Childhood diarrhea Allergy, Food intolerance, Eosinophilic inflammation or Something else?

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Objectives

- To understand, diagnose and treat physiologic responses that cause diarrhea
- To understand, diagnose and treat allergic processes that cause diarrhea - IgE, FPIES, cow's milk allergy
- To understand, diagnose and treat food intolerances - lactose intolerance, food hypersensitivity
- To understand, diagnose and treat eosinophilic gastrointestinal disease

What is a normal bowel pattern in children?

- Everyone has their own ***normal pattern*** of ***bowel movements***
- Everyone's bowels are unique to them, and what's normal for one person may not be normal for another
- A normal pattern can be 1-3 times a day at the most, or 2-3 times a week at the least, and still be considered regular, as long as it is the usual pattern for that person

Infant Bowel Pattern

- As in older children, stool patterns differ from baby to baby
- Some infants stool have a stool several times per day, some once a week - both are normal
- Newborns commonly stool more frequently than older babies, sometimes with every feed
- Breast fed babies may have softer, more frequent stools than formula fed babies – may change when solids are added

What is diarrhea?

di·ar·rhe·a/□dīə□rēə/

A condition in which feces are discharged from the bowels frequently and in a liquid form.

Synonyms: diarrhoea – looseness

- A change in normal consistency or frequency of stools

Stool color

•Normal stool color varies quite a bit from black, dark green, bright green, yellow or brown in color.

•Stools that are white and chalk-like or stools that are bloody are not normal.

Typical GI view of diarrhea

- **Bacterial infections -** *Campylobacter, Salmonella, Shigella,* and *Escherichia coli (E. coli).*
- **Viral infections - R**otavirus, norovirus, cytomegalovirus, herpes simplex virus, and viral hepatitis
- **Post-viral enteritis**
- **Parasites -** *Giardia lamblia, Entamoeba histolytica,* and *Cryptosporidium*
- **Functional bowel disorders - I**rritable bowel syndrome.
- **Intestinal diseases/Malabsorption - In**flammatory bowel disease, ulcerative colitis, Crohn's disease, celiac disease
- **Congenital disaccharridase deficiencies**
- **Pancreatic disease –** Cystic fibrosis, Schwachman's syndrome
- **Food intolerances and sensitivities –** Primary and secondary lactose intolerance
- **Toddler's diarrhea**
- **Reaction to medication -** Antibiotics, cancer drugs, and antacids containing magnesium can all cause diarrhea

Food Allergies

- Food hypersensitivity reactions affect
  - – Up to 8% of children under 3 years of age
  - – At least 2.5% of the general population
- 3x increase in prevalence of allergies over past 20 years
  - – Changes in environment
  - – Changes in the processing of foods
  - – Alteration of immunologic recognition
  - – Use of antibiotics

Categorization

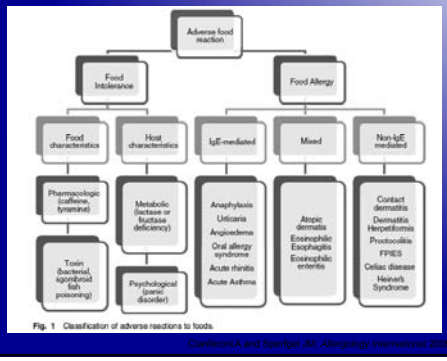
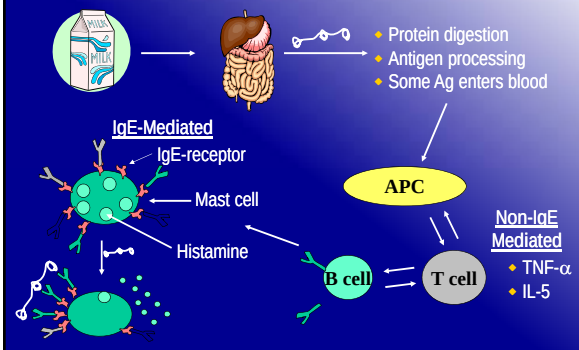


Fig. 1 Classification of adverse reactions to foods.

