GI Manifestations of Food Allergies

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Objectives

• Discuss GI cases related to various food disorders
• Distinguish between allergic and non-allergic food sensitivities
• Discuss gastrointestinal eosinophilia
• Review most common non-allergic food sensitivities
• Discuss how a gastroenterologist can use testing to define many of these disorders
**Allergies affecting the GI tract**

- Many misconceptions among patients and physicians
  - Many people believe that they have food allergies and do not have them
  - Many physicians believe that keeping foods away from people, especially infants and young children will prevent allergies
- Much that is still not known about food allergies
  - Gluten insensitivity
  - FODMAP
- GI approach often different that ALLERGY

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**Allergens**

- Major allergenic foods PROTEINS (>85% of food allergy)\(^1\)
  - Children: milk, egg, soy, wheat, peanut, tree nuts
  - Adults: peanut, tree nuts, shellfish, fish, fruits and vegetables
- Proteins or glycoproteins\(^2\) (Almost always)
  - Generally heat resistant, acid stable
- Carbohydrate allergens (rare)
  - Recent report of adult-onset mammalian meat allergy triggered by galactose-alpha-1,3-galactose

\(^3\)Commins SP, et al. JACI 2009;123:426-33
Cutaneous Reactions

- Acute urticaria/angioedema (allergic urticaria last minutes to hours, not days)
- Chronic urticaria and angioedema > 6 weeks
- Food implicated in 1.4% of 554 adults with chronic urticaria (Champion R, et al, 1969)
- 31% of 226 had positive skin test(s) to food, but only 4% had symptoms confirmed by blinded food challenge (Volonakis M, et al, 1992)
- Contact urticaria
- Contact dermatitis (food handlers)
- Foods causing ECZEMA especially in infants

Pollen-Food Syndrome (Oral Allergy Syndrome)

- Key foods: raw fruits and vegetables
- Clinical features:
  - rapid onset oral pruritus and mild angioedema
  - rarely progressive (2% have systemic reactions)
- Pathophysiology: pollen allergens are the primary sensitizers and homologous proteins in plant-derived foods elicit symptoms
- 30-70% of people with allergic rhinitis have oral allergy syndrome
- Degree of clinical reactivity may have seasonal variations

Ma S et al. JACI 2003;112:784-8.
Anaphylaxis

- Food allergy: #1 cause of anaphylaxis in the ED
- Incidence increased from average annual incidence 21/100,00 person-years in 1983-1987 to 49.8 /100,00 person-years in 1990-2010¹
- Rapid-onset, 5-20% biphasic²
- May be localized (single organ) or generalized
- Potentially fatal
- Any food can induce anaphylaxis, but the majority of the most severe reactions triggered by peanut and tree nuts

¹Decker et al, JACI 2008; 1161-65.

Adverse Food Reactions

IgE-Mediated

- Systemic (Anaphylaxis)
- Oral Allergy Syndrome
- Immediate gastrointestinal allergy
- Asthma/rhinitis
- Urticaria
- Morbilliform rashes and flushing
- Contact urticaria

IgE-Mediated

- Eosinophilic esophagitis (EoE)
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis

Non-IgE Mediated

- Food Protein-Induced Enterocolitis
- Food Protein-Induced Enteropathy
- Food Protein-Induced Proctocolitis
- Dermatitis herpetiformis
- Contact dermatitis

Immune Mechanisms of Food Allergy

- Protein digestion
- Antigen processing
- Some Ag enters blood

IgE-Mediated

IgE-receptor

Mast cell

Histamine

APC

Non-IgE Mediated

- TNF-α
- IL-5

B cell

T cell

Categorization

Fig. 1. Classification of adverse reactions to foods.

Case Presentation #1

- 2.5 month old infant with a 3 week history of blood streaked, frequent, loose stools
  - 5-7 bowel movements per day
  - Drinking formula (cow’s milk) and breast feeding
  - Also has some vomiting
  - Also with streaks of mucus
  - No weight loss
  - Otherwise well appearing

What else do you want to know??
Etiology?

