

Infant Proctocolitis

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Disclosures

- I am the founder and president of The Milk Mob
- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

Objectives

- Explain 3 different forms of food protein induced GI disorders.
- Describe 3 symptoms and signs of FPIES.
- Describe 2 characteristics of food protein enteropathy.
- Discuss the relationship between eosinophilic GI disorders and food protein induced GI disorders.
- Explain initial workup and advice for a family whose 3 month old infant has blood streaked stools.

Mom calls you because her 3 month old exclusively breastfed baby boy has blood streaked stools for the last day. The baby has been a little fussy, and has been spitting more than usual. What could this be? What is the next step?

Typical IgE Mediated Food Allergy

- Examples
 - Hives, swelling from peanuts
 - Severe vomiting, diarrhea, hives from shellfish
 - Facial swelling from eggs

IgE vs Non-IgE Mediated Syndromes

IgE Mediated

- Symptoms within minutes
- Allergic symptoms such as N&V, diarrhea, wheezing, rash, swelling, hives anaphylaxis
- Physiology understood

Non-IgE Mediated

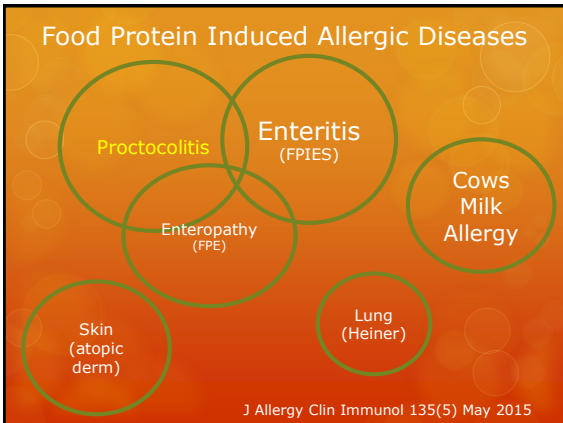
- Symptoms come on gradually
- No anaphylaxis
- Symptoms relatively mild
- Usually resolve by age 2
- Unclear physiology
 - Less well-studied
 - Hard to access gut tissue in real time to see reactions

We are covering non-IgE allergic reactions today

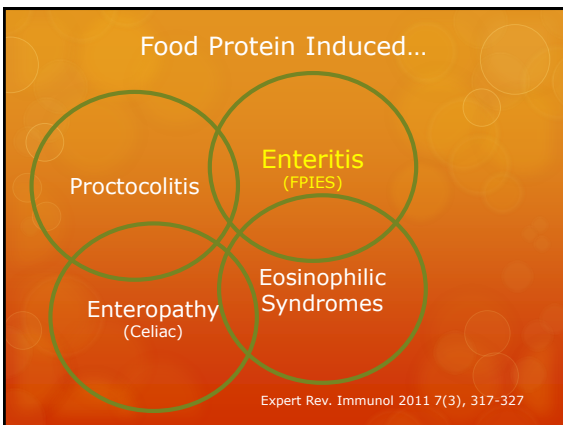


Table 1. Classification of gastrointestinal food hypersensitivity

IgE	Non-IgE
Immediate GI hypersensitivity Oral allergy syndrome	Eosinophilic allergic esophagitis Eosinophilic allergic gastritis Eosinophilic allergic gastroenterocolitis Enterocolitis induced by proteins Proctocolitis induced by proteins Enteropathy induced by proteins Celiac disease



- What is Allergic Proctocolitis?**
- An immune-mediated hypersensitivity GI disorder
 - Not mediated by IgE
 - Occurs in the large bowel
 - Instigated by food allergens in the gut
 - Maternal dietary allergens
 - less likely from allergens in formula or solids
 - Mainly in breastfed babies
- J Allergy Clin Immunol 135(5) May 2015