Ciarferoni A and Spergel JM; *Allergology International* 2009; 58: 457-466

Immune Mechanisms



Adverse Food Reactions

IgE-Mediated → **Immunologic** → **Non-IgE Mediated Cell-Mediated**

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

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

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

Sampson H. J Allergy Clin Immunol 2004;113:805-9.
Chapman J et al. Ann Allergy Asthma & Immunol 2006;96:S51-68.

Clinical Manifestations

Signs and Symptoms

	IgE	Non-IgE	Acute	Chronic
Skin				
Urticaria	✓		✓	
Angioedema	✓		✓	
Atopic dermatitis	✓	✓	✓	✓
Respiratory				
Throat tightness	✓		✓	
Asthma	✓		✓	✓
Gut				
Vomit	✓	✓	✓	✓
Diarrhea	✓	✓	✓	✓
Pain	✓	✓	✓	✓
Anaphylaxis	✓		✓	

Case 1

- 5 month old
- Within 15 minutes of eating developed rash, hives, abdominal pain, diarrhea, breathing difficulty
- Symptoms progressively worsening
- Taken to ER

- In ER

- After fluids and epinephrine

- Anaphylaxis typically presents with many different symptoms over minutes or hours with an average onset of 5 to 30 minutes if exposure is intravenous and 2 hours for foods. The most common areas affected include: skin (80–90%), respiratory (70%), gastrointestinal (30–45%), heart and vasculature (10–45%), and central nervous system (10–15%) with usually two or more being involved.

- Symptoms typically include generalized hives, itchiness, flushing or swelling of the lips. Swelling of the tongue or throat occurs in up to about 20% of cases. Respiratory symptoms and signs that may be present, including shortness of breath, wheezes or stridor. Gastrointestinal symptoms may include crampy abdominal pain, diarrhea, and vomiting.
- A feeling of anxiety or of "impending doom" has be described.

Delayed allergic reactions to red meats

- A novel and severe food allergy associated with IgE antibodies to the carbohydrate epitope α-gal.
- Delayed symptoms (3-6 hours) of anaphylaxis, angioedema, or urticaria after eating beef, pork, or lamb.
- SPT with commercial extract usually negative; improved sensitivity if SPT with fresh meat or with intradermal testing
- Most of these patients report new-onset of symptoms to meat in adulthood
- All patients from Virginia, North Carolina, Tennessee, Arkansas, and Missouri; possibility of a sensitizing exposure that may be geographically isolated (areas endemic for ticks – *Amblyomma americanum*).

Commins SP, et al. JACI 2009;123:426-33

Case 2

- 2 month old with 3 to 4 week history of diarrhea, bloody and mucus streaked stools
- No fever, vomiting, jaundice
- No medicines
- No family history of GI disease
- On milk based formula

Physical Exam

- Normal baby exam
- Benign abdominal exam
- Labs and stool cultures normal

Lower GI Bleeding in the Neonate

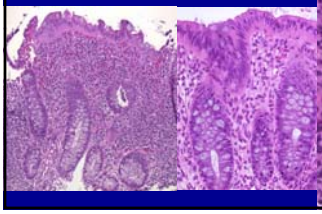
- Anal fissure
- Infectious colitis
- Milk-protein allergy
- NEC
- Meckel's, AVM, duplication cyst
- Upper GI source

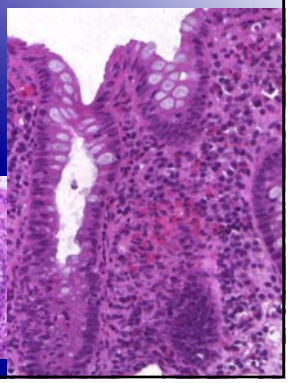
Allergic Proctocolitis

May or may not need to perform sigmoidoscopy with biopsy

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
- Up to 60% breastfed
  - β-lactoglobulin
  - Removal of dairy from mother's diet
  - Small percentage have to stop breastfeeding
- Cow's milk protein formula fed
  - 30% cross-reactivity with soy
  - >80% respond to protein hydrolysate formula

