Triggers
- Allergens
- Allografts
- Helminths
- Viruses
- Tissue Injury
Triggers
- Allergens
- Allografts
- Helminths
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Cytotoxic Secretory Products
- ECP
- EDN
- EPO
- MBP

Triggers
- Allergens
- Allografts
- Helminths
- Viruses
- Tissue Injury

Cytotoxic Secretory Products
- ECP
- EDN
- EPO
- MBP

Ribonucleases
Triggers
- Allergens
- Allografts
- Helminths
- Viruses
- Tissue Injury

Cytotoxic Secretory Products
- ECP
- EDN
- EPO
- MBP

Lipid Mediators
- Leukotrienes
- Platelet Activating Factor

Triggers
- Allergens
- Allografts
- Helminths
- Viruses
- Tissue Injury

Lipid Mediators
- Leukotrienes
- Platelet Activating Factor

Cytotoxic Secretory Products
- ECP
- EDN
- EPO
- MBP

Ribonucleases

Cytokines
- IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, IL-13, IFN-γ, GM-CSF, TGF-α/β, TNF-α

Triggers
- Allergens
- Allografts
- Helminths
- Viruses
- Tissue Injury

Chemokines
- Eotaxin
- MIP-1
- RANTES

Lipid Mediators
- Leukotrienes
- Platelet Activating Factor

Cytotoxic Secretory Products
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- EDN
- EPO
- MBP

Ribonucleases

Cytokines
- IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, IL-13, IFN-γ, GM-CSF,
  TGF-α/β, TNF-α

Triggers
- Allergens
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- Viruses
- Tissue Injury

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Lipid Mediators
- Leukotrienes
- Platelet Activating Factor

Cytotoxic Secretory Products
- ECP
- EDN
- EPO
- MBP

Neuro-mediators
- Substance P
- VIP

Cytokines
- IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, IL-13, IFN$\gamma$, GM-CSF, TGF-\(\alpha/\beta\), TNF-\(\alpha\)

Allergens
Allografts
Helminths
Viruses
Tissue Injury

Triggers

Chemokines
Eotaxin
MIP-1
RANTES

Lipid Mediators
Leukotrienes
Platelet Activating Factor

Cytotoxic Secretory Products
ECP
EDN
EPO
MBP

Ribonucleases

Neuro-mediators
Substance P
VIP

Antigen Presentation
B7.2
MHC-II

Cytokines
IL-2, IL-3, IL-4, IL-5, IL-6,
IL-8, IL-12, IL-13, IFNγ, GM-CSF,
TGF-α/β, TNF-α

Bone Marrow → GATA-1
   IL-3
   GM-CSF
   IL-5


Matthew et al; PNAS; 1998
Mishra et al. JCI; 1999
Bone Marrow → GATA-1
IL-3 → GM-CSF → IL-5

Blood → IL-5

P-selectin
CD18
ICAM-1
VLA-4
VCAM-1

GI Tract

EOTAXIN

Matthew et al; PNAS; 1998
Mishra et al. JCI; 1999
Matthew et al; PNAS; 1998
Mishra et al. JCI; 1999
Matthew et al; PNAS; 1998
Mishra et al. JCI; 1999
Gouon-Evans et al. Development; 2002
The GI tract is the predominant reservoir of Eos.

Eosinophil homing occurs early in development

Eosinophil homing occurs independent of endogenous flora

Eosinophil homing is critically regulated by eotaxin-1/CCR3

Eotaxin-1 dependent eosinophil homing is regulated by β7-integrin
IgE-mediated

Non-IgE-mediated

Food Anaphylaxis

Protein-Hypersensitivity Enteropathy

Eosinophil Associated GI Disorders (EGID)

Eosinophilic Esophagitis
Eosinophilic Gastritis
Eosinophilic Enteritis
Eosinophilic Colitis
Eosinophilic Gastroenteritis

Celiac Disease

IBD

Critical Questions: How common are EGID?
Are eosinophils effector cells in disease pathogenesis?

Rothenberg. JACI; 2004
Pediatric EE in Hamilton County

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (interquartile range)</td>
<td></td>
</tr>
<tr>
<td>Feeding disorder</td>
<td>2.0 (1.2–6.2)</td>
<td>14 (13.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.1 (3.5–12.3)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.0 (9.6–15.2)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>13.4 (10.0–16.7)</td>
<td>28 (27.2)</td>
</tr>
<tr>
<td>Food impaction</td>
<td>16.8 (13.7–19.6)</td>
<td>7 (6.8)</td>
</tr>
</tbody>
</table>

* Patients may have had more than one symptom, but only the most prominent symptom is included here. The median age varied significantly according to the primary symptom (P<0.001 by the Kruskal–Wallis test).

