Eosinophilic Disease of the Bowel

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Objectives

• To discuss clinical presentations of patients with a protein allergy or intolerance

• Discussion on FPIES

• To discuss eosinophilic esophagitis: pathogenesis, clinical presentation, therapy and future research
What triggers an eosinophil response?

- **Food antigens:** Cows milk protein, soy protein, beef protein. Other antigens like egg albumin, etc.

- **Infections:** Giardia lamblia, roundworm, hookworm, CMV, Ascaris.

- **Medications:** Post transplant meds (FK506), Gold based therapies for arthritis, chemotherapeutic agents.

- **Environmental stimuli**

Walker-Durie, Pediatric GI disease 3rd edition
Pathogenesis

• Both IgE mediated and IgE independent mechanisms are important in the development of intolerances.

• Allergic patients with intolerances tend to have higher total IgE and tissue IgE on IF, compared to non allergic patients who have increased IgA and IgM.

• Eosinophil recruitment and activation is induced by IL 3, GM-CSF and IL 5.
Gastrointestinal Food Hypersensitivity

IgE-Mediated

Anaphylaxis
Immediate GI hypersensitivity
Oral allergy syndrome

Eosinophilic Esophagitis
Eosinophilic Gastritis
Eosinophilic Enteritis
Eosinophilic Colitis

Enterocolitis syndrome
Dietary protein proctitis
Celiac Disease

Non-IgE-Mediated
Tests should not be interpreted as just positive or negative but rather as the probability of indicating true food allergy.
Pathophysiology of eosinophilic esophagitis

- Mast cell
  - IL 4
  - IL 13

- Airborne allergens

- Food allergens

- Epithelial cells, smooth muscle cells, fibroblasts

- Eosinophil
  - Eosinophil production

- Bone marrow

- Esophageal epithelium
  - Infiltration by eosinophils

Ferguson & Foxx-Orenstein, Dis Esophagus 2007; 20: 2
IL-3, GM-CSF, IL-5 in EGE


- IL-13, GM-CSF, IL-5 were increased in the GI tract of patients with intolerances.
- The presence of these cytokines was associated with a dense eosinophil infiltration of the lamina propria in the small bowel and colon.
- IL-5 supports the proliferation and terminal differentiation of eosinophil precursors and also prolongs the survival of mature eosinophils as well as a chemotactic factor.
- The genes for IL-13, GM-CSF and IL-5 are clustered on the long arm of Chr 5 (5q23-22).
Adverse Reactions to Food

Adverse Food Reaction

Immune Mediated (Food Allergy)

- IgE
- Non-IgE

Nonimmune Mediated (Food Intolerance)

- Enzymatic
- Pharmacological
- Undefined
Gastrointestinal Manifestations of Protein Allergy or Intolerance

• Gastroesophageal reflux / vomiting
• Colic / irritability / abdominal pain
• Gastrointestinal bleeding
• Diarrhea
• Constipation
• Heartburn / chest pain
• Difficulty swallowing
• Failure to thrive
Commonly Implicated Foods

- Cow milk
- Soy
- Wheat
- Egg
- Nuts
- Seafood
Allergic Proctocolitis

- **Age at onset**
  - 1 day to 6 months (most 2-8 weeks)

- **Family history**
  - High prevalence of atopy

- **Manifestations**
  - Blood-streaked, soft-to-loose stools
  - Fecal leukocytes
  - Low risk for anemia
  - Infant well appearing

- **Implicated antigens**
  - Cow milk soy, egg, corn
Allergic Proctocolitis Pathology

• **Endoscopic**
  – Colitis (erythema, friability, erosions)

• **Microscopic**
  – eosinophilia or lymphoid nodular hyperplasia
Management of Allergic Proctocolitis

• Elimination of food allergen
  – Maternal dietary restriction
  – Casein hydrolysate formula
  – Amino acid formula for severe cases

• Gross bleeding typically resolves within 72 hrs

• Occult bleeding may take several weeks to resolve
Protein Enterocolitis

• Age of onset
  – 1 day to 1 year

• Manifestations
  – Emesis
  – Abdominal Distention
  – Failure to thrive
  – Hypotension
  – Metabolic acidosis
  – Blood in stools
  – Fecal leukocytes and reducing substances

• Implicated antigens
  – Cow milk, soy, rice, poultry, fish
Management of Protein Enterocolitis

• Casein hydrolysate formula successful 90% of time
  – Amino acid formula needed in ~10% cases
  – Nasogastric feedings may be required in severe cases of malabsorption

• Symptoms resolve within 1 week

• If cow milk protein implicated, 50% tolerance by 18 months, 90% by 36 months
Food protein-induced enterocolitis syndrome (FPIES)

Less than 2 years of age at first presentation (frequent feature but not mandatory)

Exposure to the incriminated food elicits repetitive vomiting and/or diarrhea within 4 h without any other cause for the symptoms.