Sampson HA, et al; *J Pediatr Gastroenterol Nutr* 2000; 30:S87-94

Allergic Proctocolitis

Clinical features

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

Laboratory features

- Mild peripheral eosinophilia
- Elevated serum IgE
- Rare
  - Hypoalbuminemia
  - Mild anemia

Allergic Proctocolitis -- Treatment

- Breastfed infants
  - Maternal food restriction (mainly dairy)
  - Infrequently other foods
  - Sometimes need to stop breastfeeding
- Formula fed
  - Skip soy formula (30-50% cross-reactivity)
  - Protein hydrolysate (75-80% respond)
  - Amino acid formula may be necessary

Allergic Proctocolitis – Response to Treatment

- 72 hrs: Improvement in clinic symptoms
  - Resolution of diarrhea, bleeding: Up to 3 weeks
- 4-6 weeks: Histologic clearing
- Reintroduce milk at 12 mo? 18 mo? 24 mo?
  - Can RAST, prick testing guide decision?

Summary

- Milk-protein allergy is a common cause of bloody diarrhea in neonates
- Can be treated empirically with dietary restriction without diagnostic sigmoidosocpy
- Usually resolves 18-24 months

Case 3

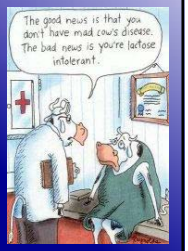
- 15 yo with a 4 year history of progressively increasing abdominal pain and diarrhea
- No weight loss (normal growth curve)
- No bleeding, vomiting, rash
- Pain and diarrhea seem to increase after eating

- Labs – CBC, Chemistry panel, stool cultures – negative
- Abdominal xray – normal
- Family history of similar problems in father and uncle

- Lactose breath test significantly abnormal
- Diagnosis - Lactose intolerance

Lactose Intolerance

- **Congenital Lactase Deficiency**
  - Extremely rare
  - Neonatal diarrhea and malabsorption
- **Primary Lactase Deficiency**
  - 70% of population
  - African, Asian descent: 90-100%
  - 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

- Symptoms same as fructose intolerance

Diagnosis

- Hydrogen breath test
- Dietary trial
- Disaccharidase analysis

Treatment

- Dietary modification
- Lactose free dairy products
- Lactase supplementation

- Food intolerances
  - *Non-allergic food hypersensitivity* is the medical name for food intolerance, loosely referred to as *food hypersensitivity*, or previously as *pseudo-allergic reactions*.
- Non-allergic food hypersensitivity should not be confused with true food allergies.

Other types of food intolerances

- Pharmacological responses to naturally occurring compounds in food, or chemical intolerance (caffeine, other organic chemicals occurring naturally in a wide variety of foods
- Food additives, preservatives, colourings and flavourings, such as sulfites or dyes

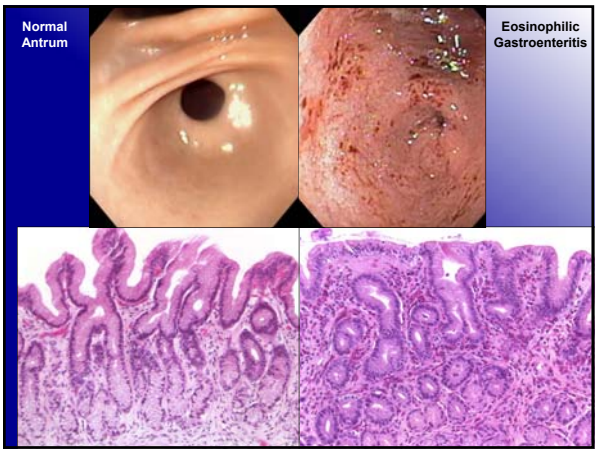
Case 4

- 10 year old
- Several years of intermittent but severe abdominal pain
- Frequent, loose stools (heme +)
- Decreased appetite

