Eosinophilic Esophagitis Diagnosis & Management

2nd Edition
Upon completion of this activity, participants should be better able to:

- To define Eosinophilic Esophagitis (EoE) and present the updated 2011 diagnostic guidelines.
- To understand the epidemiology, pathophysiology and genetics of EoE.
- To identify the clinical symptoms, allergic manifestations, endoscopic and histologic features of EoE.
- To list and define the treatments of EoE which include dietary restriction, pharmacologic therapy and esophageal dilation.
- To understand how to manage patients with EoE.
- To provide information regarding ongoing and future research on EoE.
Disclosures

Educational support for the *Eosinophilic Esophagitis Diagnosis and Management* slide set was provided by Abbott Nutrition.

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Presenter Disclosure

• Put your disclosure here
Background & Natural History
Background

- Rare cases suggestive of eosinophilic esophagitis (EoE) were described in the 1970’s
- Began to be described in early 1990’s
- Appreciated as a distinct entity in 1995
- Initially, unclear if EoE was part of the spectrum of eosinophilic gastroenteritis
- Since the mid 1990’s the number of reported cases has greatly increased worldwide

1995 Distribution of EoE

NE United States

Switzerland
2013 Distribution of EoE

- Canada
- United States
- Mexico
- Brazil
- Switzerland
- Spain
- Belgium
- England
- Netherlands
- Italy
- Germany
- France
- Middle East
- Africa
- Japan
- Australia
In a prospective case series of 30 adults with EoE (followed for a mean of 7.2 years)

- 29/30 persistent dysphagia
- 11/30 underwent at least one dilatation procedure
- Deeper biopsy tissue was available in 7, and 6 exhibited evidence of fibrosis in the lamina propria
- Although variable in number, all had a persistent, severe esophageal eosinophilia

Normal esophagus
Fibrotic
Inflammatory
Inflammatory + fibrotic

Endoscopic features at EoE diagnosis (%)

Diagnostic delay (years)
Natural History Adults

- There is still an incomplete understanding of the natural history of EoE

- Long term associated morbidity has now been reported to include the formation of esophageal strictures; either short or long segments of the esophagus, which is the result of chronic esophageal inflammation and remodeling resulting in fibrosis of the esophagus
Definition
Gastrointestinal Eosinophils

Normal eosinophil values, per high power field (hpf):

- Esophagus (0)
- Gastric antrum (2-10)
- Duodenum (10-20)
- Colon (15-30)

Average accepted values

Esophageal Eosinophilia

Differential Diagnosis

- Eosinophilic Esophagitis
- Gastroesophageal Reflux Disease
- PPI-responsive esophageal eosinophilia
- Celiac Disease
- Eosinophilic gastroenteritis
- Crohn’s Disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue disease
- Infection
- GVHD
2007 Consensus Recommendations

Clinico-pathologic diagnosis

• Presence of clinical symptoms related to esophageal dysfunction
  - Vomiting, abdominal pain, heartburn, dysphagia, reflux symptoms, feeding difficulty, etc.

• Isolated esophageal eosinophilia
  - > 15 eosinophils per 40X HPF
  - Histology of remainder of GI tract normal

• Exclusion of other GI disorders
  - Absence of pathologic GERD
    • Lack of response to PPI therapy or normal pH probe
  - Infection, Crohn’s disease, hypereosinophilic syndrome

Furuta et al. Gastroenterology. 2007; 133:1342-63.
• Scientific publications on EoE doubled
• Increasing recognition of patients with EoE
  – Poor use of the 2007 Recommendations
  – Survey by AAAAI and NASPGHAN revealed only 1/3 of physicians followed 2007 guidelines to make diagnosis
  – Many investigators still not using clinico-pathologic diagnosis - any patient with esophageal eosinophilia or food impaction and endoscopic findings = EoE

2011 Consensus Report

• Panel of 33 physicians (6 months)

• 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”

• Pediatric and adult EoE likely the same disease

Diagnostic Guideline

- EoE is a clinico-pathologic disease
- Clinically characterized by esophageal dysfunction
- Pathologically 1 or more biopsies show eosinophil predominant inflammation (15+ eosinophils in peak hpf)
- Isolated to esophagus (need for other GI biopsies)
- Other causes need to be excluded
  - Distinguish between “EoE” and “esophageal eosinophilia”
  - “PPI responsive esophageal eosinophilia”
- EoE diagnosis made by clinicians
- Rarely < 15 eos/hpf (if other path features are present)

PPI-Responsive Esophageal Eosinophilia
PPI-Responsive Esophageal Eosinophilia

- PPI-REE currently considered to be “distinct” from EoE
- Etiology
  - Gastroesophageal reflux responsive to acid suppression
  - Possible anti-inflammatory effect of PPI
  - Subset of EoE
  - Combination of GERD and EoE
- Important to make distinction
- Further research needed
## PPI-REE – Estimates

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Design</th>
<th># of patients with eosinophilia treated with PPI</th>
<th>PPI-REE (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dranove</td>
<td>2009</td>
<td>Peds</td>
<td>Retro.</td>
<td>43</td>
<td>17 (40)</td>
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<tr>
<td>Sayej</td>
<td>2009</td>
<td>Peds</td>
<td>Retro.</td>
<td>36</td>
<td>14 (39)</td>
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<tr>
<td>Molina-Infante</td>
<td>2011</td>
<td>Adult</td>
<td>Prospective</td>
<td>35</td>
<td>26 (74)</td>
</tr>
<tr>
<td>Peterson</td>
<td>2010</td>
<td>Adult</td>
<td>RCT*</td>
<td>12</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Moawad</td>
<td>2011</td>
<td>Adult</td>
<td>RCT*</td>
<td>20</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Dellon</td>
<td>2013</td>
<td>Adult</td>
<td>Prospective</td>
<td>65</td>
<td>24 (37)</td>
</tr>
<tr>
<td>Schroeder</td>
<td>2013</td>
<td>Peds</td>
<td>Retro.</td>
<td>7</td>
<td>5 (71)</td>
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</table>

Epidemiology of Eosinophilic Esophagitis
### Age of Onset of EoE

<table>
<thead>
<tr>
<th>Mean age (N=30)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>At first diagnosis</td>
<td>33</td>
</tr>
<tr>
<td>At first manifestation</td>
<td>29</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean age (N=31)</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>At first diagnosis</td>
<td>34</td>
</tr>
<tr>
<td>Years “incorrect diagnosis”</td>
<td>7</td>
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</table>

## Incidence and Prevalence of EoE

<table>
<thead>
<tr>
<th>Region</th>
<th>Δ</th>
<th>Incidence*</th>
<th>Prevalence*</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohio (Pediatrics)</td>
<td>↑</td>
<td>1.3</td>
<td>6.9</td>
<td>'00-'05</td>
</tr>
<tr>
<td>Minnesota (Mixed)</td>
<td>↑</td>
<td>.9</td>
<td>10.5</td>
<td>'76-'05</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>↑</td>
<td>Not done</td>
<td>.09</td>
<td>'95-'04</td>
</tr>
<tr>
<td>Adults</td>
<td>↑</td>
<td>.6</td>
<td>1.5</td>
<td>'81-'02</td>
</tr>
<tr>
<td><strong>Switzerland</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>↑</td>
<td>.15</td>
<td>2.9</td>
<td>'00-'06</td>
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</table>

* (all per 10,000 population)