Case #1

- Differential Diagnosis
  - Causes of Lower GI bleeding
    - Constipation – Fissures
    - Infections
    - Inflammatory bowel disease
  - Food allergy
Bloody Stools in Healthy Infants
Is It Always Allergic?

22 healthy infants (<6 mo) with rectal bleeding → Sigmoidoscopy

36% of infants would have had diet unnecessarily changed
Consider everything on differential diagnosis


Possible therapy if food allergy considered

A. Change maternal diet?
B. Stop breast-feeding?
C. Empirically change formula to:
   - Soy?
   - Protein hydrolysate?
   - Elemental amino acid?

• Perform tests?
  - What tests?
  - What to expect?

Don’t change diet just for the sake of doing something – HAVE A PLAN
Types of formulas

- Cow’s milk formulas (with or without lactase)
  - Other additives (DHA, prebiotics, starch, etc)

- Soy based formula
  - Galactosemia, Hereditary Lactase deficiency, Vegan

- Protein hydrolysate
  - Classified “hypoallergenic”; predigested casein
  - ~ 50%-60% free amino acids; lactose free
    - Used for GI malabsorption; cow’s milk/soy allergy
    - GI surgery; liver disease

- Elemental or Amino Acid based formulas
  - Free AA’s, MCT, corn syrup solids, lactose free
  - True “hypoallergenic”
  - Severe allergies; eosinophilic GI; short gut; others

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Seen by Pediatric GI Specialist

Normal

Rectum and Sigmoid
Allergic Proctocolitis

- Patchy eosinophilic infiltrate, variable in severity.
- Neutrophilic cryptitis can be seen (not to extent of infectious colitis or IBD)
- No chronic mucosal changes

Allergic Proctocolitis

- 2-6% of infants in developed countries
- Usually cow’s milk protein formula fed
  - 30% cross-reactivity with soy
  - >80% respond to protein hydrolysate formula
- Up to 60% breastfed
  - β-lactoglobulin
  - Removal of dairy from mother’s diet
  - Small percentage have to stop breastfeeding

### Allergic Proctocolitis

#### Clinical features
- Blood streaked stools
- Diarrhea
- Mucus in stool
- Normal weight gain
- Well-appearing
- Eczema, atopy - rare

#### Laboratory features
- Can have a mild peripheral eosinophilia
- Can have an elevated serum IgE
- Rare
  - Hypoalbuminemia
  - Mild anemia

### Allergic Proctocolitis -- Treatment

- Formula fed
  - Protein hydrolysate (80% respond)
  - Amino acid formula if necessary
  - Soy formula (30%-60% cross-reactivity)
- Breastfed infants
  - Maternal dairy restriction
  - Infrequently other foods
  - Rarely need to stop breastfeeding
- 3-14 days: Improvement in clinic symptoms
  - Complete resolution of diarrhea, bleeding: Up to 4-6 weeks
Cow’s Milk Allergy

- Most likely cell-mediated or T-cell mediated disease
- Not IgE mediated – no anaphylaxis
- Almost always resolves
  - 12 mo? 18 mo? 24 mo? Sometimes longer?
- Food Reintroduction
  - First attempt at 12 months of age (NO DAIRY before)
  - First milk challenge in office (1 oz)
  - If tolerates – add slowly for next few weeks
  - If fully tolerates then can add cheese, yogurt, etc.
  - IF DOES NOT TOLERATE – (Retry 6 months later)
- Can RAST, skin prick testing help guide your decision?

Case presentation #2

- 8 month old
  - Initially breastfed (except for formula first 3 weeks)
  - Solids introduced at 6 months (rice cereal, fruits, vegetables)
- Yogurt given for first time @ 8 months of age
  - 1 hour later: Irritability and severe vomiting
  - 2 hours later: Brought to Emergency Room limp, listless
  - Needed IV fluids
  - Sepsis infection - work-up negative
  - Returned to baseline after several hours of IVF and was discharged home 24 hours later doing well
Case Presentation #2 (continued)

- Two days later → Older brother gave him yogurt again by accident
- Same symptoms but worse
- In Emergency Room, limp and ill-appearing
- Afebrile, HR 157 bpm, BP 63/45
- Treatment: subcutaneous epinephrine without improvement and IVF which helped
- No respiratory of skin problems
- Diagnosis is…?

