Eosinophilic Gastrointestinal Diseases

Jonathan M. Spergel, MD, PhD
Division of Allergy and Immunology
The Children’s Hospital of Philadelphia
Perelman School of Medicine at Univ. of Pennsylvania

Eosinophilic Esophagitis (EoE)

- Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.
- Diagnosed is based on clinical-pathologic findings on biopsy with greater than 15 eosinophils/HPF
  - Exclude other causes of esophageal eosinophilia
    - GERD, Celiac, IBD, Allergic Rhinitis
  - EoE is a lifelong chronic condition

World Map of EoE

Other Causes of Eosinophilia

- GERD
- Celiac
- IBD
- Fungal Infection
- Allergic Rhinitis
- Drug Allergy

Gastrointestinal Eosinophils

Normal values, per 400x microscopic field:
- Esophagus (0)
- Gastric antrum (2-20)
- Duodenum (2-20)
- Colon (10-50)

Disclosure

- Grants
  - Ception/Cephalon, APFED, DOD, NIH, Nutricia
- Consultant
  - DBV
**Symptoms of EoE**

- **EoE – Clinical manifestations**
  - Symptoms similar to those of GERD
  - Histology does not respond to PPI
  - Age related differences in symptoms
  - Symptoms may be intermittent
  - Male > Female
  - May progress to esophageal fibrosis and esophageal dysfunction if not managed appropriately.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Common Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Food refusal, FTT, feeding intolerances/aversions</td>
</tr>
<tr>
<td>Children</td>
<td>Vomiting, dysphagia, abdominal pain, heartburn, regurgitation, feeding refusal, feeding aversions</td>
</tr>
<tr>
<td>Adult</td>
<td>Dysphagia, food impaction, heartburn, reflux</td>
</tr>
</tbody>
</table>

**Symptom Progression in EoE**

*Finding Difficulty Age 11 yr*

*Heartburn Age 11 yr*

*Esophageal Stricture*

**Chronic EoE: Adults**

**Pathogenesis**

**Similarities to Atopic Dermatitis and Asthma**

- Allergen
- Atopic Dermatitis
- Airway eosinophilia
- Airway Hyperreactivity
- **EoE ASTHMA**

**Mouse Model of Epicutaneous Sensitization**

- Allergen
- Atopic Dermatitis
- Airway eosinophilia
- Airway Hyperreactivity
- **EoE ASTHMA**

**Esophageal Remodeling in Pediatric EoE**

- VWF positive vessels per hpf
- VCAM positive vessels per hpf

Furukawa et al. Gastroenterology 2007
Spergel et al. J Pediatr Gastroenterol Nutr 2009
Dysphagia or Inflammatory Intensity Pathogenesis
Similarities to Atopic Dermatitis and Asthma

Allergen
Atopic Dermatitis
Airway eosinophilia
Airway Hyperreactivity
**EoE ASTHMA**

The role of basophils in EoE

- TSLP promotes mature basophil survival and new basophil population with TSLP-R
  
  Siracusa et al, Nature 2011

The role of basophils in EoE

TSLP-elicited basophils make more IL-4, IL-6, CCL3, CCL4 and CCL12 compared to IL-3-elicited basophils.

Siracusa et al, Nature 2011

The role of basophils in EoE

ST2/T1, also IL33 receptor, leads to basophil activation

IL-33 leads to Eosinophil, TH2, mast cells and basophil activation

Siracusa et al, Nature 2011

The role of basophils in EoE

Role of Mast Cells

- Mast Cells invade Esophagus
- Secrete TGF-b1
- Induce Smooth muscle contraction