### Prevalence of EoE in the U.S.

<table>
<thead>
<tr>
<th>Source population</th>
<th>EoE cases</th>
<th>Prevalence (per 100,000)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;20</td>
<td>3,587,571</td>
<td>1,813</td>
</tr>
<tr>
<td>20-64</td>
<td>7,981,646</td>
<td>4,700</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,544,574</td>
<td>4,257</td>
</tr>
<tr>
<td>Female</td>
<td>6,024,643</td>
<td>2,256</td>
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<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>2,226,470</td>
<td>1,054</td>
</tr>
<tr>
<td>South</td>
<td>4,529,151</td>
<td>2,507</td>
</tr>
<tr>
<td>Midwest</td>
<td>3,569,432</td>
<td>2,567</td>
</tr>
<tr>
<td>West</td>
<td>1,244,164</td>
<td>385</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>11,569,217</td>
<td>6,513</td>
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</table>

Prevalence of EoE by Age & Sex

Pediatric Incidence of EoE
**Frequency of EoE in a Single County‡**

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
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</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td>22</td>
<td>24</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td><strong>Incidence</strong>†</td>
<td>0.909</td>
<td>0.991</td>
<td>1.033</td>
<td>1.281</td>
</tr>
<tr>
<td><strong>Prevalence</strong>*</td>
<td>0.991</td>
<td>1.983</td>
<td>3.016</td>
<td>4.296</td>
</tr>
</tbody>
</table>

‡ Hamilton County, OH
* per 10,000 population age 0-19 years
† Chi-square test for trend NS

Adult Incidence of EoE
Incidence and Prevalence of EoE in Olten-County Switzerland

Biology of the Eosinophil
Eosinophil Biology

Allergen or other stimulus

Eosinophil granule proteins
- major basic protein
- eosinophil derived neurotoxin
- eosinophil cationic protein
- eosinophil peroxidase

Cytokines

Arachidonic acid products

Neurotransmitters
Secretory Products of Eosinophils

Granule-derived proteins
- Major basic protein (MBP1)
- Eosinophil cationic protein (ECP)
- Eosinophil-derived neurotoxin (EDN)
- Eosinophil peroxidase
- MBP homolog (MBP2)

Lipid mediators
- Leukotriene C4/D4
- Platelet activating factor
- 5-HETE
- 5,15- and 8,15-diHETE
- Prostaglandin E1, E2
- Thromboxane B2

Reactive oxygen intermediates
- Oxygen and peroxide
- Hydroxyl radicals
- Singlet oxygen

Cytokines
- MBP homolog (MBP2)
- Eosinophil cationic protein (ECP)
- Eosinophil-derived neurotoxin (EDN)
- Eosinophil peroxidase

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Eosinophils & Tissue Damage

Granule proteins:

- Cationic toxins able to disrupt membranes
- Toxic to helminths & bacteria
- Toxic to cells from numerous organs, including bronchial epithelium, keratinocytes, pneumocytes, gut epithelium
- Potent stimuli to resident cells for the production of inflammatory cytokines
Eosinophils & Tissue Damage

- Eosinophil granule proteins activate cells, including eosinophils themselves, basophils, neutrophils, mast cells & bronchial epithelial cells

- In turn, many of these activated cells produce new molecules
Granule Proteins

• Alter the function of molecules (M2 muscarinic receptors, clotting and complement components)
• Neutralize viruses by possession of Rnase activity
• Toxic concentrations of granule proteins present at sites of tissue injury (heart, skin, GI tract)
• Can occur in absence of intact eosinophils
Pathophysiology of EoE
Potential Pathophysiology of EoE

- Intraluminal allergen exposure
  - Predominately food antigens
- Mucosal production of eosinophilic chemoattractants
- Influx of eosinophils
- Release of inflammatory mediators
- Esophageal dysfunction

Cells Related to EoE

- Esophageal eosinophils
- An expansion of Th2 cells are found
- Both Th2 cells and eosinophils play a critical role in the pathogenesis of EoE
- Other cells
  - Esophageal mast cells
  - Esophageal basophils
Schematic Representation of EoE Pathogenesis

Cytokines Related to EoE

• Increased expression of human eotaxin-3 and interleukin-5
• Murine inflammation is dependent on interleukin-5 and interleukin-13
• Murine collagen deposition dependent on interleukin-5
• Secretion of cytokines (IL-5 and IL-13) that favor both IgE synthesis and eosinophilia.
• Human fibrosis associated with increased collagen deposition, TGFβ and pSMAD
Cytokines and Growth Factors

- IL-1β
- IL-2
- IL-3
- IL-4
- IL-5
- IL-6
- IL-8
- IL-10
- IL-11
- IL-12
- IL-13
- IL-16
- RANTES
- Eotaxin
- MIP-1α
- GM-CSF
- TNF-α
- SCF
- TGF-α
- TGF-β1
- PDGF
- NGF
- BDGF
- NT-3
Molecular Microenvironment in EoE

Activation, Proliferation
ECM synthesis

Epithelium
Basal Zone Hyperplasia
Esophageal Thickening
Luminal Narrowing

TGF-β
TGF-α
IL-13
MBP
EPO

Eotaxin-3
Periostin
IL-5

Increased Extracellular Matrix
Subepithelial Fibrosis
Fixed Narrowings/Rings
Strictures
Food Impactions

Activation, Proliferation
ECM Synthesis

Myofibroblasts

Increased Eosinophil Trafficking
Dilated Intercellular Spaces
Esophageal Thickening
Linear Furrows
Luminal Narrowing
Food Impactions

Activation
Angiogenesis

Endothelium

Activation
Angiogenesis

Activated tissue eosinophil

Proliferation
Hyperplasia

Smooth Muscle Cells

Dysmotility
Dysphagia
Transient Rings
Food Impactions

Genetics
EoE patients have a unique gene expression profile

230 Genes Downregulated

344 Genes Upregulated

EoE - Genetics

- Increased incidence in siblings and 1st degree relatives
- Identified gene locus at chromosome 5q22
- TSLP gene (Thymic Stromal Lymphopoetin Protein)

MicroRNA (miR) Expression in Human Allergic and Control Tissue

EoE Diagnostic Panel Analyzed as a Function of Impedance Guided Analysis

Eotaxin-3 Expression in EoE Tissues

Strong expression of eotaxin-3 in esophageal biopsies of EoE patients vs NL and CE patients

Fibrosis
Esophageal Fibrosis

• Occurs in adults

• Occurs in animal model
  – In response to allergen challenge

• Occurs in pediatric patients
  – With dysphagia
  – With strictures and EoE

Role of Eosinophils in Fibrosis

- Elevated eosinophils in the lamina propria of EoE patients
- Human esophageal eosinophils express TGFβ₁
- Mice lacking eosinophils have decreased esophageal fibrosis
- Mice lacking IL-5 have decreased esophageal fibrosis

Esophageal Tissue Remodeling

- Components of EoE remodeling
  - Fibrosis
  - Collagen deposition
  - Pro-fibrotic factors
  - Pro-fibrotic signaling molecules
  - Angiogenesis
  - Vascular activation

Pro-Fibrotic Factors

• TGFβ
  – Increased in pediatric EoE as compared to normal and GERD
  
  – Phosphorylated Smad2/3
    • Downstream transcription factor for TGFβ₁
    • Increased in EoE as compared with normal and GERD

• Periostin
  – Increased in animals following allergen challenge
  – Increased in pediatric EoE
  – Increases eosinophil adhesion to fibronectin

