
- Post dilation, 93% of patients reported slight or no dysphagia
- Esophageal diameter increased from 11 mm pre to 16 mm post dilation
- 3 mm incremental dilation per session; median 2 sessions per patient (range 1-13)
- Median duration symptom improvement: 15 months


Esophageal Dilation in EoE: Effectiveness
Retrospective Analysis of 474 dilations in 207 patients

93% of patients reported slight or no dysphagia following esophageal dilation


Esophageal Dilation in EoE: Chest Pain
Retrospective Analysis of 474 dilations in 207 patients

38% of patients experienced moderate to severe post dilation pain lasting less than 4 days in most

Esophageal Dilation in EoE:
Dilation in EoE has a high degree of patient acceptance based on patient survey (n=42)

100 % of surveyed patients were agreeable to having a repeat esophageal dilation for EoE

Esophageal Dilation Does Not Affect the Underlying Esophageal Inflammatory Process
Dilation without anti-eosinophil therapy

Esophageal Dilation in EoE: To Do or Not to Do

<table>
<thead>
<tr>
<th>Not to Do</th>
<th>To Do</th>
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<tr>
<td>No influence on underlying inflammation</td>
<td>Provides long lasting relief of dysphagia</td>
</tr>
<tr>
<td>Significant risk of mucosal laceration with associated chest pain</td>
<td>Pain is transient. Dilation has high patient acceptance</td>
</tr>
<tr>
<td>Risk of esophageal perforation</td>
<td>Risk is low. All perforations reported have been partial ruptures</td>
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Topical steroids

- Swallowed not inhaled
  - Fluticasone 220ug 2-4 puffs BID
  - Budesonide 0.5-1 mg BID
- Instruction to rinse & gargle with water after administration

"Esophageal dilation with or without concomitant medical or dietary therapy can provide relief of dysphagia in selected patients with EoE. In the absence of high-grade esophageal stenosis, a trial of medical or dietary therapy before esophageal dilation is reasonable."

EoE Updated Consensus Recommendations. J Allergy Clin Immunol 2011
Randomized, Double-Blind Placebo Controlled Trials Budesonide

36 Adults with EoE: Placebo or budesonide 1 mg BID x 15 days
24 Children with EoE: Placebo or budesonide 0.5-1 mg BID x 3 months

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). (Spiegel, Liacouras Ann Allergy Asthma Immunol 2005)
- **Non-directed elimination diet:** Empiric exclusion of common food allergens. (Kagalwalla, Li Clin Gastro Hep 2006)

Summary: Steroids in EoE

- Improve symptoms, esophageal eosinophilia and endoscopic features in majority of pediatric and adult patients
- Symptom recurrence in 90% after withdrawal
- Topical steroids (fluticasone or budesonide) are better tolerated than systemic steroids
  - Esophageal candidiasis is uncommon and seldom clinically significant. Other long term side effects (osteoporosis, ocular effects, adrenal insufficiency) have not been well evaluated for swallowed topical steroids
- Optimal duration of therapy and role of maintenance being studied

Effect of SFED on Esophageal Eosinophilia

70% achieved histologic response defined by < 10 eos/hpf
64% achieved histologic response defined by < 5 eos/hpf

Effect of SFED on Dysphagia Score

* P <0.01

Six Food Elimination Diet (SFED)
**Prospective Study in Adults (n=50)**
6 wk elimination (milk, soy, nuts, eggs, wheat, seafood/shellfish)
Effect of Reintroduction of Foods on Esophageal Eosinophilia

Summary: Dietary Therapy in EoE
- Improve symptoms, esophageal eosinophilia and endoscopic features in most pediatric and adult patients
- Selective elimination diets are better tolerated than elemental diets that often require gastric tube feeding
- Requires close supervision by dietician and multiple follow up endoscopies
- Role allergy testing, optimal duration of therapy and method of food reintroduction being studied

Suggested Algorithm for Management Of Eosinophilic Esophagitis

EoE: Interdisciplinary Approach
- Gastroenterology: Nirmala Gonsalves MD, Ikuo Hirano MD, Peter Kahrilas MD, John Pandolfino MD, Christine Ebert BS, Patty Samar RN, Martha Vega RN, Angelika Zalewski
- Allergy & Immunology: Paul Bryce PhD, 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: TIGERS, Alex Straumann MD (Bern), Alain Schoepfer MD (Lucerne), Sami Achem MD (Mayo), Steve Ackerman PhD (UIC), Glenn Furuta (Denver), Amir Kagalwalla MD & Barry Warshil MD (Childrens Memorial)
- Research Support: CURED, Denise and David Bunning, NIH
- Medical students, residents, GI fellows
- Patients

Eosinophilic Esophagitis (EoE)
- What is EoE?
  A chronic, immune/antigen driven esophageal disease.
  Clinicopathologic diagnosis: EEI ≠ EoE
- What are the clinical features of EoE?
  Dysphagia esp. in younger males with h/o atopy
- Is EoE “asthma of the esophagus”?
  Similarities in epidemiology, mechanisms and therapies
- What are the complications of EoE?
  Impaired quality of life; food impaction; esophageal stricture
- What is the best treatment for EoE?
  Dilation, topical steroids and elimination diet effective