Repeated exposure to causative food elicits gastrointestinal symptoms without alternative cause.

Absence of symptoms that may suggest an IgE-mediated reaction.

Avoidance of the offending protein from the diet results in resolution of symptoms.

Re-exposure or oral food challenge elicits typical symptoms within 2–4 h. Two typical episodes are needed to deliver the definitive diagnosis.
# Acute and chronic FPIES clinical manifestations

<table>
<thead>
<tr>
<th>Acute FPIES</th>
<th>Chronic FPIES</th>
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<tbody>
<tr>
<td>Important and repetitive vomiting (constant)</td>
<td>Regurgitation, small amounts</td>
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<tr>
<td>Lethargy (frequent)</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Hyporeactivity (frequent)</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Pallor (frequent)</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diarrhea, sometimes bloody</td>
</tr>
<tr>
<td>Dehydration (rare)</td>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Hypothermia (rare)</td>
<td></td>
</tr>
<tr>
<td>Hypotension (rare)</td>
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Allergy Prevention - Infants

- Estimated 2-3% infants develop food allergies
- Many allergies continue on into childhood and adulthood
- Increased duration of exclusive BF associated w/ decrease in childhood allergy
- Many studies have examined other methods in preventing allergies in infancy and childhood
Allergy Prevention - Infants

- Preventative Measures:
  - maternal allergen avoidance during pregnancy and lactation
  - exclusively breastfeeding
  - avoidance of potential allergens until 12mo
  - *hydrolyzed formulas*: changing the protein to make it less allergenic
To determine whether hydrolyzed formulas (HF) are preventative in allergies and food intolerances; what type of formula and which infants will benefit

Included in analysis were randomized trials with ≥ 80% participant follow up (n=18)

Comparison of hydrolyzed infant formulas to HM or cow’s milk formulas (CMF)
Meta-analysis, Osborn 2007

Results:

• 14/18 studies used high-risk infants
Meta-analysis, Osborn 2007

Results:

- Partially HF vs CMF (n=7)
  - significant reduction in allergy

Prolonged use of HF vs CMF (n=12)
  - significant reduction in all infant allergies, some into childhood

- Extensively HF vs Partially HF with prolonged use (n=3)
  - no significant difference in allergy or food intolerance
Meta-analysis, Osborn 2007
Discussion/Conclusion:

• No evidence that HF better than HM in short term or prolonged use

• There is evidence of benefit from HF vs CMF for prevention of allergy in infants and children

• “When babies are not exclusively breastfed, using hydrolyzed infant formulas instead of ordinary cow’s milk and soy milk formulas can reduce allergies in babies and children at significant risk”
Prebiotic (Oligosaccharide) Addition to Infant Formula

• “Food” for beneficial bacteria in the gut
• Not digested in upper GI tract
• Oligosaccharides added to mimic breast milk prebiotic function
• Alter intestinal microflora to favor beneficial bacteria to support the developing GI and immune systems
Prebiotics Are Oligosaccharides That Are Added to Infant Formulas to Support Beneficial Bacteria in the Gut

Prebiotics travel through the GI tract undigested by human enzymes.
Galactooligosaccharides (GOS) Have Been Extensively Studied in Infant Formulas

7 In Vitro Studies

15 Adult Studies

33 Animal Studies

15 Infant Studies (>2000 infants)
GOS/FOS (9:1) Increased IgA More Like the Breastfed Infant

GOS/FOS (9:1) Cumulative Incidence of Allergy Decreased

Episodes per infant. Study was conducted with hydrolyzed formula. Infants were over 2 years and had high risk of allergy.

