Faculty Disclosure for
Seema Aceves, MD, PhD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from: None
Consulted for: None
Held common stock in: Meritage Pharma (no income)
Research, clinical trial, or drug study funds received from: None

I will be discussing products that are investigational or not labeled for the use under discussion.
The Emergence of EoE
Normal: 0 eosinophils
GERD: 0-7 eos
Baseline eosinophilia
EoE Emergence

Dobbins et al, 1977
Eosinophilic gastroenteritis
Esophageal involvement

Landres et al, 1978
Achalasia
Smooth Muscle Hypertrophy
Eosinophilic Esophageal Infiltration

Picus and Frank, 1981
16 yo male
Dysphagia
Peripheral Eosinophilia
Esophageal Eosinophilia
Stricture

Lee et al, 1985
11 patients
Dysphagia
Stricture
Asthma
Peripheral Eosinophilia

Vitellas et al, 1993
13 Males
Esophageal eosinophilia
Dysphagia (92%)
Strictures (77%)
Peripheral eosinophilia (92%)

1977 to 1993
EoE Emergence

Atwood et al, 1993
Normal pH probe
Eos/hpf: 56

Kelly et al, 1995
23 Children
No response to PPI
17 weeks elemental formula
Or 3 weeks corticosteroids
Resolution of esophageal eosinophilia

Orenstein et al, 2000
30 Children
81% Male
14% Food Impaction
Eos/hpf: >45 distal and proximal

1993 to 2000
Differential Diagnosis

- Gastroesophageal Reflux Disease
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis with esophageal involvement
- PPI Responsive Esophageal Eosinophilia
- Hypereosinophilic syndrome
- Parasitic infection
- Drug allergy
- Connective tissue disorder (scleroderma)
- Celiac Disease with esophageal eosinophilia
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

Conceptual definition

Eosinophilic esophagitis represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

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Diagnostic guideline

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 eosinophils/hpf (peak value) 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,
Symptoms and Clinical Features
Symptoms in Children

- Feeding Disorder: 13%
- Vomiting: 26%
- Abdominal Pain: 26%
- Dysphagia: 27%
- Food Impaction: 7%

Noel et al, NEJM 2004
Symptoms in Adults

Kwiatek et al, Gastro 2009
# Symptom Score Components

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Not at all</th>
<th>Mild: No interference with daily activities, Meds as needed</th>
<th>Severe: Regularly interferes with daily activities or requires daily meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your child ever have burning in the chest?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your child ever feel food coming back up into his/her throat?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your child complain about stomach pains?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is your child often irritable for no apparent reason?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often does your child complain about feeling like throwing up?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often does your child eat too little or get full before finishing his/her meal?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often does your child wake up during the night from belly pain?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often has your child noticed blood in his/her stool in the last 3 months?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your child have difficulty swallowing?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Normal
- Allergy NonEE
- GERD
- EE

Aceves et al, Ann of Allergy 2009
Endoscopic Features
## Inflammation and Clinical Features

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Endoscopy</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial:</strong>&lt;br&gt;Average Epithelial Score&lt;br&gt;Prox+Mid+Distal</td>
<td>Thickened/Furrows $r=0.82^<em>$&lt;br&gt;White Plaques, $r=0.64^</em>$&lt;br&gt;Pallor $r=0.62^*$</td>
<td>Dysphagia + Anorexia/Early Satiety $r=0.32^*$</td>
</tr>
<tr>
<td><img src="image1.png" alt="Epithelial Image" /></td>
<td><img src="image2.png" alt="Endoscopy Images" /></td>
<td></td>
</tr>
<tr>
<td><strong>Lamina Propria:</strong>&lt;br&gt;Fibrosis + Eosinophils</td>
<td>Thickened/Furrows $r=0.64^*$</td>
<td>Dysphagia $r=0.45^*$</td>
</tr>
<tr>
<td><img src="image3.png" alt="Lamina Propria Image" /></td>
<td><img src="image4.png" alt="Endoscopy Images" /></td>
<td></td>
</tr>
</tbody>
</table>