Food Protein Induced Enterocolitis Syndrome (FPIES)

- Different than Cow’s milk allergy
- Onset: Typically 1st year of life
- Milk most common
  - 50% also react to soy
  - 33% will react to solids
- Multiple solid foods described
  - 80% react to >1 food protein
  - 60% also react to milk, soy
- Rarely happens from breast feeding
- Often needs an Amino acid based formula
Food Protein Induced Enterocolitis (FPIES) – Clinical features

• Repetitive vomiting (~2 hours post ingestion)
• Diarrhea (~5 hours post ingestion)
  • Can have occult blood, WBCs
• Dehydration that may progress to:
  • Lethargy
  • Acidemia
  • Hypotension
  • Methemoglobinemia
• Occasional hypoalbuminemia and FTT

FPIES Management

• IV fluid boluses
• Supportive care
• Epinephrine typically NOT helpful
• Avoidance
Food Protein Induced Enterocolitis Syndrome (FPIES)

- Majority of patients become tolerant to inciting food by 3-5 years of age – able to fully reintroduce
- Not IgE mediated – T cell
- Diagnostic gold standard: Oral food challenge
- Oral food challenges required prior to food reintroduction – must be done in a hospital

Allergic Proctocolitis (CMA) or FPIES

**CMA**
- Diarrhea and mucus
- Blood streaked stools
- Normal weight gain
- Well-appearing
- Remove milk or soy
- Days to weeks to occur
- Usually resolves (age 1-2)
- Not life threatening
- Can challenge in office

**FPIES**
- Severe abdominal pain
- Vomiting and Diarrhea
- Rapid onset
- Majority need immediate medical help
- Any food (dairy usually)
- If improves takes many years
- Can be life threatening
- Challenge in hospital
Case #3

• 3 month old with severe irritability, and abdominal distention
• Stools 2-3 times a week, hard, no bleeding
• Occasional vomiting
• Poor weight gain
• Almost never happy, playful

Because of constipation and significant abdominal distention
  ▪ Concern for an anatomic colonic problem
Differential Diagnosis

• Constipation
• Hirschprung’s disease
• Colonic stricture
• Malrotation/Volvulus
• Colitis
• Thyroid disease
• Allergy

Tests performed

• Abdominal xray and unprepped barium enema
  ▪ Abnormal in appearance

• Rectal suction performed - biopsy normal ganglion cells; however large number of eosinophils
Allergic Proctocolitis

Allergic Proctocolitis - Treatment

- Same treatment as Case 1
Case #4

- 6 week old infant with severe irritability
- Always “crying for hours at a time”
- Parents report that the baby is “very gasy”
- Also infant has excessive “stomach gurgling”
- On cow’s milk formula
- Growing well, good weight gain
- No respiratory or skin problems
- At times very happy playful
- What do you think?

Case #4

- Physical exam
  - Normal

- Labs
  - Blood count, chemistries – normal
  - Abdominal xray – normal
Differential Diagnosis

- GI disease
  - Reflux, allergy, infections, malrotation, constipation, liver disease, etc
- Other system diseases
  - Renal disease, Central nervous system disease, Urinary tract infection, testicular torsion, metabolic disease
- Bone fracture, Child abuse
- Scratched cornea
- NEED TO BE SURE NO OTHER ETIOLOGY

What is colic?