Eosinophilic GI Disorders

- Both IgE mediated and IgE independent mechanisms are involved
- Include eosinophilic esophagitis, gastroenteritis and colitis
Triggers of an Eosinophilic Response

- Food antigens
- Parasitic infections
- Medications
- Environmental stimuli
Symptoms Associated with Eosinophilic Esophagitis (EE)

- Vomiting / reflux
- Epigastric pain
- Heartburn
- Dysphagia
Table 1. Presenting Symptoms among 103 Pediatric Patients with Eosinophilic Esophagitis.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Median Age (Interquartile Range)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<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>
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Table 2. History of Atopy in the 103 Pediatric Patients.

<table>
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<tr>
<th>Variable</th>
<th>Percent of Patients</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>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>

NEJM 2004 August, Aug 26;351(9):940-1.

Eosinophilic Esophagitis: Rising Incidence: Editorial

Noel RJ, Putnam PE, Rothenberg ME.
Age of Diagnosis in Study of 381 Children with EE

Liacouras CA et al, Clin Gastroenterol Hepatol, 2005
Eosinophilic Esophagitis in Children: Symptoms, Histology and pH Probe Results.

- Median age at presentation was 10.8 years (range, 1-17 years).
- Symptoms: Dysphagia with solid food (66%), Abdominal pain (42%), vomiting (8%).
- Food allergy was reported in 50% and asthma in 33%.

- Esophageal pH probe monitoring, performed in nine patients, revealed no abnormal acid reflux. Episodic alkalinization of the esophagus.

- Upper endoscopic: White specks on the esophageal mucosa in 42%, esophageal narrowing in 33%, esophageal rings in 25%, and esophageal furrowing in 8%

- Mean eosinophils per high-power field was 65 (range, 20-200).

- Histologic characteristics included peripapillary clusters of eosinophils (33%), increased papillary height (50%), and basal cell hyperplasia (34%).

• Thickened pale mucosa with longitudinal furrow and fold pattern and absent vascular pattern.

• Pin-point white exudate.

• GASTROINTESTINAL ENDOSCOPY VOLUME 57, NO. 1, 2003
Pathophysiology

• EoE has been shown to be a Th2-mediated disorder
  – Includes both IgE and non-IgE mediated response to food allergen

• High rates of association with other allergic disease
  – 28 – 86% of adults
  – 42 – 93% of pediatric patients
Medical Treatment Options

- Allergic referral
  - RAST or skin prick testing for food allergen triggers
  - Food elimination diet
- Topical steroids
  - Swallowed Fluticasone propionate
  - Viscous budesonide
- Systemic steroids
- The use of PPI is not universally recommended.
Fluticasone Propionate

• **DOSE:** No fixed recommendations.

- 2-4 years: 44mcg/puff 2 puffs b.i.d. x 6-8wk
- 5-10 yrs: 110mcg/puff
- 11-21 yrs: 220mcg/puff

**Do not eat or drink for 30 minutes after consuming the medications.**

Some studies have treated for as long as 12 weeks and some for as short as 4 weeks.

No studies have commented on recurrent use and dosage as well as maintenance of remission.
Effect of Amino Acid-Based Formula on Esophageal Eosinophil Counts

Liacouras CA et al, Glin Gastroenterol Hepatol, 2005
Pre- and Post-treatment Peak Esophageal Eosinophil Counts after Six-Food Elimination Diet

Kagalwalla AF et al, Clin Gastroenterol Hepatol, 2006
Suggested management approach

• Treatment of UGI symptoms for 6-8 weeks with acid blockade with high dose PPI

  • If symptoms persist EGD with proximal and distal biopsy

  • If histology suggests EE pH probe to rule out acid contribution

  • Consultation with allergist for identifiable dietary and environmental allergens

  • Treatment with allergen avoidance, 6 food elimination diet, elemental diet or corticosteroids with endpoints of symptom relief and mucosal healing with decrease eosinophils

  • Follow up for long term complications including stricture formation.

Eosinophilic esophagitis: it’s not just kid’s stuff; GI endoscopy; Vol 56, No 2, 2002. V Gox, S Nurko, G Furuta.
Summary

• Food intolerances in childhood are common, especially in high risk patient populations;
• Preventive strategies have proven efficacy;
• Prebiotic formulas may be beneficial;
• Eosinophilic proctitis: common and easy to manage
• Eosinophilic esophagitis is common and most patients require prolonged therapy.