Fibrosis and Eosinophil Trafficking

EoE as a Progressive Disease

OR = 2.1 (1.7-2.7) per 10 year increase for developing a fibrostenotic EoE phenotype

Pediatric Clinical Symptoms
Clinical Features

• Male predominance (about 3:1)
• Multiple reports of familial clustering (within and across generations)
• Association with food allergy and atopy
• Chronic condition in adults and children

Furuta et al. Gastroenterology. 2007; 133:1342-1363.
EoE Presentation by Age

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

Age (Years)
Clinical Symptoms - Pain

- Present in 5-68% of children
- Frequent, but not universal complaint
- May be chest pain or abdominal pain (epigastric or generalized)
- GERD-like symptoms in 5-82% of children
- Odynophagia is not typical
- May be responsive to acid suppression therapy
Clinical Symptoms - Vomiting

• Present in 8-100% of children with EoE

• Not clinically distinguishable from other causes of vomiting

• Symptom frequently misclassified as GERD and there is often a delay in diagnosis

• Typically true vomiting over effortless regurgitation

• Chronic, episodic and unpredictable

• May not occur immediately after food ingestion
Clinical Symptoms- Dysphagia

• The most common symptom of EoE in adults

• In children, dysphagia manifests in several ways:
  – Choking, gagging, food refusal
  – The sensation of food sticking or going down slowly
  – Food impaction

• Often occurs even in the absence of esophageal stricture or small caliber esophagus
Adult Clinical Symptoms
Presenting Symptoms of EoE in Adults


* P value for $\chi^2$ comparing the proportion of males vs. females
Etiology of Dysphagia
Retrospective Study 1371 Adults Undergoing EGD for Dysphagia

### Gender in Adult EoE

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases of EoE</strong></td>
<td>270</td>
<td>93</td>
<td>363</td>
</tr>
<tr>
<td><strong>Patients in the Cohort</strong></td>
<td>35083</td>
<td>35947</td>
<td>71030‡</td>
</tr>
<tr>
<td><strong>Relative Risk (Unadjusted)</strong></td>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td>2.4 - 3.8 (p&lt;.001)</td>
<td></td>
</tr>
</tbody>
</table>

* Patients in the Caris pathology database with at least one esophageal biopsy

EoE Histology by Age

EoE and Atopy
Prevalence of Atopic Disease in EoE

• Asthma, allergic rhinitis, atopic dermatitis and IgE mediated food allergies are common and increasing in the general population

• Patients with eosinophilic gastrointestinal disorders have a higher prevalence of all atopic disorders

• Studies report between 50% to 93% of EoE patients have some type of atopic disorder
  – Rise in EoE mirrors rise in atopy
  – Atopy much more common in patients with EoE
## Incidence of Atopic Symptoms

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Rhinoconjunctivitis</td>
<td>57.4</td>
</tr>
<tr>
<td>Wheezing</td>
<td>36.8</td>
</tr>
<tr>
<td>Food allergy*</td>
<td>46</td>
</tr>
<tr>
<td>Family history atopy</td>
<td>73.5</td>
</tr>
<tr>
<td>Family history EoE</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*H/O positive skin-prick, RAST, or clinical response*
## Prevalence 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>

EoE and IgE Mediated Food Allergy in Children

• Prevalence in U.S. children (Sampson)
  – 2%-8% under 3 years of age
  – 3% aged 3 years and older

• Children with EoE
  – Majority have food allergy
    • Improvement with elimination diets
    • IgE-mediated sensitization
  – Food-induced anaphylaxis
    • 5.7% of 620 children - Spergel (Philadelphia):
    • 9% of 89 children - Assa'ad (Cincinnati):
    • 24% of 45 children - Sugnanam (Australia):

EoE and Atopy in Adults

• Adults
  – 20% have allergic rhinitis
  – 6.7% have asthma
  – 4% have food allergy

• Associated atopy with EoE
  – 31 adults, 68% had asthma, atopic dermatitis or allergic rhinitis (Simon)
  – 23 patients, 78% had sensitivity to aeroallergens (allergic rhinitis) and 82% had specific IgE to foods (Roy-Ghanta)

Association with Environmental Allergies
Seasonal Variation in EoE

20 year old female, history of multi-sensitization to aeroallergens. Symptoms of allergy and EoE peaked during pollen season.

Seasonal Diagnosis

- New diagnosis of EoE in Iowa
- Decrease in winter (out of pollen season)

**TABLE 1.** Number of Newly Diagnosed EoE Patients and Number of Eosinophils/hpf Based on Seasons

<table>
<thead>
<tr>
<th></th>
<th>SPRING</th>
<th>SUMMER</th>
<th>FALL</th>
<th>WINTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. EoE patients</td>
<td>65</td>
<td>69</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Mean*</td>
<td>32.4</td>
<td>39.1</td>
<td>36.7</td>
<td>29.7</td>
</tr>
<tr>
<td>Median*</td>
<td>30.0</td>
<td>35.0</td>
<td>30.0</td>
<td>24.5</td>
</tr>
<tr>
<td>Standard deviation*</td>
<td>17.1</td>
<td>20.6</td>
<td>17.0</td>
<td>13.9</td>
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<tr>
<td>Range*</td>
<td>15-100</td>
<td>15-100</td>
<td>15-80</td>
<td>15-70</td>
</tr>
</tbody>
</table>

*Eosinophils/hpf.

Pollen and EoE

• Study Population
  – 38 patients without GERD but with atopy
    • 16 with allergic rhinitis
    • 22 with allergic rhinitis and asthma
  – 25 controls without GERD without atopy
  – 24 patients with GERD without atopy
• Endoscopy during grass pollen season

Pollen and EoE

- Esophageal eosinophils were found in
  - 0 control patients
  - 10 (26%) with allergic rhinitis
  - 5 (21%) of GERD patients

- Eosinophils per HPF
  - 5.5 ± 7.3 in allergic rhinitis patients
  - 1.7 ± 1.5 in GERD patients

Sensitization to Foods/Inhalants in EoE

Radiologic Findings
Esophageal Rings
Small Caliber Esophagus
Endoscopic Findings
Esophageal Furrowing
Esophageal Furrowing Before & After Treatment
White Plaques
White Plaques
Before and After Treatment
Esophageal Rings
Esophageal Fragility
# Prevalence of Endoscopic Findings

<table>
<thead>
<tr>
<th>Pooled prevalence (%)</th>
<th>Rings</th>
<th>Stricture</th>
<th>Narrow caliber</th>
<th>Linear furrows</th>
<th>White plaques</th>
<th>Decreased vasculature</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>44</td>
<td>21</td>
<td>9</td>
<td>48</td>
<td>27</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Adults</td>
<td>57</td>
<td>25</td>
<td>9</td>
<td>48</td>
<td>19</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Children</td>
<td>11</td>
<td>8</td>
<td>11</td>
<td>46</td>
<td>36</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Retrospective</td>
<td>39</td>
<td>22</td>
<td>9</td>
<td>44</td>
<td>22</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Prospective</td>
<td>59</td>
<td>17</td>
<td>11</td>
<td>61</td>
<td>44</td>
<td>57</td>
<td>7</td>
</tr>
</tbody>
</table>