- Symptoms of Food Protein-Induced Enterocolitis Syndrome (FPIES)**
- May be acute or chronic presentation
 - Sudden nausea/vomiting/dehydration
 - Can be severe leading to shock
 - Chronic exposure
 - Weight loss or failure to gain weight
 - Abdominal pain, low serum protein, malabsorption

Typical Case of FPIES

- 2-3 hrs after eating, child vomits extensively
- Profuse diarrhea occurs 5-10 hours later
- Parents assume stomach flu
- In severe cases:
 - Child appears pale, ill, lethargic
 - Brought to the ER
 - Child is worked up for causes of shock
 - All tests are negative and child is fine the next day

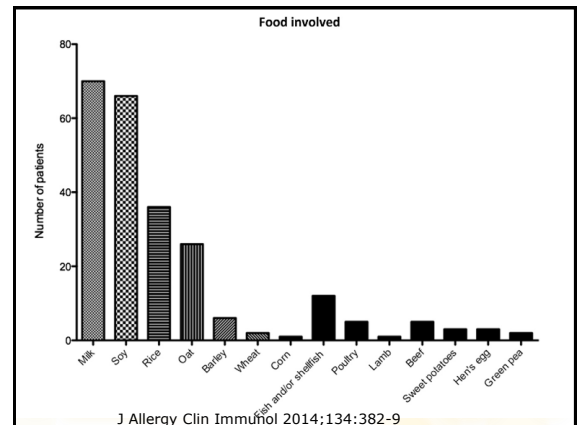
Diagnosing Food Protein-Induced Enterocolitis Syndrome (FPIES)

- No diagnostic test available
 - Rule out infectious disease or toxin exposure
- Milk/soy FPIES rare in exclusively bfed infants
 - Most common in formula fed infants
 - Bfeeding is protective

Characteristics of FPIES Patients

- 160 patients
 - Median age at diagnosis = 15 mo
 - 8% diagnosed >5 years of age
 - Majority have a history of allergies
 - 61% reacted to 1 food, 26% to 2 foods, 9% to 3 or more foods
 - Adult onset FPIES mainly with seafood

J Allergy Clin Immunol 2014;134:382-9



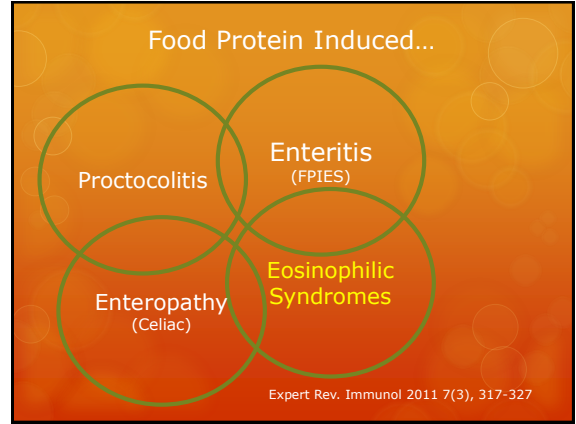
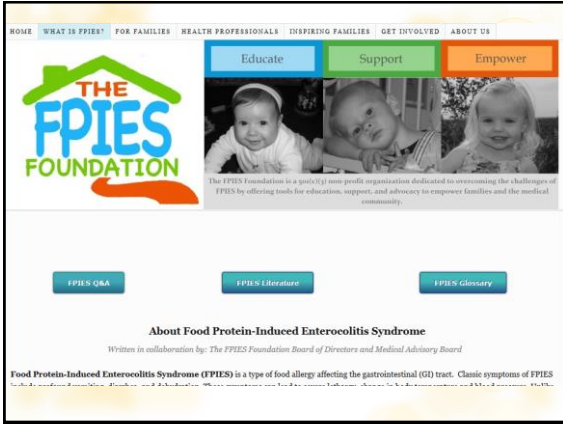
Management

- Manage symptoms
 - Hospitalize if needed
- Diagnosis based on ruling out other causes of symptoms
- Avoid offending food(s)
- Oral food challenges under medical supervision, IV in place
 - Try every 12-24 mo
 - Higher risk with IgE Ab

