Eosinophilic Esophagitis:

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Disclosure

- I have no financial disclosures or conflicts of interests to report
- NO FDA APPROVED THERAPIES
  - Therapies are “off-label”
  - Very few double-blind, placebo controlled randomized trials and most are adult studies
Objectives-Sea-change in 6 years

- Define the clinicopathologic disorder Eosinophilic Esophagitis (EoE)
- Review pathophysiology of EoE
- Review the role of allergy in EoE
- Review current therapy strategies for EoE
Eosinophilic Esophagitis (EoE)

- Primary “Clinicopathologic” disorder of the esophagus...a syndrome
- Esophageal/Upper GI symptoms...adults
- Esophageal biopsies with \( \geq 15 \) eos/hpf, in \( \geq 2 \) areas (absence in Gastric, Duodenum)
- Absence of pathologic GERD (normal Ph study or lack of response to PPI)
Eosinophilic Esophagitis (EoE)

- Primary “Clinicopathologic” disorder of the esophagus... a syndrome
- Esophageal/Upper GI symptoms... adults
- Esophageal biopsies with ≥ 15 eos/hpf, in ≥2 areas (absence in Gastric, Duodenum)
- Absence of pathologic GERD (normal Ph study or lack of response to PPI)
What Else to Consider

- GERD
- Infection
- Mechanical Trauma-pill esophagitis
- Crohn’s disease
- Eosinophilic Gastroenteritis
- Eosinophilic Leukemia
- Drugs
- Eosinophilic disorders (Well’s, Löffler’s, Shulman’s, Churg-Strauss, Addison’s)
What Else to Consider

- GERD - Concurrent and synergistic?
- Infection
- Mechanical Trauma - pill esophagitis
- Crohn’s disease
- Eosinophilic Gastroenteritis
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- Drugs
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- Celiac

- Graft Versus Host
Eosinophilic Esophagitis (EoE)

- 1st described 1977 Dobbins et al case report
  - Normal pH, eos gastroenteritis
- 1978 Landres et al 1st case of eosinophilic infiltration and dysfunction of esophagus
- Initially attributed to GERD
Intraepithelial eosinophils:
A new diagnostic criterion for reflux esophagitis

H S Winter, J L Madara, R J Stafford
R J Grand J E Quinlan, H Goldman
Epidemiology

- Currently incidence 7-11/100K/yr
- Prevalence appears to be increasing
  - 57/100k to 153/100k (Heine et al, 2015)
  - Canada: Increased EGD’s (Syed et al, 2012)
  - Dutch increased prev beyond EGD’s (Dellon et al, 2015)
- Males:Females 3-4:1
  - 70-80% cases series are males
- Has been reported on all continents including Africa (but still no Antarctica)
## Clinical Presentation

<table>
<thead>
<tr>
<th>Children</th>
<th>Adolescents/Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding aversion</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Textural aversion</td>
<td>Food Impaction</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>“GERD refractory to medical management”</td>
</tr>
<tr>
<td>Heartburn</td>
<td>“GERD refractory to surgical management”</td>
</tr>
<tr>
<td>Regurgitation</td>
<td></td>
</tr>
<tr>
<td>Emesis</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Dysphagia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Food impaction</strong></td>
<td></td>
</tr>
</tbody>
</table>

rare in young children
A: Mild: Subtle circumferential ridges seen on esophageal distension
Moderate: Distinct rings that do not occlude passage of diagnostic endoscope
Severe: Distinct rings that do not permit passage of diagnostic endoscope

B: Mild: White lesions occupying < 10% of the esophageal surface area
Severe: White lesions involving ≥ 10% of surface area of esophagus

C: Mild: Vertical lines without visible depth
Severe: Vertical lines with clear depth (indentation) into the mucosa

D: Normal: Distinct vasculature
Mild: Decrease clarity of vessel
Severe: Vessels are no longer appreciated

E: Example 1
Example 2
Time 0
Time 1 (with insufflation)

F
Pathophysiology

Leung et al, 2015
Pathophysiology

Leung et al, 2015
### Table 2

Updated similarities and differences between GORD, PPI-REE and EoE.