## Operating Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rings</th>
<th>Stricture</th>
<th>Linear furrows</th>
<th>White plaques</th>
<th>Decreased vasculature</th>
<th>Abnormal endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity (%)</strong></td>
<td>48</td>
<td>15</td>
<td>40</td>
<td>27</td>
<td>43</td>
<td>87</td>
</tr>
<tr>
<td><strong>Specificity (%)</strong></td>
<td>91</td>
<td>95</td>
<td>95</td>
<td>94</td>
<td>90</td>
<td>47</td>
</tr>
<tr>
<td><strong>PPV (%)</strong></td>
<td>64</td>
<td>51</td>
<td>73</td>
<td>67</td>
<td>65</td>
<td>42</td>
</tr>
<tr>
<td><strong>NPV (%)</strong></td>
<td>84</td>
<td>76</td>
<td>83</td>
<td>74</td>
<td>79</td>
<td>89</td>
</tr>
</tbody>
</table>

Classification/Grading System for Endoscopically Detected Esophageal Features of EoE - EREFS

**E**dema (pallor)

**R**ings ("trachealization")

**E**xudates (plaques)

**F**urrows (vertical lines)

**S**tricture

- Mucosal fragility
- Narrow caliber esophagus

Hirano et al. *Gut.* 2013; 62(4); 489-495.
Histology of EoE
EoE Histology
EoE Histology
EoE Histology
EoE Histology
Eosinophilia is often patchy

Multiple biopsies are necessary

EoE currently determined by the number of eosinophils in most affected field
Number of Biopsies to Diagnose Adult EoE

Number of Biopsies to Diagnose Pediatric EoE

Distal Esophageal Stricture
Small Caliber Esophagus
Pill Impaction
Sliding Hiatal Hernia
EGD Induced Laceration of Mucosa
Endoscopic Progression in an Untreated EoE Patient

Initial presentation, age 7, with GER symptoms, refused therapy

3 years later; intermittent dysphagia; refused therapy

5 years after initial presentation; severe daily dysphagia – treated with systemic steroids

1 week after treatment with solumedrol - symptoms and histology significantly improved
Treatment with PPIs
Rationale for PPI Therapy

- GERD causes eosinophilia  
  - Usually less than 7 eosinophils/hpf but can be greater
- GERD and EoE co-exist but are unrelated  
  - 20% to 40% of adults have GERD
- EoE contributes to or causes GERD  
  - Eosinophil secretory products alter esophageal motility, permeability, and fibrosis causing secondary GERD
- GERD contributes to or causes EoE  
  - Increased esophageal permeability results in exposure of deep epithelial layers to antigens
- A trial of proton pump inhibitors (PPI’s), even when diagnosis of EoE appears clear-cut, is always recommended

# Eosinophils Respond to PPI’s Adolescents/Young Adults

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)/sex</strong></td>
<td>14/M</td>
<td>25/M</td>
<td>13/F</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Pain</td>
<td>Food impaction</td>
<td>Dysphagia</td>
</tr>
<tr>
<td><strong>Environmental Allergies</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Omeprazole 10 mg BID</td>
<td>Omeprazole 20 mg BID</td>
<td>Omeprazole 20 mg QD</td>
</tr>
<tr>
<td><strong>Eosinophils/hpf</strong></td>
<td><strong>Before treatment</strong></td>
<td><strong>After treatment</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Eosinophils Respond to PPI’s Adults

Before PPI therapy
After PPI therapy

Eosinophilic esophagitis
PPI-Responsive EEI

Comparing PPI Responders and Non-Responders

Esophageal Eosinophils: EoE or GERD

• Retrospective review
  – 40 of 3,648 pts had more than 20 eosinophils/hpf
    • 8 (20%) had confirmed EoE
    • 28 (70%) had GERD
  – No significant difference in maximum number of eosinophils between GERD and EoE
  – No difference in eosinophilic abscesses, surface layering or basal zone hyperplasia

PPI Therapy and EoE

• Acid suppression with PPI’s
  – Important for making the diagnosis of EoE
  – Useful for treating symptoms associated with EoE that may be due to secondary GERD
  – Possible primary therapy for esophageal eosinophilia not related to acid suppression but instead to another, as yet identified, PPI related response
  – Proton pump inhibitor therapy alone, is insufficient for the treatment of EoE
Comparison to GERD
## Diagnostic Comparison of the Average Patient with either EoE or GERD

<table>
<thead>
<tr>
<th></th>
<th>EoE</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Intermittent</td>
<td>Persistent</td>
</tr>
<tr>
<td>pH Probe</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Acid blockade</td>
<td>Unresponsive</td>
<td>Responsive</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Often repeated needed</td>
<td>Typically none or once</td>
</tr>
<tr>
<td>Pathology</td>
<td>&gt; 15 eos/hpf</td>
<td>1-5 eos/hpf</td>
</tr>
</tbody>
</table>
Dilation
Savary Esophageal Dilators
Laceration After 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
Complications after Dilation
Complications after Dilation
Esophageal Dilation in EoE: Low Risk of Esophageal Complications

474 dilations 0 perforations
70 dilations 0 perforations
15 dilations 0 perforations
293 dilations 3 perforations
Esophageal Dilation in EoE: Effectiveness, Safety and Impact on Underlying Inflammation

- Retrospective study of 474 dilations in 207 adults
- 63 patients treated with dilation alone
  - 93% of patients reported slight or no dysphagia after dilation
- 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)
- No perforations; post procedure pain 74%
Dilation Summary
Esophageal Dilation in EoE

- Dilation does not address the underlying disease process
- Relapse is common after dilation although prolonged remission can occur
- Significant risk of long mucosal lacerations and pain
- Esophageal perforation risk is low but consequences can be substantial
- Pharmacologic and dietary therapy is effective at relieving symptoms and treating strictures
- *Whenever possible, pharmacologic or dietary therapy should be attempted prior to esophageal dilation*

Steroid Treatment in Pediatrics
Systemic Corticosteroids

• Initial report in 1998 (Liacouras)
• 20 patients treated with methylprednisolone
  – 1.5 mg/kg/day for 4 weeks, weaned over next 6 weeks
• Clinical and histological resolution noted in majority
  – 34.2 eos/hpf to 1.5 eos/hpf at Week 4
• Considerations: Side effects, unclear incidence of relapse and duration to relapse

Oral Steroid Studies


1 mg/kg BID; max 30 mg BID
Topical Corticosteroids

- Initial report by Faubion et al, in 1998, in 4 children
- Fluticasone now a common therapy
- Demonstrated improved symptoms and histology
- Side effects not common, and often mild (*Candidiasis* can be seen)

Topical Steroids (Swallowed Fluticasone)

Design:  
RCT  
Retrosp  
Prosp  
RCT

Max Dose:  
880 mcg/day  
1320 mcg/day  
880 mcg/day  
1760 mcg/day

*Post treatment data on 16 patients.