- Healthy infants - no other cause for symptoms
- Severe crying for at least 3 hours a day for 4 or more days a week
- Infants less than 4 months of age
- No clear etiology
Red flags – Probably not colic

- Fever over 38.5°C
- Maternal drug use
- Poor weight gain, poor feeding
- Bilious vomiting
- Signs of physical abuse
- Recent head trauma
- Decreased activity or seizure

Treatment of colic

- Behavior modification (Taubman)
- Use of simethicone (possible placebo)
- Describing colic to parents and explaining that it will improve
  - Rocking, swings (supervised)
  - Driving in car
  - Swaddling
- Most other medications SHOULD NOT BE USED – side effects

Pediatrics 1984;74:998-1003
Case Presentation #5

- 16 yo girl with intermittent abdominal pain, distention, and diarrhea
- Otherwise no problems – no bleeding, vomiting
- Possibly related eating specific foods

- Further questioning - ice cream, milk intake

Lactose Breath Test

[Graphs showing lactose breath test results for different times, with annotation for interpretation]
Lactose Intolerance

- **Congenital Lactase Deficiency**
  - Extremely rare
  - Neonatal diarrhea and malabsorption

- **Primary Lactase Deficiency**
  - ~ 50-70% of population
  - African, Asian descent: 90-100%
  - Latin Americans ~ 50%
  - Decline in lactase levels starting after age 5

- **Secondary Lactase Deficiency**
  - Small bowel injury
  - Celiac disease, infection, Crohn’s disease, radiation or drug induced enteritis
Lactose Intolerance

**Diagnosis**
- Hydrogen breath test
- Dietary trial
- Disaccharidase analysis (biopsy)

**Treatment**
- Dietary modification
- Lactose free dairy products
- Lactase supplementation
Lactose intolerance - Treatment

- Avoid Lactose containing foods
  - Not just dairy
- Use lactaid
- Make sure problem is not secondary lactose intolerance

What about other ingested sugars

- Fructose
- Sucrose
Dietary Fructose

• Naturally occurring monosaccharide
  ▪ Sucrose = Fructose + glucose
• Inexpensive sweetener
  ▪ Sodas, fruit juices, candy
• Also found in many fruits

Dietary Fructose Intolerance

• Most common symptoms: Distention, gassiness, diarrhea
• Children with isolated abdominal pain

**Diagnosis**
• Hydrogen breath test
• Dietary trial

**Treatment**
• Dietary modification

Tsampalieros A et al; Arch Dis Child 2008; 93: 1078
Dietary Fructose Intolerance

• Mechanism of intestinal absorption poorly understood

• Non-absorbed fructose
  - Osmotic load
  - Source for bacterial fermentation

• Intestinal fluid shifts
  - Distention
  - Bloating
  - Diarrhea

FODMAP

• “Fermentable oligo-, di- and monosaccharides and polyols”
• Irritable bowel syndrome
• Many non-organic GI complaints
Case #6

- 9 year old with 3 years of increasing severe abdominal pain, diarrhea, and vomiting
- Rare episodes of blood in vomitus
- Rare episodes of rectal bleeding
- Over last year lost 5-10 pounds
- History of asthma

Case #6

- Labs
- Complete Blood Count
  - Elevated white blood count
  - Elevated peripheral eosinophils
  - Decreased serum albumin
Case #6

• Differential Diagnosis
  ▪ Inflammatory Bowel disease – Crohn’s disease
  ▪ Autoimmune disease
  ▪ Eosinophilic gastroenteritis
  ▪ Other enteropathies

Normal Antrum
Eosinophilic Gastroenteritis
Eosinophilic Gastroenteritis

Mucosal type

Mural type

Eosinophilic Gastroenteritis

- Rare
- Eosinophilic infiltrate through GI tract
- GI symptoms
  - Vomiting, diarrhea, abdominal pain, protein losing enteropathy, obstruction
- Exclusion of known causes of GI eosinophilia
- Etiology unknown
  - Immunologic dysregulation
  - Food antigens
- Difficult to treat
  - Steroids
  - Dietary changes
Eosinophilic Gastroenteritis

**Clinical characteristics**

- Vomiting
- Severe abdominal pain
- Diarrhea, protein losing enteropathy
- Gastrointestinal bleeding
- Intestinal obstruction, perforation
- Peripheral eosinophilia, (50%?)
- Associated allergies: eczema, asthma, rhinitis, atopy

Eosinophilic GI Disease

**Treatment**

- **Diet**
  - Restricted diet
  - Amino Acid based formula
- **Medications**
  - Prednisone
  - Immunosuppressives
    - 6 mercaptopurine (6-MP)
    - Methotrexate
  - Biologics (future)
    - Anti IL-5
Eosinophilic Gastroenteropathies
The New Epidemic

Spectrum of disease or unique diseases?