$p<0.05$

Aceves et al, Annals of All Immunol 2009
Histologic Features

>15 eosinophils per hpf
Eosinophil Degranulation
Basal Zone Hyperplasia
Dilated Intercellular Spaces
Histologic Features

Liacouras et al, 2011 Updated Consensus Recommendations, JACI
Diagnostic Threshold

Shah et al, Am J Gastro 2009
### High Rates of Atopy

<table>
<thead>
<tr>
<th>Author/population</th>
<th>Number of patients with EoE</th>
<th>Asthma</th>
<th>Allergic Rhinitis</th>
<th>Atopic Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy in the General Population</td>
<td></td>
<td>8.5%</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Spergel, et al; Philadelphia</td>
<td>620</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
</tr>
<tr>
<td>Assa’ad, et al; Cincinnati</td>
<td>89</td>
<td>39%</td>
<td>30%</td>
<td>19%</td>
</tr>
<tr>
<td>Sugnanam, et al; Australia</td>
<td>45</td>
<td>66%</td>
<td>93%</td>
<td>55%</td>
</tr>
<tr>
<td>Guajardo, et al; World wide registry</td>
<td>39</td>
<td>38%</td>
<td>64%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Triggers for Eosinophilia

Aero-Allergens
Food Allergens
Aerollergens and EoE: Causal Link

- Instillation of:
  - Intranasal Aspergillus
  - Intranasal HDM
  - Intranasal Cockroach
  - Drives Murine EoE

Mishra et al., J Clin Invest 2001
Rayapaudi et al, J Leuko Biol 2010
Pollens and EoE

Fogg et al, JACI 2003
Triggers: Foods
Common Foods Causing EoE

Kagalwalla et al, JPGN 2011

Wheat: 60%
Milk: 50%

Gonsalves et al, Gastroenterology 2012
Recruiting Eosinophils
Eotaxin-3 Mediated Chemotaxis

53-fold increase in Eotaxin-3 gene expression in EoE versus GERD pediatric patients

IL-5: Eosinophilopoeisis and Recruitment

- EoE patients have Increased IL-5
- IL-5 Deficient Mice are Protected from EoE
- IL-5 miniosmotic pump promotes murine EoE

Straumann et al, JACI 2001
Mishra et al, 2008
- Instilling IL-13 Causes Murine EE
- Resolved with anti-IL-13 Antibody

- IL-13 treatment promotes EoE transcriptome
- IL-13 induces the Eotaxin-3 promoter

Mishra & Rothenberg, Gastroenterology 2003
Blanchard et al, Clin Exp Allergy 2005
T Cells

- Increased CD3+
- Increased CD8+
- Murine EoE induction relies on T cells

Lucendo et al, 2007
Mishra et al, 2007
Zhu et al, 2009
Thymic Stromal Lymphopoietin

Rothenberg et al, Nature Genetics 2010
Noti et al, Nature Medicine 2013
Mast Cells

• Mast Cells: Elevated, Specific Gene Profile
• May help distinguish EoE from GERD

Epithelial Tryptase
Mast Cells in EoE vs GERD
Diagnostic Implications

Dellon et al, Am J Gastro 2011
Abonia et al, JACI 2010
Basophils

Noti et al, Nature Medicine 2013
Eosinophil-Mast Cell Couplets

Otani et al, JACI 2013
IL-9 Positive Cells

A

B

Otani et al, JACI 2013
Eosinophils Make IL-9 in EoE

Otani et al, JACI 2013
TGFβ1

Remodeling

IL-5

IL-9
Therapeutic Options

Diet

Topical Corticosteroids
Dietary Intervention in Children

Efficacy Rates >90% in most studies

Efficacy Rates: SFED 50-74%
Testing Based 50-63%

Elimination Diet Options

• Testing Based
  – Skin Prick Testing
  – Skin Patch Testing

• Empiric Food Elimination
  – Milk, Egg, Soy, Wheat, Peanuts, Tree Nuts, Fish, Shellfish
Resolutions Rates