<table>
<thead>
<tr>
<th></th>
<th>GORD</th>
<th>PPI-REE</th>
<th>EoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aetiology</strong></td>
<td>Gastric content reflux</td>
<td>Unknown</td>
<td>Food/airborne allergens</td>
</tr>
<tr>
<td><strong>EoE diagnostic panel</strong></td>
<td>Different to PPI-REE and EoE</td>
<td>Similar to EoE</td>
<td>Similar to PPI-REE</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Heartburn, regurgitation,</td>
<td>Dysphagia, food bolus</td>
<td>Dysphagia, food bolus</td>
</tr>
<tr>
<td></td>
<td>less often dysphagia</td>
<td>impaction, less often heartburn</td>
<td>impaction, less often heartburn</td>
</tr>
<tr>
<td><strong>Oesophageal involvement</strong></td>
<td>Distal</td>
<td>Distal &gt; proximal</td>
<td>Proximal &gt; distal</td>
</tr>
<tr>
<td><strong>Oesophageal pH monitoring</strong></td>
<td>Erosive GORD</td>
<td>70% increased acid exposure</td>
<td>50–70% normal acid exposure</td>
</tr>
<tr>
<td></td>
<td>80% increased acid exposure</td>
<td>30% normal acid exposure</td>
<td>30–50% increased acid exposure</td>
</tr>
<tr>
<td><strong>Type of immune response/involving cytokines</strong></td>
<td>50% normal acid exposure</td>
<td>Th2</td>
<td>Th2</td>
</tr>
<tr>
<td><strong>Inflammatory cells</strong></td>
<td>Th1, IL-8, MCP-1, RANTES</td>
<td>Eotaxin-3, IL-13, IL-5</td>
<td>Eotaxin-3, IL-13, IL-5</td>
</tr>
<tr>
<td></td>
<td>Neutrophils, lymphocytes,</td>
<td>Eosinophils and mast cells</td>
<td>Eosinophils and mast cells</td>
</tr>
<tr>
<td></td>
<td>low-grade eosinophilia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>PPI therapy effective in</td>
<td>PPI therapy effective in</td>
<td>PPI therapy not effective,</td>
</tr>
<tr>
<td></td>
<td>most patients; fundoplication</td>
<td>all patients</td>
<td>Steroids/Diet</td>
</tr>
</tbody>
</table>

- PPI-REE and EOE are genetically and phenotypically indistinguishable
- PPI-REE is a *subtype* of EoE

Molina-Infante, 2015
Evidence for Allergy in EoE

- 50-80% of patients with EoE are atopic
  - Atopic dermatitis (prev 4-60%)
  - Allergic rhinitis (prev 40-74%)
  - Asthma (prev 40-70%)
  - Food Allergies (IgE mediated prev 15-43%)

- Most patients improve on allergen-free diets
- 30% of population believe they have a food allergy
- 1-8% may actually have a food allergy
- Sensitization ≠ Allergy

- EoE is associated with Th2 profile
  - IL-4, IL-5, IL-13
  - More evidence points away from IgE

Furuta et al, 2007
Ballmer-Weber, 2014
- 10 kids Dx resistant reflux (6 fundos)
- Min 6 wks of elemental formula
- 8/10 Sx resolved
- 2/10 Sx improved
- All ↓ Eos on Bx
- All had return of Sx after open diet

Kelly et al Gastro 1995
Spectrum of Food/Allergic Diseases

- IgE-dependent (immediate)
  - Urticaria/Angioedema
  - Oral allergy Syndrome (pollen-food)
  - Anaphylaxis
  - Food-associated exercise-induced anaphylaxis

- “Mixed” IgE/Non-IgE (delayed/chronic)
  - Atopic dermatitis

- Non-IgE, Cell-mediated
  - Dietary protein enterocolitis
  - Dietary protein proctitis
  - Celiac
  - Crohn’s

EoE
How do we Guide Therapy?

- **PPI’s** to assess for PPI-REE

- **Diet**
  - Targeted Elimination (Skin Prick, Patch, IgE-directed serum & component) low PPV, < 45% remission
  - Empiric Elimination (6FED, 4FED, Dairy/Wheat)...better
  - Elemental...best but $$$, poor QoL

- **Steroids**
  - Topical (Budesonide vs Fluticasone)
  - Systemic

- **Biologics**
  - Anti-IL4r (Dupilumab)

- **Dilation**...you missed the boat
Diet Empiric

• Remission=no symptoms, ≤15 Eos/HPF
• 6FED (Dairy, Wheat, Egg, Soy*/Legumes, Peanut/Tree Nut, Fish)
  – 72% “remission”
• 4FED (Dairy, Wheat, Egg, Legumes*)
  – 72% “remission”
• Dairy
  – 64-65% “remission”

