Eosinophilic Esophagitis: Pathogenesis and Role of Food Allergy

Norma Rubini, MD, PhD
Associate Professor of Allergy and Immunology
Federal University of the State of Rio de Janeiro
UNIRIO
Eosinophilic Esophagitis

History

• 1993 – Atwood et al – 11 adults with dysphagia, normal pH probe and eosinophilic infiltration in esophagus mucosa

• 1995 – Kelly et al – 10 children with severe GERD unresponsive to medicines

✓ Elemental diet => resolution of symptoms and reduction in eosinophils count

✓ Food challenges => recurrence of symptoms in 9/10

Atwood SE et al, Dig Dis Sci 1993
Kelly K et al, Gastroenterology 1995
Eosinophilic Esophagitis

Epidemiology

- **Prevalence**
  - Pediatric population – Hamilton County, Ohio - 4:10,000
  - Adult Swiss cohort – 2:10,000 adults
  - Recent studies in Europe and USA – 6:10,000 individuals

- **Male to female rate – 3:1**
- **Caucasian ( ~ 80%)**
- **Atopy ( ~ 60%)**

Noel RJ et al, N Engl J Med 2004,
DeBrosse CW et al, JACI 2010,
Sperry SLW et al, Am J Gastroenterology 2011
Philpott H et al, Clin Exp Allergy 2014
Eosinophilic Esophagitis

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.”

Liacouros et al, Eosinophilic esophagitis: Updated consensus recommendations for children and adults, JACI 2011; 128: 3-20
Pathogenesis of EoE

Genetic heritability
- Strong familial association (7 – 10%)
- High sibling risk ratio ($\lambda_s \sim 80$)

Immune / antigenic stimulus

Eosinophilic inflammation
- IgE mediated
- Non-IgE mediated

Straumann A and Shoepfer A, Gut 2014
Raheem M et al, Frontiers Ped 2014
Wechler JB and Bryce PJ, Gastroenterol Clin N Am 2014
EoE – Pathological process

• Acute narrowing of the esophageal lumen by inflammation and oedema.

• Fixed narrowing and limited distensibility of the lumen by remodeling.

• Dynamic and variable narrowing caused by muscular contraction or spasm.

Philpott H et al, Pharmacol Ther 2014
Pathogenesis of EoE

Modified from Wechler JB e Bryce PJ, Gastroenterol Clin N Am 2014 and Sherril and Rothenberg, JACI 2011
Genetic risk variants in EoE

Sherril and Rothenberg, JACI 2011;128: 23-32
# Eosinophilic Esophagitis

## Established risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Proposed mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>TSLP on sex chromosomes, Relaxin</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Non-X linked SNP’s (e.g. Filaggrin, Eotaxin-3)</td>
</tr>
<tr>
<td>Atopy</td>
<td>IgE mediated inflammatory infiltration</td>
</tr>
</tbody>
</table>

Philpott H et al, Clin Exp Allergy 2014
## Putative risk factors for EoE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Proposed mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired barrier function</td>
<td>Increased antigen exposure</td>
</tr>
<tr>
<td>Impaired tolerance to food antigens</td>
<td>Timing and nature of food antigen exposure</td>
</tr>
<tr>
<td>Commercially prepared foods</td>
<td>Agglutinated proteins incite immune reaction</td>
</tr>
<tr>
<td>Proton pump inhibitor use</td>
<td>Proteins are not denatured =&gt; greater antigen exposure</td>
</tr>
<tr>
<td>Aeroallergens in spring/summer</td>
<td>Exposure of air passages =&gt; inflammatory reaction and trafficking of eosinophils</td>
</tr>
<tr>
<td>Living in a temperate or arid climate</td>
<td>Low vitamin D and/or higher aeroallergen exposure</td>
</tr>
<tr>
<td>Migration as adult</td>
<td>Novel antigen incite immune reaction</td>
</tr>
<tr>
<td>Increased fibrotic remodeling</td>
<td>Decreased relaxin expression, SNP’s for TGF-β and ACE</td>
</tr>
</tbody>
</table>