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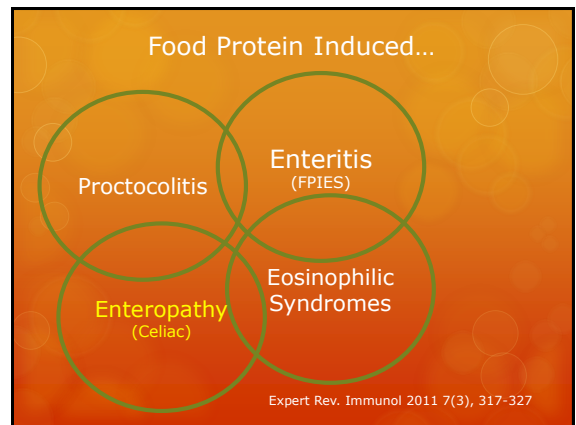
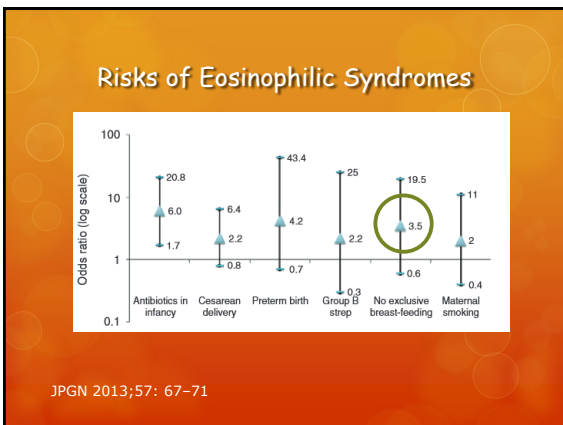
Prognosis of FPIES

- 24% of subjects had IgE antibodies to the FPIES-inducing food(s)
 - Less likely to grow out of a reaction
- If no IgE antibodies, median age of outgrowing FPIES:
 - Rice- 4.7 years old
 - Oats- 4 yo
 - Soy- 6.7 yo
 - Milk- 5.1 yo



- ### Eosinophilic Syndromes
- > Eosinophilic esophagitis, gastritis, gastroenteritis
 - > Symptoms include:
 - > GERD
 - > refusal to eat
 - > poor growth
 - > irritability
 - > poor food tolerance
 - > Abdominal pain

- ### Eosinophilic Syndrome
- > ~80% have allergies
 - > Unclear if these are true allergic conditions
 - > Dx based on GI sx, eosinophils on bx, and no other cause of sx.
 - > Must have an endoscopy to diagnose



Food Protein-Induced Enteropathy

Allergy International 2013;62:297-307

- Chronic diarrhea, vomiting, and poor growth in first 2 years of life, usually under 12 mo
- Most commonly from cows milk, soy, rice, chicken, egg, fish.
- Requires endoscopy to diagnose
 - Small intestine villous atrophy
 - Similar to Celiac
- Allergy testing is negative
- Resolves by age 2

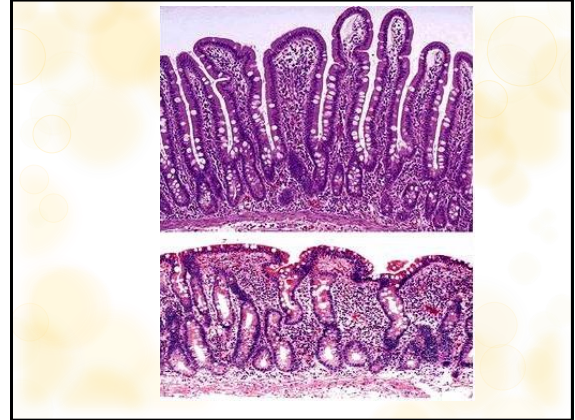


Table 1. Food protein-induced non-IgE-mediated and mixed gastrointestinal syndromes.