Issues with Swallowed Fluticasone

- Variable dosing regimens in studies:
  - Strength (44, 100, 220 mcg/actuation)
  - Frequency (2-4 puffs bid to qid)
  - Duration
  - Weaning schedule, etc
- 2 puffs qid x4 wks, tid x3 wks, bid x3 wks, qd x2 wks, stop
  - 1-10 year old: 110 mcg/actuation
  - ≥ 11 year old: 220 mcg/actuation
- Side effects uncommon; Candidal overgrowth encountered
- Long-term safety and pK not rigorously studied

Randomized Trial of Fluticasone vs Prednisone in Pediatric EoE (n=80)

(Slide courtesy Dr Hirano)
Comparing Types of Corticosteroids

Liquid Budesonide

- 20 children with EoE (baseline: 87 eos/hpf)
- Prescribed liquid budesonide (1-2 mg once daily) mixed with a sucralose (Splenda®) paste
  - 16 responders (< 8 eos/hpf);
  - 3 partial responders (8-23 eos/hpf);
  - 1 non-responder (no change in eos) after 3-4 months of treatment;
  - No significant adverse effects; esophageal Candidiasis in one patient

Topical Budesonide Resolves LP Eosinophilia and Fibrosis

A

LP Eosinophils

B

Fibrosis Score

Aceves et al. *Allergy*. 2010;65(1);109-116.
Steroid Treatment in Adults
Fluticasone in Adults

• Retrospective study
  – 21 adult patients with EoE, mean age 40
  – Treatment with fluticasone swallowed twice daily for 6 wks
  – All patients with complete resolution of solid food dysphagia

• Side effects
  – Transient xerostomia
  – No cases of oral Candidiasis

Fluticasone Decreases Symptoms in Adults

Symptoms include: dysphagia, chest pain, heartburn, regurgitation, vomiting, abdominal pain

(p<0.001)

Remedios et al. Gastrointest Endosc. 2006; 63:3-12.
Fluticasone Lowers Esophageal Eos in Adults

Remedios et al. Gastrointest Endosc. 2006; 63:3-12.
Randomized Controlled Trial of Topical Fluticasone in Adult EoE

- 42 pts with EoE treated with fluticasone 880 mcg BID or placebo x 6 weeks; 34 completed trial
- Significant histologic response (defined by < 15 eos/hpf)
  - 71% of fluticasone vs 10% of placebo (p<.01) by ITT analysis
  - 79% fluticasone vs 13% placebo (p<.01) by PP analysis
- Symptom response was similar between groups
  - 71% fluticasone vs. 48% placebo by ITT analysis
  - 68% fluticasone vs. 74% placebo by PP analysis

Prospective, n=30 Adults, Fluticasone x 3 mos

Fluticasone Effect on Esophagus

Caliber of the esophagus

Before treatment
After treatment

p<0.05

Rings
Stenosis
Normal

% patients

Fluticasone Effect on Esophagus in EoE

Prospective, n=30 Adults, Fluticasone x 3 mos

Before treatment
After treatment

p<0.05

Liquid Budesonide
Randomized, Double-Blind Placebo Controlled Trial Budesonide (BEE Trial)

36 Adults with EoE
Placebo or budesonide 1 mg BID x 15 days

Eosinophils per hpf

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>62.01</td>
<td>3.83</td>
</tr>
<tr>
<td>Placebo</td>
<td>44.56</td>
<td>43.85</td>
</tr>
</tbody>
</table>

Topical Steroid: Endoscopic Improvement

Corticosteroid Summary
Guidelines for Corticosteroids in EoE

• Systemic and topical corticosteroids effectively resolve the acute clinico-pathological features of EoE.

• When discontinued, the disease generally recurs.

• Systemic corticosteroids may be utilized in emergent cases such as dysphagia requiring hospitalization, dehydration due to swallowing difficulties and weight loss, etc.
  – Because of the potential for significant toxicity their long-term use is not recommended.

• Topical corticosteroids are effective in inducing a remission of EoE when utilized in high doses (pediatrics & adults).
  – The incidence of long term side effects with this form of administration has not been formally studied but currently it is well tolerated (fungal infections).

• Topical corticosteroids are used for maintenance of EoE but have not been well studied.

Furuta et al. Gastroenterology. 2007; 133:1342-63.
Dietary Treatment in Pediatrics
History of Diet and EoE

- In 1995: “Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula”
  - 10 patients with refractory reflux symptoms
  - 6 had received anti-reflux surgery without resolution
  - All with markedly elevated esophageal eosinophils

- Patients given a trial of an “elemental diet”
  - Amino acid based formula
  - Minimized any risk of food allergy

Diet and Eosinophilic Esophagitis

- After elemental diet:
  - Symptom resolution in 8 patients, improvement in 2
  - Improvement occurred within 3 weeks
  - Biopsies improved as well
- Symptoms returned after food was reintroduced
- Conclusions:
  - EoE is an allergic phenomenon
  - EoE improves with food elimination

![Graph showing Maximum Intraepithelial Esophageal Eosinophil Counts / 40 x field](chart.png)
Dietary Management
Amino Acid–Based Formula

- 172 Patients (128 nasogastric tube, 32 oral, 4 failed, 8 noncompliant)
  - 160 patients completed therapy
- Patients evaluated 4-6 weeks after instituting diet

<table>
<thead>
<tr>
<th>160 Patients</th>
<th>Pre-diet</th>
<th>Post-diet</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils per hpf</td>
<td>38.7 ± 10.3</td>
<td>1.1 ± 0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>30</td>
<td>1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GERD symptoms</td>
<td>134</td>
<td>3</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

EoE – Elemental Diet

Before

After
Types of Dietary Therapy for EoE

• Total Elimination Diet
  – Amino-Acid based formula

• Selective Diet
  – Empiric Diet
  – Directed (Targeted) Diet
Advantages of Elemental Diet

• When administered correctly:
  – > 95% demonstrate clinical and histologic response
  – Allows systematic re-introduction of foods

• Can lead to prolonged remission clinically and histologically without the need for medications

• Causative foods may be able to be reintroduced successfully later (tolerance)
Obstacles to Elemental Diet

- Elemental formula is unpalatable
- Commonly needs nasogastric or gastrostomy tube to administer
- Nutritional status must be monitored closely
- Elemental formulas are expensive
  - Variable insurance coverage
  - Usually significant out of pocket expense
- Quality of Life issues
Selective Elimination Diet

- Removal of a limited number of foods
- 2 types of dietary restriction
  - Empiric (based on history of the most likely foods)
    - “The usual suspects”
    - Milk, soy, egg, peanut, wheat, fish, meats
  - Directed (based on allergy testing or clinical symptoms)
    - Clinical history
    - Allergy testing (skin prick tests, atopy patch tests)
Empiric Elimination Diet

- Six food elimination diet (SFED)
- 60 EoE patients – retrospective review
  - 35 given diet without milk, soy, wheat, egg, peanut, nut and fish
  - 25 given amino acid formula
- Biopsies done at start compared with 6 weeks of diet therapy
- Improvement in restricted group 75% while amino acid group 90%

SFED Follow-up

• Single Food Reintroduction in 36 children
• Specific food sensitivities
  – 74% to milk
  – 26% to wheat
  – 17% to egg
  – 10% to soy
  – 6% to peanut
• Single food in 72%, 2 foods in 8% and 3 foods in 8%

Empiric Diet Elimination

- Easy, do not need testing
- Few studies in the literature
- May not eliminate all foods necessary to induce remission
- May eliminate foods that are not necessary to be eliminated
- May prolong the process of food elimination and re-introduction
Elimination by history/symptoms (or guessing) is challenging

- Reactions may be delayed several days after exposure
- Reactions may persist several days after exposure
- More than one food may be causing reaction

Elimination based on diagnostic testing is inaccurate
Methods of Direct Allergy Testing for EoE

- Bifurcated Needle
- Milk
- Soy
- Corn
- Beef
- Chicken
- Wheat
- Potato
- Egg
- Oat
- Rice
- Saline
Food Testing in EoE