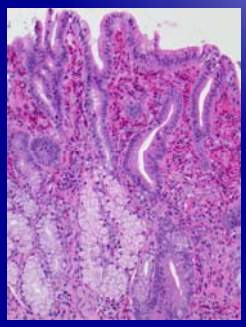
Testing

- Heme + stools
- Hemoglobin 10.5
- Albumin 3.3 mg/dL

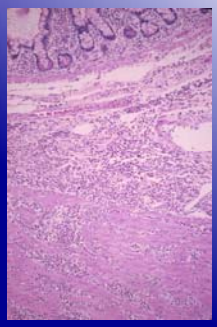
- UGI/SBFT – gastric mucosal thickening



Eosinophilic Gastroenteritis



Mucosal type



Mural type

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 Gastroenteritis

- Very 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 Gastroenteropathies

Spectrum of disease or unique diseases?

Colon — Esophagus

Allergic proctocolitis

Eosinophilic esophagitis
NO DIARRHEA

Eosinophilic gastroenteritis

EoG - Treatment

- Diet
  - Test for food allergies
  - Skin prick and Atopy patch
  - Usually need amino acid based formulas
- Corticosteroids
  - Aggressive dosing
- Immunosuppresants
  - 6 mercaptopurine

Case 5

- 1 year old
- Exclusively breast fed (except formula first 3 wks)
  - Solids introduced at 6 months (rice cereal, fruits, vegetables)
- Yogurt given for first time
  - 1 hr later: Irritability and continuous emesis
  - 2 hrs later: Brought to ED limp, listless
  - Sepsis work-up negative
  - Returned to baseline after 2 hrs IVF and was discharged home 24 hrs later

Case 5 (continued)

- Two days later → Older brother gave him yogurt again
- Same symptoms
- In ED, limp and ill-appearing
- Afebrile, HR 157 bpm, BP 63/45
- Treatment: subcutaneous epinephrine without improvement and IVF which helped
- Negative sepsis workup
- Diagnosis is…?

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

Food Protein Induced Enterocolitis Syndrome (FPIES)

- 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
- May tolerate <u>breast milk with maternal restrictions</u>
  - CHOP Allergy → Amino acid formulas

Food Protein Induced Enterocolitis Syndrome (FPIES)

- Majority of patients become tolerant to inciting food by 3 years of age
- Not IgE mediated
- Diagnostic gold standard: Oral food challenge
- Patch testing
  - Sensitivity 100%, specificity 71% in small study
- Oral food challenges required prior to food

FPIES Management

- IV fluid boluses
- Supportive care
- Epinephrine typically NOT helpful
- Avoidance

Case 6

- 11 year old
- Poor weight gain, diarrhea, fatigue
- No vomiting, regurgitation, no fever

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Physical Examination

- Lethargic, irritable but otherwise normal physical exam
- CBC and Chemistry panel normal
- Stool cultures - normal

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Differential Diagnosis

- Pancreatic Insufficiency
- Lactose intolerance
- Infection – bacterial, parasitic (Giardia)
- Small bowel bacterial overgrowth
- Biliary disease
- Celiac disease
- Crohn's disease

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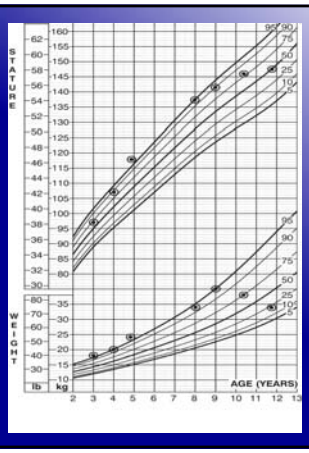