Feature	FPIES	Food protein-induced proctocolitis	Food protein-induced enteropathy	Eosinophilic gastroenteropathies*
Onset	Days to 1 year†	Days to 6 months	<24 months	Any age
Symptoms				
Ereeds	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe (rare)	No	Moderate	Moderate
Shock	15-20%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Allergy evaluation				
Food prick skin test	Negative	Negative	Negative	Positive ~50%
Serum food-specific IgE	Negative	Negative	Negative	Positive ~50%
Total IgE	Normal	Normal	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Positive ~50%
Risky findings				
Villous injury	Patchy, variable	No	Variable	Variable
Colitis	Prominent	Focal	No	May be present
Mucosal erosions	Occasional	Occasional, linear	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltration, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 1.5-3 h; diarrhea in 5-8 h	Rectal bleeding in 6-72 h	Vomiting, diarrhea, or both in 40-72 h	Vomiting and diarrhea in hours to days

*Eosinophilic gastroenteropathies: eosinophilic gastritis and gastroenterocolitis.
†Anecdotal reports suggest that FPIES may start at an older age to foods such as fish or shellfish.
FPIES, food protein-induced enterocolitis syndrome.
Adapted with permission from [1].

Expert Rev. Immunol 2011 7(3), 317-327

Food Protein Induced...

Proctocolitis

Enteritis (FPIES)

Enteropathy (Celiac)

Eosinophilic Syndromes

Expert Rev. Immunol 2011 7(3), 317-327

Incidence of Allergic Proctocolitis

- Not well defined
- Often hard to separate out from other food-protein induced GI illnesses
- Approx 0.5-1% of breastfed infants have an allergy to dairy while nursing (based on 1 study)

Typical Presentation of APC

- Bloody, mucousy stools
- Usually 2-6 weeks of age, but can be 1 day- 4 months
- The baby appears well
 - Rare anemia
 - Good growth
 - Occasionally fussy
- Other sx such as vomiting, GERD, failure to gain imply additional or other enteropathy

Pathophysiology

- Reaction to proteins in mom's diet
 - Cows milk protein & soy most common
- Large bowel edema, erosions of mucosa, eosinophilic infiltration of the intestinal lining
- Sensitization could start in utero
 - Occasionally symptoms are seen day 1
 - Restricting mom's diet during pregnancy currently not recommended

Role of Gut Flora in Bloody Stools

- Food Protein induced enteritis syndromes not well understood
- Gut microbiome plays a major role in gut maturity and immunity
 - Increased inflammation w/aberrant gut flora
- Gut microbiome differs between babies with bloody stools and controls
 - Less bifidobacteria in babies with bloody stools

Pediatr Res 2014 Oct 21
Folia Microbiol. **54** (2), 167-171 (2009)
Microbiol Immunol 2012; **56**: 657-663

Diagnosing Allergic Proctocolitis

- Other labs usually not helpful
 - Negative allergy testing
- All other labs should be negative
 - Normal abdominal film
 - Negative stool cultures
 - Normal blood count

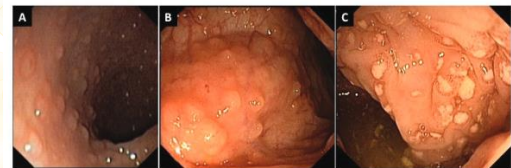


Figure 1 Endoscopic findings showing colonic (A), ileal (NH) (B) and rectal aphthoid ulcers (C) in a child with dietary protein-induced allergic proctocolitis.