- 74% patients were atopic (asthma, ARC, or AD)
- 1/3 have negative skin prick tests
- Most common foods were
  - Egg, soy, milk, peanuts, beef, chicken, wheat, corn, peas, and potato
- 1/4 have negative atopy patch tests
  - 1/8 have both negative skin prick tests and atopy patch tests
  - Wheat, corn, soy, milk, beef, rice, chicken, egg, rye, oat, and potato

TABLE III. Comparison of food prick skin testing and atopy patch testing precision in patients with eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Food</th>
<th>Prick skin test precision</th>
<th>Atopy patch testing precision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Milk</td>
<td>26.6</td>
<td>87.8</td>
</tr>
<tr>
<td>Egg</td>
<td>70.0</td>
<td>85.8</td>
</tr>
<tr>
<td>Soy</td>
<td>40.4</td>
<td>82.1</td>
</tr>
<tr>
<td>Wheat</td>
<td>18.1</td>
<td>87.4</td>
</tr>
<tr>
<td>Peanut</td>
<td>88.2</td>
<td>88.4</td>
</tr>
<tr>
<td>Corn</td>
<td>30.6</td>
<td>91.5</td>
</tr>
<tr>
<td>Beef</td>
<td>45.7</td>
<td>92.3</td>
</tr>
<tr>
<td>Chicken</td>
<td>55.9</td>
<td>89.5</td>
</tr>
<tr>
<td>Rice</td>
<td>13.3</td>
<td>97.5</td>
</tr>
<tr>
<td>Potato</td>
<td>42.1</td>
<td>97.0</td>
</tr>
<tr>
<td>Pork</td>
<td>29.4</td>
<td>95.4</td>
</tr>
</tbody>
</table>

NLR, Negative likelihood ratio; PLR, positive likelihood ratio.

*Values in bold type represent a NLR of <0.20 or less or a PLR > 5.00, which, when applied to the pretest probability of having the disease can estimate the posttest probability of the disease. All values in the table are from reference 51 except rice, which are from reference 48; these data are exclusively from a pediatric population, and these values may not be applicable in adult populations.

Response of 3 Types of Dietary Restriction

% of patients clinically and histologically significantly improved

# of esophageal eosinophils still present after treatment

<table>
<thead>
<tr>
<th>Dietary Restriction</th>
<th>% Clinically Improved</th>
<th># Eosinophils After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric - Kagalwalla</td>
<td>74%</td>
<td>13.6</td>
</tr>
<tr>
<td>Directed - Spergel</td>
<td>77%</td>
<td>12.8</td>
</tr>
<tr>
<td>Liacouras</td>
<td>95%</td>
<td>1.1</td>
</tr>
</tbody>
</table>

## TABLE V. Comparison of food prick skin testing and atopy patch testing precision in patients with eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Approach</th>
<th>Definition</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental</td>
<td>Diet exclusively consisting of amino acid–based formula</td>
<td>• Hypoallergenic</td>
<td>• Taste (may require feeding tube)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nutritionally comprehensive</td>
<td>• Expense</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduces symptoms and eosinophil counts</td>
<td>• Age appropriateness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduces symptoms and eosinophil counts</td>
<td>• Excludes all food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May have adverse impact on quality of life</td>
</tr>
<tr>
<td>Empiric diet</td>
<td>Diet that eliminates the major food allergens from the diet (typically milk, egg, wheat, soy, peanut/tree nut, and fish/shellfish, though variants exist)</td>
<td>• Allergy testing not required</td>
<td>• Some avoidance may be unnecessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Studied across all ages</td>
<td>• Only four foods may be necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduces symptoms and eosinophil counts</td>
<td>• Expense</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be nutritionally incomplete</td>
</tr>
<tr>
<td>Targeted diet</td>
<td>Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)</td>
<td>• Most specific therapy</td>
<td>• Testing precision and technique is inconsistent across centers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can preserve diet</td>
<td>• Milk testing precision very poor when negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Established sensitivity, specificity, and NLR/PLR to assist with add-back</td>
<td>• Empiric milk elimination as an addition greatly improves response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduces symptoms and eosinophil counts</td>
<td>• Some avoidance may be unnecessary (sensitization without clinical allergy)</td>
</tr>
</tbody>
</table>
Foods Causing EoE

• Foods found in single elimination or reintroduction with positive biopsies
  – Milk > Egg, Soy > Corn, Wheat, Beef > Chicken > Peanuts, Rice, Potato > Oat, Barley, Turkey, and Pea

• Most EoE patients, average 4 to 5 foods

• Up to 25% have severe food allergies - unable to tolerate ANY food without symptoms and histologic changes
# Food Reintroduction

After Normal Biopsy

<table>
<thead>
<tr>
<th>Reintroduction Strategy</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested order</td>
<td>Fish/shellfish</td>
<td>Fish/shellfish</td>
</tr>
<tr>
<td></td>
<td>Peanut/tree nut</td>
<td>Egg</td>
</tr>
<tr>
<td></td>
<td>Soy</td>
<td>Peanut/tree nut</td>
</tr>
<tr>
<td></td>
<td>Wheat</td>
<td>Soy</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>Milk</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td>Wheat</td>
</tr>
</tbody>
</table>
**TABLE IV.** Comparison of identification of dietary triggers and successful food reintroduction

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (y)</th>
<th>Milk, %</th>
<th>Egg, %</th>
<th>Soy, %</th>
<th>Wheat, %</th>
<th>Peanut/tree nut, %</th>
<th>Fish/Shellfish, %</th>
<th>Legumes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonsalves</td>
<td>20</td>
<td>22-55</td>
<td>50</td>
<td>5</td>
<td>10</td>
<td>60</td>
<td>10</td>
<td></td>
<td></td>
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<tr>
<td>Kagalwalla</td>
<td>36</td>
<td>3-18</td>
<td>74</td>
<td>17</td>
<td>10</td>
<td>26</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>Lucendo</td>
<td>42</td>
<td>17-57</td>
<td>62</td>
<td>26.2</td>
<td>14.3</td>
<td>28.6</td>
<td>16.7</td>
<td>19</td>
<td>23.8</td>
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<tr>
<td>Henderson</td>
<td>26</td>
<td>0.9-22</td>
<td>65</td>
<td>40</td>
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<td>37</td>
<td></td>
<td></td>
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<tr>
<td>Spergel</td>
<td>319</td>
<td>1-18</td>
<td>66.1</td>
<td>24.5</td>
<td>16.3</td>
<td>22.6</td>
<td>5.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total†</td>
<td>442</td>
<td></td>
<td>64.0</td>
<td>22.2</td>
<td>15.4</td>
<td>24.9</td>
<td>5.9</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

*Foods that cause changes in esophageal eosinophil counts on reintroduction; multiple foods were reintroduced in the same patient.
†Total percentages represent an average of all 5 studies.
Dietary Treatment in Adults
Dietary Therapy in Adults

Six Food Elimination Diet is highly effective at reducing symptoms, histology & endoscopic changes in adult EoE

Prospective Study in Adults (n=50)
6 wk elimination (milk, wheat, soy, egg, nuts, seafood)

70% had peak eos <10/hpf

Before Diet | After Diet

94% Had Decrease in Symptom Score

Effect of Food Reintroduction on Esophageal Eosinophilia

* p<0.0001
Endoscopic Improvement

Pre Diet

Post Diet

Reintroduction of Wheat

Causative Foods in Adult EoE in the US

- 60% Wheat
- 50% Milk
- 10% Soy
- 10% Nut
- 5% Egg

- 3 Patients had > 1 Food trigger
- SPT Predictive in 13%

SFED in Adults

P < 0.001

- Eosinophilic inflammation (>15 eos/hpf)
- Absence of eosinophilic inflammation (<15 eos/hpf)