The role of Atopy in EoE

EoE

Genetic Risk Factor

TSLP

IL-13

CCL26

TGFß

POSTN

FLG

barrier function

proliferation

fibrosis

eosinophilia

dendritic cell

Th2 cell

fibroblast

epithelial cells

mast cell

allergic

Insult ± GERD

mastocytosis

basophil
Association of Atopy with EoE

<table>
<thead>
<tr>
<th>Ref</th>
<th># of Pts</th>
<th>Age (Yrs)</th>
<th>Asthma</th>
<th>AR</th>
<th>AD</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>620</td>
<td>8m-20</td>
<td>10%</td>
<td>20-40%</td>
<td>20-20%</td>
<td>1-6%</td>
</tr>
<tr>
<td>Spergel</td>
<td>89</td>
<td>3m-18 yr</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Assad</td>
<td>45</td>
<td>3m-16 yr</td>
<td>39%</td>
<td>30%</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>Sugnanam</td>
<td>39</td>
<td>1m-31</td>
<td>66%</td>
<td>93%</td>
<td>4%</td>
<td>26%</td>
</tr>
<tr>
<td>Guajardo</td>
<td>23</td>
<td>18-57</td>
<td>26%</td>
<td>78%</td>
<td>4%</td>
<td>--</td>
</tr>
</tbody>
</table>

Seasonal Variation in EoE

20 year old female, history of multisensitization to aeroallergens. Symptoms of allergy and EE peaked during pollen season.

Treatment Options

- Food avoidance
- Elimination diet
- Combination elimination diet and elemental supplementation
- Nutritional therapy
- Combination of diet and steroids
- Pharmacological therapy
- Eos/HPF
- EoE diagnosis
- Educate family on options

Pharmacologic Therapy

Systemic Steroids – effective at improving symptoms and histology of EoE in 95% of pts
- Upon discontinuation, 99% had recurrence of symptoms
- (Long term use) Side effects: bone abnormalities, poor growth, adrenal suppression
- May be needed short term for extreme cases

Topical/swallowed Steroids – less toxic to pt while still 50-85% effective
- A mainstay of EoE treatment in adults and children.
- Upon discontinuation almost all patients have a recurrence of symptoms
- Often, large doses needed
- Side effects: esophageal candidiasis

Link Between Food Allergy and EoE

- Dobbins (1977): 51 yo with GERD, food allergy and esophageal eosinophilia
- Kelly and Sampson (1995)
  - 10 patients (5 yr range: 8 mo-12.5 yr)
  - Given amino-acid based formula (> 6 weeks)
    - Neocate® or Neocate 1+®
    - 6 prior Nissen fundoplication
    - Endoscopy pre- & post-trial
- Liacouras et al, Clin Gastroenterol Hepatol 2005
- Furuta et al, Gastroenterology 2007
Kelly, 1995

Dietary Management
Amino Acid-Based Formula

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-Diet</th>
<th>Post-Diet</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils/HPF</td>
<td>38.7 ± 10.3</td>
<td>1.1 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>30</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GERD Symptoms</td>
<td>134</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- 172 patients (128 nasogastric tubes, 32 oral, 4 failed, 8 noncompliant)
- Patients evaluated 4-6 weeks after starting diet

Liacouras et al, Clin. Gastroenterol Hepatol 2005

How to Select the foods?

Selective Diet: Guess

- 60 children
  - 35 children on elimination diet of milk, soy, wheat, egg, peanut and seafood
  - 25 children on elemental diet
- Repeat endoscopy 6 weeks later
- 74% of six-food diet had <10 eos/hpf
- 88% of elemental diet had <10 eos/hpf


SFED follow-up

- Single Food Reintroduction in 36 children
- 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%

Kagalwalla et al. JPGN 2011

Food Testing in EoE

- 74% Atopic (asthma, ARC, or AD)
- 1/3 have negative skin tests
- Most common foods were
  - Egg, soy, milk, peanuts, beef, chicken, wheat, corn, pear, and potato
- 1/4 have negative APT
  - 1/8 have both negative SPT and APT
  - Wheat, corn, soy, milk, beef, rice, chicken, egg, rye, oat, and potato
Predictive Values: Combination of SPT and APT