- Elemental Formula
  - 96%

- Empiric Elimination Diet
  - 53-81%

- Directed Elimination Diet
  - 53-65%

Henderson et al, JACI 2012
Spergel et al, JACI 2012
Predictive Values of Testing

• Positive Predictive Value
  – 44%

• Negative Predictive Value – varies by center
  – SPT + APT: 92% except for milk (44%)
  – 40-67%

Henderson et al, JACI 2012
Spergel et al, JACI 2012
EoE Food Triggers in Adults

Wheat: 60%
Milk: 50%

Gonsalves et al, Gastroenterology 2012
We Need Standardization, Validation and Trials to Show What Tests Mean in the Context of EoE
Potential “Side Effects” of Diet: IgE Mediated Reactions

• 24% of EoE patients with a history of food anaphylaxis

  Sugnanam et al, Allergy 2007

• Avoidance of IgE positive food:
  – Loss of tolerance
  – Need to skin test prior to avoidance and reintroduction?
  – Need for epinephrine prescriptions?
Dietary Algorithm

- Food Avoidance
- Food Reintroduction
- Endoscopy after each food or food groups
- Each eliminated and reintroduced food potentially equivalent to one endoscopy

Defining Safe Use of Anesthesia in Children
Bob Rappaport, M.D., R. Daniel Mellon, Ph.D., Arthur Simone, M.D., Ph.D., and Janet Woodcock, M.D.

The NEW ENGLAND JOURNAL of MEDICINE
Topical Corticosteroids

• Multiple randomized controlled trials
• Pediatric and Adult data
• Use of MDI
  – Puff and forcefully swallowed
• Use of viscous suspension
• Swallowed to coat esophagus
  – Use of nebulizer
  – Large vs Small particle?
Topical Corticosteroids

- Konikoff RCT Pediatric FP 12 weeks: 50%
- Schaeffer RCT Pediatric FP 4 weeks: 94% Improved, 50% Resolved
- Dohil RCT Pediatric Budesonide 12 weeks: 87%
- Straumann RCT Adult Budesonide 15 days: 72%
Topical Fluticasone

Konikoff et al, Gastroenterology 2006
Oral Viscous Budesonide

- Overall Response Rate to viscous budesonide: 87%
- Overall Response Rate to Placebo + PPI: 0%

Dohil et al, Gastroenterology 2010
Comparing Nebulized/Swallowed to Swallowed

Dellon et al, Gastro 2012
Pediatric EoE: Anti-IL-5

Peak oesophageal eosinophils (mean±SD)

Assa’ad et al, Gastroenterology 2011
Reslizumab in children and adolescents with eosinophilic esophagitis: Results of a double-blind, randomized, placebo-controlled trial

Jonathan M. Spergel, MD, PhD, Marc E. Rothenberg, MD, PhD, Margaret H. Collins, MD, Glenn T. Furuta, MD, Jonathan E. Markowitz, MD, George Fuchs, MD, Molly A. O’Gorman, MD, Juan Pablo Abonia, MD, James Young, MS, Timothy Henkel, MD, PhD, H. Jeffrey Wilkins, MD, and Chris A. Liacouras, MD Philadelphia and Frazer, Pa, Cincinnati, Ohio, Aurora, Colo, Greenville, SC, Little Rock, Ark, Salt Lake City, Utah, and Ann Arbor, Mich
EoE Remodeling

Epithelium: Basal Zone Hyperplasia
Dilated Intercellular Spaces
Lamina Propria (LP): Fibrosis
Angiogenesis
Smooth Muscle Hypertrophy
Airway Remodeling in Asthma
Pathogenesis of Complications
Molecular Mechanisms of Esophageal Fibrosis
Increased Subepithelial Fibrosis in EoE