Further testing

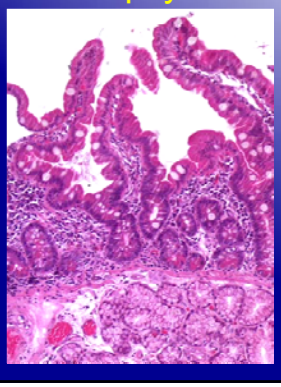
- ANTI-ENDOMYSIAL IgA: **Positive (1:160)**
- Ig A: **50**
- ANTI-TTG IgA: **133.9**

- Upper endoscopy performed

Further Investigations

- Upper endoscopy with biopsy performed

Duodenal Biopsy - normal



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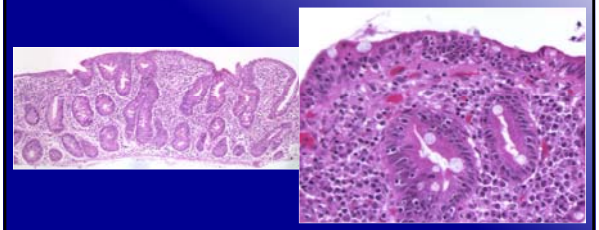
Duodenal biopsy - case

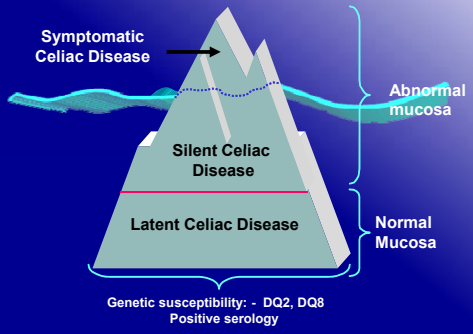


Gold standard: Duodenal biopsies - Villous blunting, intraepithelial lymphocytosis

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

The Celiac Iceberg



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

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97

Farrell RJ, and Kelly CP. *Am J Gastroenterol* 2001;96:3237-46.

Celiac Disease

- Permanent intolerance to gluten associated with proximal small bowel mucosal disease
- Removal of gluten leads to full clinical and histologic remission
- Highest prevalence amongst N. Europeans, esp W. Ireland (1 in 300)
- 0.4% prevalence in healthy US blood donors

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Case 7

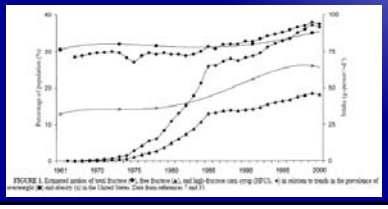
- 3 yo boy presents with abdominal pain and diarrhea x 6 weeks
  - 4-6 loose, non-bloody BMs per day
  - "Never had a formed BM"
- No vomiting or weight loss
- Diet: "Normal"
- Well appearing
- Infectious stool studies: Negative

More dietary history

- Patient constantly drinking from sippy cup
- You calculate 50-70 oz water/juice daily

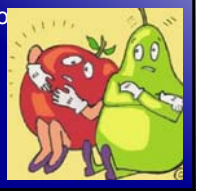
Dietary Fructose

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



Dietary Fructose Intolerance

- Mechanism of intestinal absorption poorly understood
- Non-absorbed fructose
  - Osmotic load
  - Source for bacterial fermentatio
- Intestinal fluid shifts
  - Distention
  - Bloating
  - Diarrhea



Dietary Fructose Intolerance

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

Diagnosis

- Hydrogen breath test
- Dietary trial

Treatment

- Dietary modification

Gomara RE, et al; *J Pediatr Gastroenterol Nutr* 2008; 47:303-308
Tsampalieros A et al; *Arch Dis Child* 2008; 93: 1078

Key Points

- Consider allergic diseases in children presenting with diarrhea
- Eosinophilic GI disease: Increasing in incidence
- GI manifestations of food allergy often occur without typical allergic symptoms
- Empiric dietary changes can be expensive and difficult – utilize diagnostic tests whenever possible
- Lactose & Fructose → Common cause of childhood diarrhea and abdominal pain
- Lactose intolerance may be secondary to other GI disorders
- Celiac disease – under-diagnosed