Baseline: Wheat, Milk, Eggs, Rice, Legumes, Nuts, Fish & Seafood, Corn, Soya, After 1 year

Dietary Therapy in Adults in Spain

Empiric elimination of wheat, rice, corn, milk, eggs, soy, peanuts, legumes, fish, shellfish

Prospective Study in Adults (n=67)
73% had eos <15/hpf after treatment

Causative Foods in Adult EoE in Spain

Food Triggers
- 36% had 1
- 31% had 2
- 33% >3

Allergy testing not predictive

SFED Diet

- SFED significantly improves symptoms, endoscopic features and histopathology in adults with EoE with 52% achieving <10 eos/hpf

- Skin prick testing was predictive in only 21% of patients therefore dietary elimination based solely on skin prick testing may not be effective in adults

Elemental Diet in Adults with EoE

• 18 adults
• 72% with eos <10 after ED for 6 wks
• Improvement in endoscopic features and histology, not symptoms

Dietary Summary
Guidelines for Dietary Therapy in EoE

• Dietary therapy (AA formula, SFED, directed diet) should be considered and discussed in all patients with a diagnosis of EoE.

• The use of dietary therapy may lead to a complete or near-complete resolution of both the clinical and histologic abnormalities.

• Dietary therapy may reverse esophageal fibrosis.

• Consultation with a registered dietician is strongly recommended to ensure proper calories and micronutrients.

Nutrition in EoE
Role of Dietician in EoE

• Assessment of nutritional status
• Determination of dietary adequacy
• Working within dietary restrictions to provide balanced, acceptable diet
• Education of patient & family
• Identification /assessment of barriers to effective nutritional therapy
Role of Dietician in EoE

• Meeting nutritional requirements despite diet restrictions
• Providing ongoing education and support to enhance adherence to restrictions
• Managing problematic feeding behaviors
• Facilitating thorough communication among clinicians and families
Components of Nutrition Assessment

• Accurate anthropometric data
• Detailed diet & symptom history
• Evaluation of dietary adequacy
• Identification of feeding difficulties/food refusal behaviors
• Biochemical
Diet History—Know Where You’re Starting

- Types of food/beverages, volume consumed, brand names, ingredients of homemade foods
- Multi-vitamin infusion, herbals, supplemental formulas
- Product labels, school menus
- Review of meal & snack structure (time, location)
- Multiple caregivers involved
Diet History—Established Patient

- Review current list of allergens (determine if and how confirmed)
- Are additional foods avoided? If so, why?
- Assess adherence to diet & confidence in allergen-avoidance
Nutritional Considerations: Dietary Adequacy

- Single-food hypersensitivity managed well with appropriate food choices/substitutions
- Risk of dietary inadequacy increases with multiple allergens
- Micronutrient supplementation often necessary
- Dietary fiber supplementation may be needed
  - Alternate grains tend to be low in fiber
  - No/little fiber in elemental formulas
  - Increase fruits & vegetables as able; some commercial fiber supplements can be used
Elimination Diets

Essentials

• Careful identification of allergens

• Education of patient, family, other caregivers

• Assessment and monitoring to ensure adequate intake, preservation/improvement of nutritional status

• Supplementation with elemental formula may be needed
Food Allergen Labeling and Consumer Protection Act (FALCPA)

- Requires foods manufactured on or after 1/1/06 to include declaration of presence of a “major food allergen”:
  
  Milk  Egg  Wheat
  Peanut  Tree nut*  Soybean
  Fish*  Crustacean shellfish*

- *Specific type will be used (e.g., almond/walnut, flounder/cod, crab/shrimp, etc.)

- All packaged food sold in U.S.(domestic/imported)
Elimination Diets: Keys to Success

• Reading food labels crucial to successful avoidance
  – Should be read each time patient/family shops
  – Contacting manufacturer only way to clarify presence of “minor” allergen
    – Avoid food if any doubts or if ingredient list not available.
    – Educate family re: FALCPA

• Education on cross-contamination (home/restaurants)

• Acquainting families with resources to assist with food shopping/prep, restaurant eating, etc.

• Emphasizing what CAN be eaten vs. what cannot
Elemental Diet

- 100% amino-acid based formula as sole source of nutrition (Neocate, Elecare, etc.)
- Can use in combination with elemental semi-solid (Neocate Nutra)
- Usually no solid food. Water OK. Certain fruit juices /Gatorade/candy (Dum-Dums/Smarties) may be permitted
- Typically 4-6 weeks, then repeat endoscopy
- Tube feeding if volume goals cannot be met by mouth
Elemental Formulas: Enhancing Acceptance

• Flavoring formulas sometimes helpful
  – Flavor packets from manufacturer
  – Chocolate/strawberry syrup (allergen-free)
  – Sugar-based drink mixes (Kool-Aid, Crystal Light)

• Serve chilled; smoothies/popsicles

• Closed cup (with/without straw) sometimes helpful
Practical Considerations

• Cost

• Food refusal behaviors
  – May persist after allergens are removed or biopsies normalize (in EoE); refer to feeding specialist sooner vs. later

• Access to allergen-free products remains limited in some areas
  – May require modification of plan (if able)
Family Support

• Work with schools to educate staff and minimize risk of allergen exposure (FARE program)
  – Provide safe, non-perishable foods for snack time, parties
  – Emergency kit /Epi must be available
  – Other FARE resources (restaurants, camps, etc.)
• Thorough, updated, easily understood education materials
• Team communication (Allergy/GI/Nutrition)
• Provide information to empower patients families and encourage self-education. Practice the “art” of delivering the science.
Family Support

• Depression
  – Kids (perceived deprivation; hard being “different”)
  – Parents can have significant fears (food safety/cross-contamination, tube feedings, letting others care for their children, question ability to safely feed their own children)

• Address concerns when they arise and refer directly or work with PCP to encourage families to seek support when needed
Allergy Testing
Types of Allergy Testing

• Prick Skin
• Specific IgE
• Atopy Patch
• Others
  – Provocation/neutralization, cytotoxic tests, applied kinesiology (muscle response testing), hair analysis, electrodermal testing, food-specific IgG or IgG4 (IgG “RAST”)
Prick Skin Test

• Test for specific IgE to food

• Tests for immediate reactions
  – Hives, respiratory symptoms, anaphylaxis
  – Food reactions are reproducible

• Size of reaction does not indicate severity of reaction

• Predictive values vary for each food, test and by age
Skin Test Devices/Reactions

Bifurcated Needle
Atopy Patch Test

• For non-IgE mediated reaction
• First developed for contact dermatitis in 1890s
• Developed for foods in 1990s
• Used in atopic dermatitis and EGIDs
• Reagents are not standardized
Atopy Patch Testing

- Milk
- Soy
- Corn
- Beef
- Chicken
- Wheat
- Potato
- Egg
- Oat
- Rice
- Saline
Other Treatments for EoE
Other Treatments for EoE

• In addition to the more accepted treatments for EoE, there are a few treatments that have been reported in small patient samples
  – Mast-cell stabilizers
  – Leukotriene receptor antagonists
  – Anti-tumor necrosis alpha antibodies
Mast Cell Stabilizers