BMC gastroenterology 2011 11:82

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Severe Cases

- Consider starting with a strict maternal elimination diet
 - Lamb, pears, squash, rice
- Once symptoms resolve, add a new allergen once a week
- Addition of pancreatic enzymes
 - No randomized controlled trials
 - Theoretically breaks down allergens in mom's gut before absorption
 - Two Creon 6000 with each meal, one with each snack

Management of Resistant Cases

- 7% of APC not responsive to maternal diet restrictions
- 14 exclusively bfed infants with APC refractory to maternal allergen avoidance (soy, milk, eggs)
 - Blood and mucous in stool, watery stools
- Blood tests for IgE, skin prick tests were negative
- Patch testing
 - variably + to milk, soy, eggs, wheat, rice
 - 100% + to breastmilk (with no cows milk, soy, eggs)
- 100% cleared rectal mucosa abnormalities after 2 mo on AAF diet

Allergic proctocolitis refractory to maternal hypoallergenic diet
Lucarelli et al. BMC Gastroenterology 2011, 11:82

Mom calls you because her 4 month old exclusively breastfed baby girl has had blood streaked frequent mucousy stools for 5 weeks. She is overall gaining weight normally, does spit up frequently, has lots of gas. She is mildly fussy.

- Her pediatrician first suggested a dairy and soy free diet.
- After 1 week, that didn't help, so mom stopped nuts, eggs, fish, wheat and citrus.
- After 2 more weeks, that didn't help.
- She was referred to pediatric GI 1 week ago, who told her that she should stop breastfeeding because the baby is allergic to her milk. Start alimantum formula.

Next Steps?

- If gaining well and appears healthy, consider leaving mom on the diet that caused the least blood in the stool, and allow mom to continue breastfeeding
- Lower mom's milk supply- no data, but effective

Breastfed Babies Receiving Formula Supplementation

- Change to a soy based formula first.
- If sx are severe and persistent, an amino acid-based formula is preferred over hydrolyzed cows milk formula.

Re-introducing Allergens for Food Protein Allergic Proctocolitis

- Consider allergy testing if other allergic symptoms
- If baby otherwise well
 - Reintroduce offending allergens 6-9 mo after initial reaction, or at 12 mo old

Distinguishing Eosinophilic GI Syndromes with Food Protein Induced GI Syndromes (Eosinophilic esophagitis, E. gastroenteritis, E. colitis)

- Eosinophilic syndromes are inflammatory w/eos infiltrating gut lining
- Biopsies of FPIES and proctocolitis have eosinophilia
- Clinical sx tend to differ
 - Eosinophilic syndromes triggered by many foods
 - Food protein enteritis syndromes caused by fewer foods
 - FPIES has more acute sx than the eosinophilic syndromes

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Relationship between FPIES and Allergic Proctocolitis

- Allergic proctocolitis may be a milder form of FPIES
 - FPIES usually occurs in the rectum, along with other areas
 - The protective factors in breastmilk may prevent full expression of FPIES
 - Exposure to antigens are much less in breastmilk

Mom tells you at a 2 month visit that her exclusively breastfed infant is often fussy. He strains to poop, fusses with feedings, but does not spit up much.

Association of FP Induced Allergic GI Syndromes with Infant Constipation, GERD, Fussiness

- Cows Milk Allergy Assoc with gastric motility disorders, ie constipation, reflux, delayed gastric emptying
- 28-78% success rate in resolving constipation by eliminating dairy
 - Increased eosinophilic infiltration of anal sphincter causes increased anal pressure at rest (due to CM allergy)

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Mom calls you because her 3 month old exclusively breastfed baby boy has blood streaked stools for the last day. The baby has been a little fussy, and has been spitting more than usual. What could this be? What is the next step?

What questions do we want to ask?

What symptoms would indicate that this is not Allergic proctocolitis?

What would be indications to send the baby for further evaluation?



Conclusions

- It is important to distinguish between IgE and non IgE mediated intestinal reactions to foods.
- There are at least 3 different types of food protein induced gastroenteritis.
 - Allergic proctocolitis
 - Food protein induced enterocolitis syndrome (FPIES)
 - Enteropathies such as Celiac Sprue
- Babies with classic allergic proctocolitis do not need further workup unless they have other allergy symptoms.
- Mothers need nutritional support if asked to be on an elimination diet
- Cows milk allergy may also cause GERD, constipation, and infant fussiness.