Modified from Philpott H et al, Clin Exp Allergy 2014
Endoscopic features

Liacouros et al, JACI 2011; 128: 3-20
Eosinophilic Esophagitis

Histologic features
• Mucosal eosinophilia (>15 / hpf)
• Eosinophil microabscess formation
• Superficial layering of eosinophils
• Extracellular eosinophil granules
• Epithelial desquamation
• Basal zone hyperplasia
• Dilated intercellular spaces
• Subepithelial fibrosis / sclerosis
• Mastocytosis and mast cell degranulation
• CD8 lymphocytes and B cells

Liacouros CA et al, JACI 2011; 128: 3-20
Histopathologic features

Eosinophilic infiltration (110 eosinophils/hpf) and superficial layering of eosinophils

MBM, male, Caucasian, 22 years – EoE and milk allergy

N Rubini, 2012
EoE and food allergy

- High prevalence of concomitant atopic diseases (>50%).

- Elevated serum IgE and blood eosinophilia – 50% to 60%.

- Food hypersensitivity has been reported in 19% - 73% of children and 13% - 25% of adults with EoE.

- Clinicopathological responsiveness to dietary therapy.

- De novo EoE has been observed with oral immunotherapy used for treatment of food allergies.

Liacouros et al, JACI 2011
Haheem M et al, Frontiers Ped 2014
Straumann A, Schoepfer A, Gut 2014
Allergic sensitization in pediatric patients with EoE

SPT – foods and inhalants
specific IgE – foods and inhalants
APT – foods

Foods – 68%

Both Food and Inhalant (38%)
Food only (21%)
Food by patch test only (9%)
Inhalant only (13%)
Neither Food nor Inhalant (19%)

N = 53

Erwin et al, Ann Allergy Asthma Immunol 2010; 104: 496-502
Allergic sensitization in pediatric patients with EoE

N = 53

Erwin et al, Ann Allergy Asthma Immunol 2010; 104: 496-502
## EoE and Food Allergy – Skin Prick test

<table>
<thead>
<tr>
<th>Food (n)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (46)</td>
<td>95.7</td>
<td>57.7</td>
<td>42.3</td>
<td>97.6</td>
</tr>
<tr>
<td>Egg (39)</td>
<td>84.8</td>
<td>75.4</td>
<td>65.1</td>
<td>90.2</td>
</tr>
<tr>
<td>Soy (28)</td>
<td>70.0</td>
<td>68.9</td>
<td>37.8</td>
<td>89.5</td>
</tr>
<tr>
<td>Wheat (26)</td>
<td>77.8</td>
<td>64.7</td>
<td>18.9</td>
<td>96.5</td>
</tr>
<tr>
<td>Corn (26)</td>
<td>57.1</td>
<td>71.3</td>
<td>13.8</td>
<td>95.4</td>
</tr>
<tr>
<td>Beef (23)</td>
<td>81.8</td>
<td>74.7</td>
<td>30.0</td>
<td>96.9</td>
</tr>
<tr>
<td>Chicken (15)</td>
<td>50.0</td>
<td>83.3</td>
<td>26.3</td>
<td>93.3</td>
</tr>
<tr>
<td>Rice (14)</td>
<td>50.0</td>
<td>85.6</td>
<td>13.3</td>
<td>97.5</td>
</tr>
<tr>
<td>Potato (11)</td>
<td>60.0</td>
<td>89.9</td>
<td>25.0</td>
<td>97.6</td>
</tr>
</tbody>
</table>

n = 316  
Spergel JM et al, JACI 2007; 119:11
## EoE and Food Allergy – Atopy Patch Test (APT)