• Agents
  – Cromolyn sodium (Gastrocrom®)
  – Ketotifen fumarate

• Actions
  – Block IgE-mediated calcium channels on the mast cell membrane
  – Prevents the release of mast cell granules that contain histamine and leukotrienes
Mast Cell Stabilizers

• Long history of use in asthma and allergic conjunctivitis

• Numerous anecdotal reports in eosinophilic gastrointestinal disorders

• Potential benefits
  – Excellent safety profile
  – Minimal side effects
  – Ease of administration
Response of EoE to Cromolyn Sodium

- 14 patients
- GER symptoms
  - 0/13 improved
- Dysphagia
  - 0/1 improved

Ketotifen Fumarate

- Mast cell stabilizer with anti-histamine activity
- May have direct inhibitory effects on eosinophils
- No reported trials for EoE
  - Several reports of improvement in patients with eosinophilic gastroenteritis
- Available in the United States as an ophthalmic preparation and in Europe as an oral form
Leukotriene Receptor Antagonists

- Montelukast (Singulair®)
  - Blocks the action of leukotriene D4 at CysLT1
  - CysLT1 found in eosinophils, among other places

- Trial of 8 EoE patients
  - 7 of 8 patients with dysphagia had resolution of symptoms
  - 5 patients remained in clinical remission for 14 months
  - Patients relapsed within 3 weeks of stopping the medication
  - No histologic changes occurred

Biologic Treatment
Interleukin 5 (IL-5)

- Cytokine that regulates eosinophil function
  - Proliferation and release from bone marrow
  - Maturation
  - Survival
  - Activation

- Overproduction of IL5 in transgenic mice leads to eosinophilic esophagitis

Anti-IL5

- Investigational monoclonal antibody - direct antagonist of IL-5
- Effective for hypereosinophilic syndrome
- Effective in a small series of adults with EoE (n = 4), with dramatic reduction in esophageal eosinophilia
- Pediatric trials in progress

Anti-Interleukin 5

- IL-5 is the predominant cytokine mediating eosinophil function; eosinophil lifeline

- Pediatric and Adult trials –

- Eos counts reduced in most; complete histologic resolution in only a small #. No change in symptoms in adults.

Anti-IL5 on Esophageal Eosinophils

![Graph showing the effect of Anti-IL5 on esophageal eosinophils before and after treatment. The graph indicates a significant decrease in eosinophils/hpt (P<0.05).]
Anti-IL5 - Current Studies

• Mepolizumab
  – Utilized 3 different doses of anti-IL5 via 4 week infusions
  – Significantly reduced esophageal eosinophilic inflammation
  – Symptom improvement difficult to assess

• Reslizumab
  – Placebo controlled trial
  – Anti-IL5 significantly reduced esophageal eosinophils
  – Symptom improvement similar between placebo and anti-IL5

Assaad et.al. Gastroenterol. 2011;141:1593-1604
Overall Treatment Approaches
Treatment

- EoE has become a significant component of most practices in both pediatric and adult gastroenterology.
- Centers for the care of patients with EoE have been developed to coordinate multiple health care providers including allergy/immunology, gastroenterology, and nutrition.
A trial of PPI therapy is required for patients with presumed eosinophilic esophagitis, even if the diagnosis seems clear-cut.
Treatment Goals of EoE

• Eliminate symptoms
  – Dysphagia
  – Heartburn

• Prevent complications
  – Esophageal stenoses
  – Esophageal fragility
Proposed Endpoints for Treatment of Eosinophilic Esophagitis

Symptomatic Remission

Histological Remission

Endoscopic Remission

Rings

Furrows

Exudates

Endoscopic photos from Dr. Ikuo Hirano
Is Symptomatic Remission Sufficient?

For Requiring Histological Remission

- Experimental and clinical evidence that eosinophils cause tissue remodeling (e.g. collagen deposition)\(^1\)
- Therefore, elimination of esophageal eosinophils should prevent complications

Against Requiring Histological Remission

- Requires endoscopy (expense, inconvenience, risk)
- Might need higher doses and additional meds (expense, inconvenience, risk)
- No proof of efficacy in preventing complications

Suggested Algorithm for Management of Eosinophilic Esophagitis

Suspected EoE

- 0-4 Eos/hpf
  - GERD or PPI Responsive Eosinophilia (PPIREE)

- 5-14 Eos/hpf
  - GERD, PPIREE or Indeterminate EoE

- > 15 Eos/hpf
  - EoE
    - Topical Steroid or Dietary Therapy

EGD with Bx

- PPI 8 wks, Ongoing or Intermittent Symptoms

Follow up

- Symptoms +/- Pathology (? Non-adherence)

  - Symptomatic Stricture with Histologic Remission
  - Consider Maintenance Therapy
  - Esophageal Dilation

Elemental Diet
- Systemic Steroid
- Esophageal Dilation
- High Dose Topical Steroid (?)
- Biologic Therapy (?)

Future
The Next Frontiers

• Steroid formulations with greater viscosity and/or esophageal tissue adherence; other delivery methods

• Antibodies targeting IL-13 and eotaxin

• Prostaglandin D2 inhibitor – ‘CRTH2’

• ? co-therapy with PPI – augment CRTH2; block eotaxin-3 release

• Other mechanisms of PPI effects

• FDA approval of drugs currently used or under study
EoE - Future Testing Methods

- Esophageal biomarkers
- Serum biomarkers
- Esophageal String Test
  - Capsule filled with a 90 cm string, swallowed with string to remain in place (taped to face) for a period of time
  - String removed and proximal secretions evaluated for biomarkers of disease

**Oral Immunotherapy Induces EoE**

- **Allergy to Hens Egg (HE)**
  - Urticaria after HE ingestion
  - Specific IgE positive for HE
  - Egg avoidance

- **Specific Oral Tolerance Induction (SOTI)** for HE and after 2 months, tolerance of 1 whole heated egg

- **EGD after 6 weeks treatments with omeprazole 10 mg/die; diagnosis of EoE**
- **Complete allergy evaluation confirming HE Allergy**
- **3 months treatment with Methylprednisolone, 1.5 mg/kg/die**
- **Egg avoidance**

- **Age 4**: Acute episode of severe anaphylaxis after an accidental HE ingestion
  - Stricter egg avoidance

- **Age 10**: Dyspepsia, solid food dysphagia 5 months after completing SOTI

- **Age 11**: No EoE symptoms
  - Follow up EGD: endoscopic improvement
  - Histological findings: less than 5 Eos per hpf

- **Age 12**: Follow up EGD endoscopic improvement

- **Age 10 + 9 Months**: Follow up EGD endoscopic improvement

**Seen after egg, milk and peanut oral immunotherapy**

**Incidence about 5-20%**

**Indicates foods causes EoE and it is not TH₂ mechanism**


Advocacy Groups
Advocacy Groups

• American Partnership for Eosinophilic Disorders
  – www.apfed.org

• Campaign Urging Research for Eosinophilic Disorders
  – www.curedfoundation.org

• Food Allergy Network
  – www.foodallergy.org
Conclusions

- EoE is a clinico-pathologic disorder diagnosed by clinicians
- EoE can occur “at any age”
- Pediatric and Adult EoE are likely the same disease
- Incidence and prevalence continue to increase
- Important that you make the distinction between
  - Eosinophilic Esophagitis
  - Esophageal Eosinophilia
  - “PPI-responsive” esophageal eosinophilia
- “Stay tuned”
  - Expect changes to occur within the guidelines as therapy, research and interest continues