<table>
<thead>
<tr>
<th>Food</th>
<th>Combined SPT and APT</th>
<th>PPV</th>
<th>NPV</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (n=99)</td>
<td></td>
<td>93.0%</td>
<td>32.4%</td>
<td>84.6%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Egg (n=36)</td>
<td></td>
<td>65.5%</td>
<td>86.0%</td>
<td>86.7%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Wheat (n=37)</td>
<td></td>
<td>73.7%</td>
<td>99.1%</td>
<td>80.9%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Soy (n=25)</td>
<td></td>
<td>43.2%</td>
<td>92.6%</td>
<td>79.5%</td>
<td>87.6%</td>
</tr>
<tr>
<td>Beef (n=21)</td>
<td></td>
<td>48.4%</td>
<td>96.2%</td>
<td>84.9%</td>
<td>86.2%</td>
</tr>
<tr>
<td>Chicken (n=20)</td>
<td></td>
<td>46.3%</td>
<td>99.0%</td>
<td>83.3%</td>
<td>84.6%</td>
</tr>
<tr>
<td>Corn (n=17)</td>
<td></td>
<td>62.5%</td>
<td>98.6%</td>
<td>81.7%</td>
<td>95.0%</td>
</tr>
<tr>
<td>Potato (n=12)</td>
<td></td>
<td>47.4%</td>
<td>98.2%</td>
<td>91.5%</td>
<td>81.8%</td>
</tr>
<tr>
<td>Rice (n=11)</td>
<td></td>
<td>32.3%</td>
<td>99.0%</td>
<td>82.5%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Pork (n=11)</td>
<td></td>
<td>38.5%</td>
<td>97.5%</td>
<td>93.1%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

Spergel et al, JACI 2007 and unpublished data

Specific IgE

- 53 adult patients
- 80% had positive sIgE to food or aeroallergens
- sIgE was most sensitive

Erwin et al, J Allergy Clin Immunol 2010

What method is best?

<table>
<thead>
<tr>
<th>Method</th>
<th>SPT/ APT</th>
<th>MILK</th>
<th>Milk, Egg, Wheat</th>
<th>SFED</th>
<th>SPT/ APT + Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of Resolution</td>
<td>57%</td>
<td>30%</td>
<td>48%</td>
<td>60%</td>
<td>77%</td>
</tr>
</tbody>
</table>

- Retrospectively examined all patients with defined food identified
- Excluded patients on ICS or anti-IL5
- Examined which diet method lead to normalization of histology

Common Challenge - Diet Adherence

Nutritional Balance

Nutrition Therapy

- Pharmacologic therapy has been shown effective but long term use and possible side effects must be considered
- Elimination diet is effective - keeping in mind nutrient deficiencies may occur
- Elemental diet is the most effective nutrition therapy. Compliance/cost may be an issue for some patients

Elemental diet is the most effective nutrition therapy. Compliance/cost may be an issue for some patients

- Combination of diet and steroids for difficult to treat patient
- Combination of elimination diet with elemental supplementation may be the best fit for patients and families dealing with EoE.

"Dietary therapy should be considered as an effective therapy in all children diagnosed with EoE."
Acknowledgements

Allergy Section
- Michele Shuler
- Terri Brown Whitehorn
- Antonella Cianferoni
- Rushani Saltzman
- Mariel Boyd
- Laura Gober
- Kathy Penzone
- Jennifer Heimall
- Mariel Boyd
- Emily Dudek
- Katie Ryumann
- Malkora Maggadottir

Center for Applied Genomics
- Hakon Harkonson
- Patrick Sleiman

GI Division
- Chris Liacouras
- Joshua Friedman
- Mel-Lin Wang
- Ritu Verma

Pathology/Vet
- David Artis
- Mark Sircusa

HUP
- Gary Falk
- Benjamin Soule

Collaborators
- Seema Aceves
- Glenn Furuta
- Mark Rothenberg