<table>
<thead>
<tr>
<th>Food</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sens(%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>83.3</td>
<td>58.7</td>
<td>43.5</td>
<td>90.2</td>
</tr>
<tr>
<td>Egg</td>
<td>78.3</td>
<td>82.8</td>
<td>62.1</td>
<td>91.4</td>
</tr>
<tr>
<td>Soy</td>
<td>66.7</td>
<td>87.3</td>
<td>66.7</td>
<td>87.3</td>
</tr>
<tr>
<td>Wheat</td>
<td>74.2</td>
<td>83.9</td>
<td>71.9</td>
<td>85.5</td>
</tr>
<tr>
<td>Corn</td>
<td>65.8</td>
<td>93.9</td>
<td>89.3</td>
<td>78.0</td>
</tr>
<tr>
<td>Beef</td>
<td>94.4</td>
<td>87.0</td>
<td>65.4</td>
<td>98.4</td>
</tr>
<tr>
<td>Chicken</td>
<td>66.7</td>
<td>95.7</td>
<td>80.0</td>
<td>91.7</td>
</tr>
<tr>
<td>Rice</td>
<td>59.1</td>
<td>96.9</td>
<td>86.7</td>
<td>87.5</td>
</tr>
<tr>
<td>Potato</td>
<td>53.8</td>
<td>94.6</td>
<td>63.6</td>
<td>92.1</td>
</tr>
</tbody>
</table>

n = 316

Spergel JM et al, JACI 2007; 119:11
# EoE and Food Allergy - APT + SPT

<table>
<thead>
<tr>
<th>Food</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sens(%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>81</td>
<td>44</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>Egg</td>
<td>60</td>
<td>93</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Wheat</td>
<td>42</td>
<td>88</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>Soy</td>
<td>33</td>
<td>93</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>Peanut</td>
<td>22</td>
<td>99</td>
<td>94</td>
<td>83</td>
</tr>
<tr>
<td>Beef</td>
<td>31</td>
<td>96</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Corn</td>
<td>42</td>
<td>99</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td>Chicken</td>
<td>32</td>
<td>98</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>Potato</td>
<td>36</td>
<td>98</td>
<td>81</td>
<td>90</td>
</tr>
</tbody>
</table>

n = 319

Spergel JM et al, JACI 2012; 130: 461
<table>
<thead>
<tr>
<th>Item</th>
<th>Elemental diet</th>
<th>Allergy testing elimination diet</th>
<th>Empirical elimination diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicopathological success rate</td>
<td>&gt;80%</td>
<td>Children – 50% - 70%</td>
<td>50% - 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults – 20% - 30%</td>
<td></td>
</tr>
<tr>
<td>Number of elimination foods</td>
<td>All food groups eliminated</td>
<td>Typically ≤ 4 foods eliminated</td>
<td>≤ 6 foods eliminated</td>
</tr>
<tr>
<td>Numbers of endoscopies required</td>
<td>++++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Drawbacks</td>
<td>Costly May require feeding tube Impact on QoL ++++</td>
<td>Impact on QoL ++</td>
<td>Impact on QoL ++</td>
</tr>
</tbody>
</table>

Modified from Strautmann A and Shoepfer A, Gut 2014
Identification of causative foods in children with EoE

N = 319

Spergel JM et al, JACI 2012; 130: 461
Four-food elimination diet

- Prospective multicenter study in 4 Spanish hospitals between 2012 – 2014

- Population: 52 adults with EoE

- Four-food diet: milk, wheat, egg and soy/legumes

- Results: 28 patients (54%) achieved clinicopathological remission

Diagnostic investigation of food allergy in EoE

Eosinophilic esophagitis

Allergy testing
(Prick test, specific IgE, APT)

Identified food(s)

Eliminated food(s)

Improvement

No improvement

> 2 foods

Unidentified food

Elemental diet or empirical diet

Improvement

No improvement

Food reintroduction

Consider other causes

Modified from Spergel J, AAAAI 2007
Conclusions

• Eosinophilic esophagitis (EoE) is an inflammatory disorder that is most likely initiated by a hypersensitivity reaction to allergic insult, with a late-phase characterized by eosinophil recruitment and subsequent tissue damage.
• The most clearly defined risk factors for EoE are gender (male predominance), race (Caucasians) and atopy.
• Most patients with eosinophilic esophagitis have compelling evidence of IgE-mediated hypersensitivity to foods, as determined by increased food-specific IgE or abnormal skin prick test.
• Removal of disease-exacerbating foods has proven to be successful in treating the disease and elimination diets have thus become the mainstay of therapy in EoE.
• Diet therapy, empiric or allergic test-directed, is an accepted and efficacious alternative to elemental diet that offers improved compliance, better food choices, less food reintroduction, and fewer endoscopies.