GI Manifestations of Food Allergy

Hugh A. Sampson, M.D.
Professor of Pediatrics & Immunology
Dean for Translational Biomedical Research
Director, Jaffe Food Allergy Institute
Mount Sinai School of Medicine
New York, NY

Gastrointestinal Hypersensitivities

IgE-Mediated Non-IgE-Mediated

Oral Allergy Immediate GI Hypersensitivity
AEE AEG

Enterocolitis Enteropathy
- Cellac Disease
Proctocolitis

Immediate Gastrointestinal Hypersensitivity

- Onset - infancy & childhood
- Symptoms - nausea, abdominal cramping, vomiting within mins - 2 hrs; & /or diarrhea within 2 - 6 hrs; frequently involves other target organ, e.g. skin
- freq ingestion may ➔ “malabsorption” picture
- Foods implicated - milk, egg, peanut, soy, wheat
- Diagnosis - food-specific IgE Abs; challenge ➔ “immediate” vomiting

Eosinophilic Esophagitis, Gastroenterocolitis & Proctocolitis

Eosinophilic Esophagitis (EoE)
Eosinophilic Gastroenteritis (EG)
Eosinophilic Proctocolitis

Diagnosis based on history, endoscopy & biopsy, and response to therapy

Faculty Disclosures

- FINANCIAL INTERESTS
  I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>Allertein Therapeutics, LLC</td>
<td>Consultant, Minority Stockholder</td>
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<tr>
<td>University of Nebraska</td>
<td>Consultant</td>
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<td>Food Allergy Initiative</td>
<td>Scientific Advisor</td>
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<td>Danone Scientific Advisory Board</td>
<td>Scientific Advisor</td>
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- RESEARCH INTERESTS
  I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

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- Patents – EMP-123 (recombinant protein vaccine) & FAHF-2 (herbal product)

Eosinophilic Esophagitis Clinical Picture

- Etiology
  - Multiple food allergens (Kelly 1995)
  - Airway/cutaneous priming? (Mishra 2001; Akel 2005)
- Clinical manifestations
  - Adolescents/adults: dysphagia, chest pain, globus, food impaction
  - Younger children: Reflux symptoms (emesis, spitting up, irritability, food refusal), abdominal pain, and/or failure to thrive
- Affects males > females
- Age at onset: infant to adult
- Personal and/or family history of atopy in >50% cases

Furuta GT et al. Gastroenterology 2007; 133:1342-1363
EoE: Endoscopic Diagnosis

- Normal
- Rings
- Furrows
- Plaques
- Plaques & Furrows

EoE: Histological Diagnosis

- Normal
- EoE

Eosinophilic Esophagitis Diagnosis

- Food allergies
  - Food-specific IgE levels not always elevated
  - Prick skin tests not always positive
  - Combination: Prick skin tests and patch tests?

Prick Skin Test

Atopy Patch Test

EoE: Food Allergens

- IgE-mediated food allergy is present in ~15% of EoE
- Sensitization to multiple foods is common in EoE
- SPT and APT are not predictive of EoE triggers

<table>
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<tr>
<th>Allergen</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>Milk</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>Egg</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>Soy</td>
<td>70</td>
<td>67</td>
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<tr>
<td>Wheat</td>
<td>78</td>
<td>74</td>
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<td>Peanut</td>
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<td>Beet</td>
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<td>Corn</td>
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<td>Rice</td>
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<tr>
<td>Peanuts</td>
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<td>54</td>
</tr>
<tr>
<td>Oat</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>Barley</td>
<td>43</td>
<td>95</td>
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Spergel et al, JACI 2007

EoE: Dietary therapy

- Elemental diet
- Test-directed elimination diet
- Empiric elimination diet

Eosinophilic Esophagitis Attributable to Gastroesophageal Reflux: Improvement with an Amino Acid-Based Formula

Kelly, Lazenby, Rowe, Yardley, Peman, Sampson

Gastroenterology 1995

10 children: amino acid formula ± corn and apple

Clinical response:
- 80% symptom resolution
- 20% symptom improvement

Histologic response:

- Pre-therapy
- Post-therapy
Elemental Diet is an Effective Treatment for Eosinophilic Esophagitis in Children and Adolescents
Markowitz, Spergel, Ruchelli, Liacouras
Am J Gastroenterol 2003

51 children: amino acid formula + grape or apple
Clinical response: 96% symptom resolution

Histologic response:

26 children: removal of foods that tested positive on SPT and APT
Clinical response: 69% symptom resolution 23% partial improvement

Histologic response:

Eosinophilic Esophagitis in Adults – No Clinical Relevance of Wheat and Rye Sensitizations
Simon, Straumann, Wenk, Spichtig, Simon, Braathen
Allergy 2006

6 adults (+SPT/IgE to grass, wheat, rye, -SPT/IgE to foods)
Removal of wheat, rye, barley
Clinical response: 17% partial improvement
Histologic response: None

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors
Gonsalves, Yang, Doerfler, Ritz, Ditto, Hirano
Gastroenterology 2012

50 adults: empiric removal of common food allergens (milk, egg, wheat, soy, nuts, seafood)
Clinical response: Dysphagia score ↓ 94% patients
Histologic response:

The Use of Skin Prick Tests and Patch Tests to Identify Causative Foods in Eosinophilic Esophagitis
Spergel, Beausoleil, Mascarenhas, Liacouras
J Allergy Clin Immunol 2002

35 children: empiric removal of common food allergens (milk, egg, wheat, soy, nuts, seafood)
Clinical response: 74% improvement
Histologic response:

Effect of Six-Food Elimination Diet on Clinical and Histological Outcomes in Eosinophilic Esophagitis
Kagalwalla, Sentongo, Ritz, Hess, Nelson, Emerick, Melin-Aldana, Li
Clin Gastroenterol Hepatol 2006

EoE: Steroid Therapy

Remission rate (%)
Philadelphia Boston Cincinnati Australia New York San Diego
Prednisone Fluticasone Budesonide
Teitelbaum et al, Gastroenterology 2002
Kerkhoff et al, Gastroenterology 2006
Remes et al, Gastroenterology 2006
Chehade et al, unpublished data
Aceves et al, Am J Gastroenterol 2007
**Eosinophilic Gastritis/Gastroenteritis**

- **Epidemiology**
  - No data available
  - Less prevalent than EoE
- **Age at diagnosis**
  - Any age (infant to adult)
- **Atopic predisposition**
  - > 50% have asthma, allergic rhinitis, and/or AD
- **Clinical manifestations**
  - >50% have abdominal pain, emesis, early satiety, diarrhea
  - Failure to thrive in children
  - Subset has edema & anemia 2 protein-losing enteropathy

**EG: Histologic Diagnosis**

- **Stomach**
- **Duodenum**

**Eosinophilic Gastritis/Gastroenteritis**

- **Etiology**
  - Subset related to multiple food allergens
  - PST and serum food-IgE not predictive of food triggers
- **Dietary**
  - Sometimes effective
    - Amino acid-based formula *(Sicherer 2001, Chehade 2005)*
    - Empiric food eliminations
- **Oral corticosteroids**
  - Effective but has long-term side effects
    - Prednisone *(Lee 1993)*

**FOOD-INDUCED PROCTOCOLITIS SYNDROME**

- **Onset** - generally in first 3 months of life
- **Symptoms** - blood streaked or Heme + stools
  - anemia rare; hypoalbunemia
- **Implicated protein** - cow milk & soy protein
  - ~ 60% breast fed
  - egg, wheat, corn, fish, shellfish, and nuts
- **Diagnosis** - food challenge [0.3 - 0.6 g protein]
  - blood in stool within 6 - 72 hrs
  - Ag elimination: gross blood clears in 72 hrs

**Sigmoidoscopy Findings**

- A. Nodular hyperplasia with circumscribed erosions
- B. Nodular hyperplasia with central pit-like erosions
- C. Nodular hyperplasia in endoscopically deflated state