Noel et al; N Eng J Med, 2004
Pediatric EE in Hamilton County

Table 2. History of Atopy in the 103 Pediatric Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoconjunctivitis</td>
<td>57.4</td>
</tr>
<tr>
<td>Wheezing</td>
<td>36.8</td>
</tr>
<tr>
<td>Possible food allergy†</td>
<td>46</td>
</tr>
<tr>
<td>Family history of atopic disease</td>
<td>73.5</td>
</tr>
<tr>
<td>Family history of eosinophilic esophagitis</td>
<td>6.8</td>
</tr>
<tr>
<td>Family history of esophageal dilatation</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Noel et al; N Eng J Med, 2004
Pediatric EE in Hamilton County

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age (yr)</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>0–19</td>
<td>22</td>
<td>24</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>(in 10,000 populations)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0–4</td>
<td>1.592</td>
<td>0.494</td>
<td>1.253</td>
<td>0.328</td>
</tr>
<tr>
<td></td>
<td>5–9</td>
<td>0.531</td>
<td>0.988</td>
<td>1.253</td>
<td>1.148</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>0.707</td>
<td>0.988</td>
<td>0.940</td>
<td>1.312</td>
</tr>
<tr>
<td></td>
<td>15–19</td>
<td>0.884</td>
<td>1.318</td>
<td>1.724</td>
<td>1.148</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0–19</td>
<td>0.909</td>
<td>0.991</td>
<td>1.033</td>
<td>1.281</td>
</tr>
</tbody>
</table>

* Estimates were based on data from the 2000 Census on the population in each age group in Hamilton County, Ohio.

Noel et al; N Eng J Med, 2004
Comparative Annual Incidence in Pediatrics

- Asthma 1000
- Celiac disease 300
- Eosinophilic Esophagitis 10
- Crohn’s disease 4
- Biliary atresia 0.73

(Cases per 100,000)

Implications: National Population age 0-19: 80,473,265
- Prevalence (minimum): 22,855
- Annual incidence: 6438

Noel et al
• JR is a 16 yo boy with 2 year hx of dysphagia, epigastric pain, and weight loss, who presents to the ER with a food impaction.
• As an infant, JR suffered from moderate eczema. As a toddler, JR had frequent URI associated with chronic rhinitis and wheezing.
• Notably, JR has no history of food allergy (anaphylaxis).
# Eosinophilic Esophagitis vs. GERD

<table>
<thead>
<tr>
<th>Property</th>
<th>EE</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Familial Inheritance</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Food Allergen Sensitization</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Epithelial Hyperplasia</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Proximal Esophagitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Esophageal Eosinophils</td>
<td>Very High</td>
<td>Mild Increase</td>
</tr>
<tr>
<td>pH probe</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Rothenberg et al.
Only Intra-Pulmonary Allergen Promotes Esophageal Eosinophilia

Mishra et al JCI; 2001
Intratracheal IL-13 induces EE

Mishra et al. Gastro; 2003
Epicutaneous Allergen Sensitization Primes for Aeroallergen-induced Eosinophilic Esophagitis

Saito et al; Gastroenterology 2005
IL-5 Gene Targeted Mice Do Not Develop Eosinophilic Esophagitis

Mishra et al JCI; 2001
Allergen-induced Epithelial Hyperplasia is Ablated in IL-5 Deficient Mice

Mishra et al JCI; 2001
A PHASE I/II STUDY OF THE EFFECT OF INTRAVENOUS ANTI-IL-5 (Mepolizumab) SB 240563 ON THE OUTCOME AND MANAGEMENT OF HYPEREOSINOPHILIC SYNDROMES

Garrett et al.; JACI; 2003
Beneficial Effect of Anti-IL-5 on Patients with Hypereosinophilic Syndromes

Garrett et al.; JACI; 2003
Effect of Anti-IL-5 (Mepolizumab- SB 240563) on Eosinophilic Esophagitis

-18 yo allergic male with long standing history of dysphagia and food impactions. Endoscopically proven EE has been refractory to diet modifications, anti-GERD Rx, and glucocorticoids.

PB AEC=600/μl;
elevated plasma IL-5: 39 pg/ml (normal <7)

Garrett et al.; JACI; 2003
Therapeutic Options for EGID

- Allergen elimination-dietary and airborne antigens
- Anti-inflammatory agents (parenteral or “inhaled” glucocorticoids)
- Elemental Diet
- Systemic Glucocorticoids
- (Anti-GER Rx and anti-LTs)
- Anti-IL5 and/or anti-CCR3/eotaxin
- Imatinib (Gleevec)
Patient with EE

Allergy Testing
(40 Foods)

Non-allergic

Fluticasone Propionate

Allergic

Elimination Diet
(Failure)

Fluticasone Propionate
Effect of FP on Patients with EE

Noel et al, Clin Gastro Hep; 2004
These results indicate that the epithelial layer thickening in EE is due to epithelial hyperplasia and that fluticasone reverses this abnormality.

Noel et al, Clin Gastro Hep; 2004