Colon

Esophagus

Allergic proctocolitis  Eosinophilic esophagitis

Eosinophilic gastroenteritis

Food Hypersensitivity Syndromes

IgE  Non-IgE

Immediate Hypersensitivity
Oral Allergy Syndrome

Eosinophilic Esophagitis
Eosinophilic Gastroenteritis

Food Protein Induced Enterocolitis
Dietary Protein Enteropathy
Dietary Protein Proctitis
Case Presentation #7

- 7 year old girl presents with abdominal distention, mild abd pain
- Bowel pattern: 1 hard BM every 2-3 days
  - No withholding, high fiber diet
- Lost 4 lbs over the summer
- Parents report fatigue, fussiness
- Height at 10th percentile (previously 25-50%)
- Hb = 9.3, microcytic indices

Case #7 – Further testing

- ANTI-ENDOMYSIAL IgA: Positive (1:160)
- Ig A: 50
- ANTI-TTG IgA: 133.9

- Upper endoscopy: Duodenal biopsies consistent with celiac disease
Celiac disease – Histologic Diagnosis

- Gold standard: Duodenal biopsies
  - Villous blunting, intraepithelial lymphocytosis

![Normal](image1)
![Partial atrophy](image2)
![Total atrophy](image3)
Celiac disease

- Immune-mediated enteropathy due to permanent sensitivity to gluten in genetically susceptible individuals
  - Wheat, rye, barley
- 1:133 incidence in United States
  - First degree relative: ~1:20
- Can present with or without gastrointestinal symptoms
**Celiac Gastrointestinal Manifestations (“Classic”)**

- Chronic or recurrent diarrhea
- Abdominal distention
- Anorexia
- FTT/loss of weight
- Abdominal pain
- Vomiting
- Constipation
- Irritability

**Celiac disease – Non Gastrointestinal Manifestations**

*Most common age of presentation: older child to adult*

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications
Serological Test Comparison

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
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<tbody>
<tr>
<td>AGA-IgG</td>
<td>69 – 85</td>
<td>73 – 90</td>
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<tr>
<td>AGA-IgA</td>
<td>75 – 90</td>
<td>82 – 95</td>
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<tr>
<td>EMA (IgA)</td>
<td>85 – 98</td>
<td>97 – 100</td>
</tr>
<tr>
<td>TTG (IgA)</td>
<td>90 – 98</td>
<td>94 – 97</td>
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Serum IgA must be normal to properly interpret.

HLA Testing

- HLA-DQ2 or HLA-DQ8
- Useful in helping to identify disease when biopsies or serum markers inconclusive
- If both are negative very unlikely that celiac disease is present

Celiac Disease – Treatment

• Only treatment for celiac disease is a gluten-free diet (GFD)
• Strict, lifelong diet
• Avoid:
  • Wheat
  • Rye
  • Barley

Case 8

• 3 yo with poor weight gain and feeding difficulty
• 5 yo with intermittent vomiting and epigastric pain
• 8 yo with frequent regurgitation and heartburn that recurs after stopping a PPI
• 12 year old with complaints of “difficulty swallowing”
• 15 year with an “emergent” esophageal food impaction requiring immediate removal
• 28 year old with chronic heartburn and nausea
• 36 year old requiring emergent endoscopy for an esophageal food impaction
EoE

• Food allergy that needs joint GI & Allergy involvement

Conclusions

• Food allergies and Food Intolerances are being seen by both pediatric and adult gastroenterologists in increasing numbers
• Instead of guessing the cause of disease, testing exists to help identify many of these problems
• Gastroenterologists and allergists can be useful partners to determine accurate diagnosis of many of these disorders