*Hwang JB et al, J Korean Med Sci. 2007*

**FOOD-INDUCED PROCTOCOLITIS SYNDROME**

- **Labs / Procedures** -
  - CBC: normal or slightly decreased Hgb / Hct
  - significant anemia is rare
  - normal or slightly increased eos count
  - Stools neg for bacteria, virus, & parasites
  - Sigmoidoscopy: patchy injection ➔ severe friability & aphthoid ulceration
  - Biopsy: eos. in crypts & lamina propria
- **Natural Hx** - symptoms usually clear in 1 - 2 yrs
FOOD-INDUCED ENTEROCOLITIS SYNDROME

- Onset: generally in first 3 months of life
- Symptoms: recurrent projectile vomiting, diarrhea, abdominal distention, & FTT
  - Infants may present with dehydration &/or “septic-like” picture
  - Adults - severe vomiting ~ 2 hrs post-seafood ingestion
- Implicated protein: cow milk & soy, rice, poultry, cereal grains; Adults: shrimp & other shellfish
- Diagnosis: food challenge [0.3 - 0.6 g protein]
  - vomiting - 2 - 4 hrs; ~15% hypotensive
  - diarrhea - 5 - 10 hrs

Reported foods in 165 infants with FPIES (2001-2009)

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FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

- Labs / Procedures:
  - CBC: leukocytosis with left shift
  - Stools: Hgb +, PMN’s & Eosinophils
  - Biopsy: flattened villi, edema, & increased lymphs, eos, & mast cells
  - Cell culture: Ag + PBMC’s => ↑ TNF-α
- Natural Hx:
  - cow milk: with exclusion, 50% resolve in 1 yr, 90% in 3 years
  - soy, cereal grains & other foods tend to be more persistent; adults with shellfish allergy - ?

Dietary Protein Enteropathy

- Onset: generally in first few months of life
- Symptoms: diarrhea, steatorrhea, malabsorption, FTT, vomiting, abdominal distention, anemia, hypoproteinemia, early satiety
- Implicated protein: cow milk, soy, cereal & egg
- Diagnosis: food challenge => vomiting &/or diarrhea in 40 - 72 hrs
  - may need to confirm patchy villous atrophy post-challenge

Dietary Protein Enteropathy

- Diagnostic lab procedures -
  - radiographic: small bowel edema
  - biopsy: patchy villous atrophy; prominent lymphocytic & minor eosinophilic infiltrate in epithelium & lamina propria
  - IgE, peripheral eos, α-endomysial Ab - neg.
- Natural Hx: most cases resolve in 2 - 3 yrs
  - elimination of Ag => symptomatic clearing in 3 - 21 days

CELIAC DISEASE

- Onset: variable; dependent upon when gluten is introduced into the diet
- Symptoms: diarrhea / steatorrhea, abdominal distention & flatulence, FTT or weight loss; oral ulcers; some asymptomatic [“silent”]
- Implicated protein: wheat, rye and barley [gliadin]
- Diagnosis: “classic” laboratory and endoscopic finding on & off diet
  - 90% assoc with HLA-DQ2 & 10% with DQ8 haplotype
- Incidence: US – 1:105 Sweden - 1:300
CELIAC DISEASE

- Labs / Procedures -
  - Biopsy: extensive villous atrophy; ↑ crypt length, ↑ intraepithelial lymphocytes [esp. γ/δ]
  - Radiographic: malabsorption pattern
  - IgA α-endomysium, α-tTGase & α-gliadin Abs.
- Mechanism - tTGase deamidates specific glutamines within gliadin → DQ2 (DQ8)-specific epitopes → activation of lymphocytes
- Natural Hx - life-long; ↑ GI malignancy [lymphoma]

GI Food Allergy: Summary

- Food allergies affect up to 8% of children < 3 yrs and ~ 3.5% of the US population; ~40% GI in infants
- Most GI allergic disorders are not IgE-mediated
- Diagnosis requires characteristic history, supporting lab studies, dietary elimination & often challenge
- Therapy consists of strict avoidance and use of corticosteroids in some cases
- EoE is growing problem in both children and adults
  - elimination diet is optimal, but often not practical
  - good symptomatic relief with topical steroids