Gonzalez-Cervera, 2016
## Diet

Wechsler, 2014

<table>
<thead>
<tr>
<th>Start (least allergenic)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>End (most allergenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables (nonlegume)</td>
<td></td>
<td>Citrus fruit</td>
<td>Legumes</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Carrots, squash (all types), sweet potato, white potato, string beans, broccoli, lettuce, beets, asparagus, cauliflower, Brussels sprouts</td>
<td></td>
<td>Orange, grapefruit, lemon, lime</td>
<td>Lima beans, chickpeas, white/black/red beans</td>
<td>Corn</td>
</tr>
<tr>
<td>Fruit (noncitrus, nontropical)</td>
<td></td>
<td>Tropical fruit</td>
<td>Grains</td>
<td>Corn</td>
</tr>
<tr>
<td>Apple, pear, peaches, plum, apricot, nectarine, grape, raisins</td>
<td></td>
<td>Banana, kiwi, pineapple, mango, papaya, guava, avocado</td>
<td>Oat, barley, rye, other grains</td>
<td>Peas</td>
</tr>
<tr>
<td>Melons</td>
<td></td>
<td>Melons</td>
<td>Meat</td>
<td>Peanut</td>
</tr>
<tr>
<td>Honeydew, cantaloupe, watermelon</td>
<td></td>
<td>Meat</td>
<td>Fish/Shellfish</td>
<td>Wheat</td>
</tr>
<tr>
<td>Berries</td>
<td></td>
<td>Berries</td>
<td>Legumes</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Strawberry, blueberry, raspberry, cherry, cranberry</td>
<td></td>
<td>Legumes</td>
<td>Legumes</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Grains</td>
<td></td>
<td>Fish/Shellfish</td>
<td>Grains</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Rice, millet, quinoa</td>
<td></td>
<td>Grains</td>
<td>Grains</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td>Grains</td>
<td>Grains</td>
<td>Fish/Shellfish</td>
</tr>
<tr>
<td>Tomatoes, celery, cucumber, onion, garlic, any other vegetables</td>
<td></td>
<td>Grains</td>
<td>Grains</td>
<td>Fish/Shellfish</td>
</tr>
</tbody>
</table>
Medications

- **PPI’s:** to treat PPI-REE
  - 50% histologic improvement
  - 60% symptom improvement

- **Topical Corticosteroids**
  - Fluticasone 220 or 440mcg bid
    - 70.9% Histo, 82.3% Sx
  - Budesonide 1-2 mg qd-bid
    - 76.8% Histo, 87.9% Sx

- **Monoclonal Antibodies**
  - Anti-IL-4r (Dupilumab) looks promising

Eosinophilic Esophagitis: An Evidence-Based Approach to Therapy

González-Cervera J¹, Lucendo AJ²

Patient with symptoms of esophageal dysfunction and eosinophilic infiltration restricted to the esophagus

Double dose of PPI treatment for 8 weeks (ie, omeprazole 20-40 mg twice daily)

EGD with Biopsies

EoE that respond to PPIs (clinical and histological remission)

Persistent symptomatic alterations in esophageal caliber

Endoscopic dilation

PPI-based maintenance therapy

EoE that does not respond to PPIs

Topical corticosteroids

Dietary therapy

Persistent symptomatic alterations in esophageal caliber

Lack of response or nonadherence

Dietary therapy

Topical corticosteroids

Maintenance therapy based on topical corticosteroids/exclusion diets
EoE

- No consensus whether to treat:
  - Symptom resolution
  - Complete histologic remission
  - Lowest dose of medication; PRN?
  - Diet may require repeat EGDs

- Natural history still unclear
  - Schoepfer et al: “Swiss Cohort”
  - 17% had strictures if Dx at ≤ 2 years of Sx
  - >70% had strictures if Dx at > 20 years
Inter-Disciplinary Clinics

• GI, Allergy, Nutrition, Nurse Coordinator, Research Coordinator
• Adult Transition clinic
• Medical Decisions discussed real time
• Family Centered
• Nutrition support
• Coordination of care: procedures, labs, medications, food trials, immune therapy
• Need: Psychological support
Conclusions: Brass Tacks

- EoE is part of the “atoposphere”
- Evolution vs Entropy: natural history, therapy, monitoring
- young children + dysphagia = EoE
- PPI-REE is now a subtype of EoE
- If you are worried about EoE refer don’t Rx (a PPI)
Thank You