Aceves et al, JACI 2007
Pro-Fibrotic Factors: TGFβ1

Aceves et al, JACI 2007

MBP+TGFβ1
IL-5 and -13 Promote Eosinophil Dependent Strictures

Eosinophil Deficient mice are Protected from Strictures

Mavi et al, AJPGI 2012
Eosinophils and Fibrosis

Rubinstein et al, JPGN 2011
TGFβ1 Effects on Epithelium

Kagalwalla et al, JACI 2012
Natural History To Fibrosis, Strictures

Schoepfer et al, Gastro 2013
Esophageal Remodeling: Vascularity
Subepithelial Angiogenesis

vWF Positive Vessels per hpf

- Normal
- GERD
- EE

**

*
Vascular Activation

VCAM-1 Positive Vessels

Aceves et al, JACI 2007
Mechanisms of Smooth Muscle Dysfunction
Smooth Muscle

- Thickened muscular bundles
- Dis-coordinated smooth muscle contraction with poor relaxation
- Episodes of dysmotility correlate with dysphagia

Nurko et al, Am J Gastro, 2009
Korsapaati et al, Gastroenterol 2009
Fox et al, Gastrointest Endosc, 2003
Smooth Muscle Inflammation

Aceves et al, JACI 2010
Fig. 3—Tryptase-positive mast cells are present within both the mucosa and the muscularis of case 2. (Mast cell tryptase)

Nicholson et al, J Pathology 1997
Mast Cells and TGFβ1

Aceves et al, JACI 2007
TGFβ1 and Esophageal Smooth Muscle Cells

Aceves et al, JACI 2010
Basophils and Mast Cells Effects on Smooth Muscle

Noti et al, Nature Medicine 2013
TGFβ1: A Master Regulator of EoE Remodeling?

Abonia, J.P. et al, 2010, TGFβ1: Mediator of a feedback loop in eosinophilic esophagitis... or should we really say mastocytic esophagitis?, *Journal of Allergy and Clinical Immunology*, v.126, p.1205-1207.
Reversibility of Remodeling
Topical Budesonide Resolves LP Eosinophilia and Fibrosis

LP Eosinophils

Fibrosis Score

<7eos/hpf

>20eos/hpf

Aceves et al, Allergy 2010
Topical Budesonide Decreases TGFβ and pSmad2/3 Cells

Aceves et al, Allergy 2010
Budesonide in Adults

- 15 days of swallowed budesonide
- 75% decrease in TGFβ1

Straumann et al, Gastroenterology 2010
52 week extension of 2 week induction

Budesonide: Increased eos 0.4 → 32

Placebo: increased eos 0.7 → 65

Less Extensive but:

- Increases in TGFβ
- Increases in Tenascin
- Increases in Fibrosis

Straumann et al, Clin Gastro Hepatol 2011
Adults: Discord Between Epithelium and Sub-epithelium?

Lucendo et al, JACI 2011
Remodeling Severity and Genetics
TGFβ1 Promoter SNP C-509T
Genotype and TGFβ1 Positive Cells

Anilkumar et al JACI 2013
Genotype and Fibrosis

Anilkumar et al JACI 2013
Genotype and TCS Response

Odds of CC patient responding to TCS: 3.3 (p<0.05)

Anilkumar et al JACI 2013
Allergen

Antigen Elimination → Epithelium

- CCL-18
- TGFβ
- FGF-9
- IL-5, IL-13

Epithelium Independent

Epithelium Dependent

Remodeling:
- Fibrosis
- Vascularity
- Smooth muscle hypertrophy

Topical corticosteroids
Biologic agents

Esophageal:
- Stricture
- Lichenification
- Rigidity
- Dysmotility

Clinical:
- Food impactions
- Dysphagia

? Concordance in Children
? Lost in a subset of Adults

Aceves, JACI 2011
Conclusions

• EoE is a clinicopathologic disease
• EoE involves significant epithelium, LP, and smooth muscle remodeling
• Remodeling complications include strictures, food impactions, and dysmotility
• There may be differences in remodeling reversibility by phenotype, age, genetics, and disease duration
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