

# FPIES

## **John Leung, M.D.**

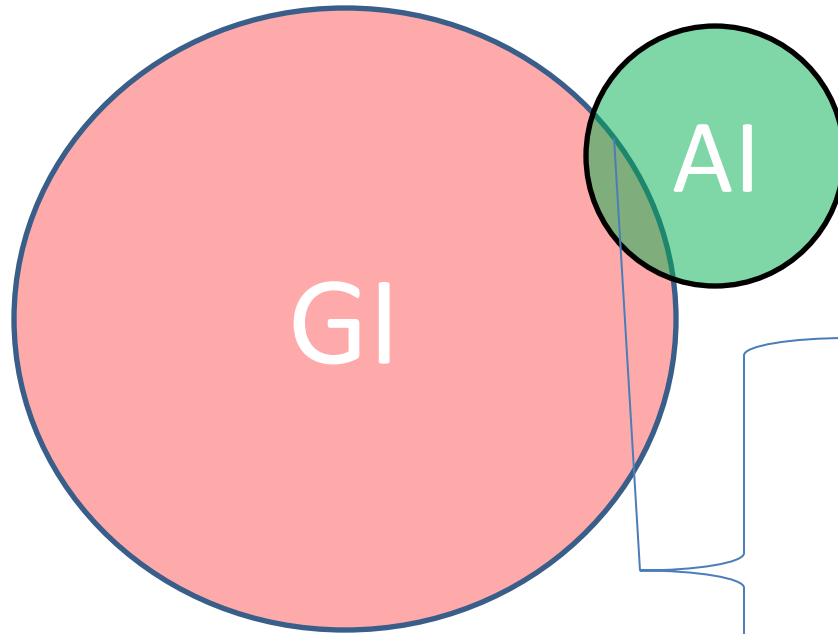
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Adjunct Associate Professor, Tufts University  
Board certified gastroenterology and allergist



# Disclosure

<b>Advisory boards:</b>	Sanoli, Regeneron, American Gastroenterology Association
<b>Clinical trials:</b>	ALK, AstraZeneca, Allakos, BMS, Ellodi, Revolo, Regeneron, Sanofi, Takeda
<b>Speaker Bureau:</b>	Sanoli, Regeneron, Abbvie

# Clinical interests



- Food intolerance/allergy
- EoE, EG/EoD, EC
- Celiac/NCGS
- Mast cell related GI disorders
- Biological desensitization
- Misc enteropathy (Lichen planus, lymphocytic, autoimmune enteropathy, CVID)

# A case study

- Extensively breastfed till 4 month old
- Recurrent projectile vomiting 2 hours after 1st ingestion cow's milk formula
- Mom reports some flushing, but no hives, no fever
- Abby looks lethargic
- Hypotension at ED, recover with IVF, Zofran and Steroids at ED
- Observe for 4 hours and sent home
- Now, Abby is at your office

# What do you recommend?

- **What is the diagnosis?**
  - Differential diagnosis
  - Should IgE mediated reaction be even considered?
- **Diagnostics**
  - IgE level and SPT?
  - Patch testing?
  - OFC?
- **Management**
  - Does mom have to avoid cow's milk if she breastfeeds?
  - Steroids? Zofran? Antihistamine?
  - Avoid CM only? Or Soy too?
  - What kind of formula? Extensively hydrolyzed vs Amino acid
  - Other solid food(s) avoidance
  - How do I reintroduce the food group back?
  - When should we reintroduce soy or CM again?
  - Baked milk challenge first?

# Definition & background

- FPIES is a non-IgE-mediated food allergy, presents with delayed, repetitive vomiting after ingestion (sometimes with diarrhea), primary in infants
- FPIES is a rare disease, 1 in 2000, ~ EoE
- ICD code (K52.21) is established in 2016 (ICD for EOE established in 2008)
- First consensus published in 2017
- MGB, 1991-2018, 203 FPIES, out of 5, 000, 000 encounters. ~60 allergists.
- $\frac{2}{3}$  of allergist providers have not seen a case of FPIES

# Concept # 1: a spectrum

Allergic  
proctocolitis



FPIES



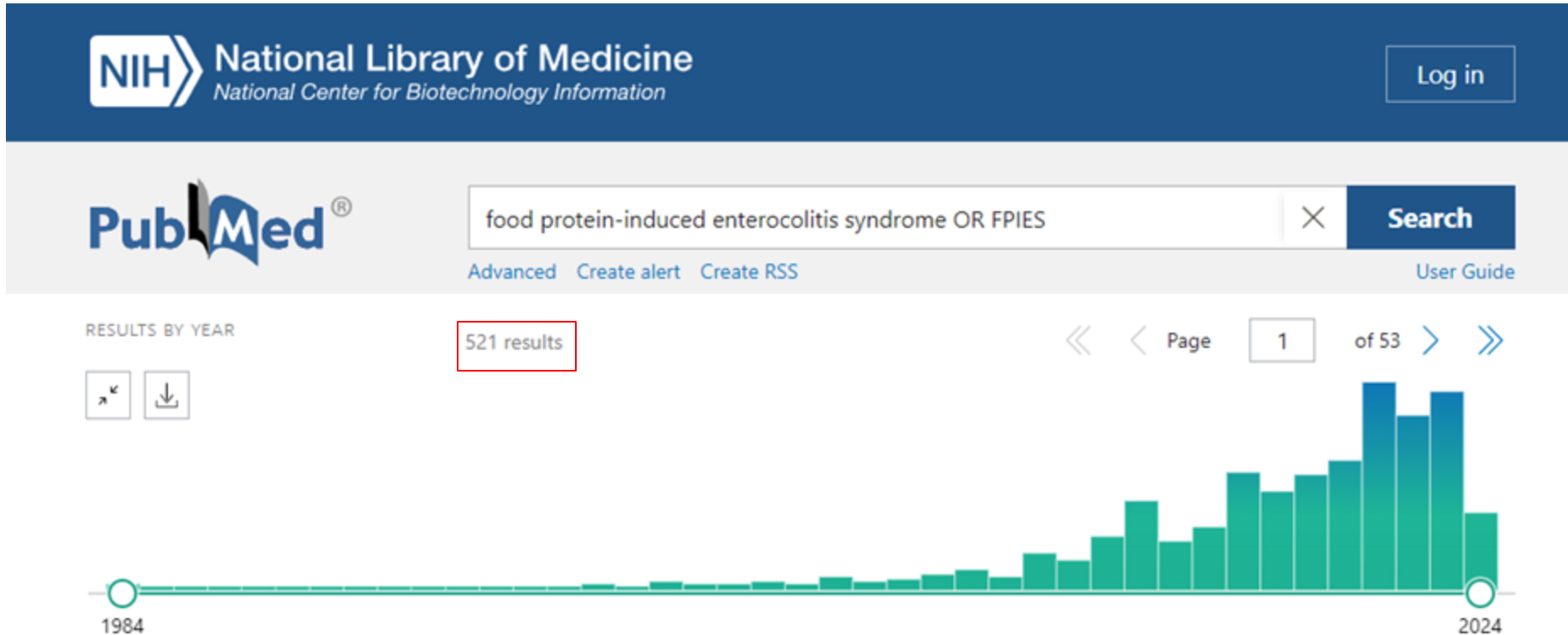
Blood in the stool,  
Comfortable  
Outgrow by 1 yo  
Breastfed = formula



Severe vomiting  
Shock /dehydration  
Outgrow by 2-3 yo  
Formula >>>>  
breastfed

# History of FPIES

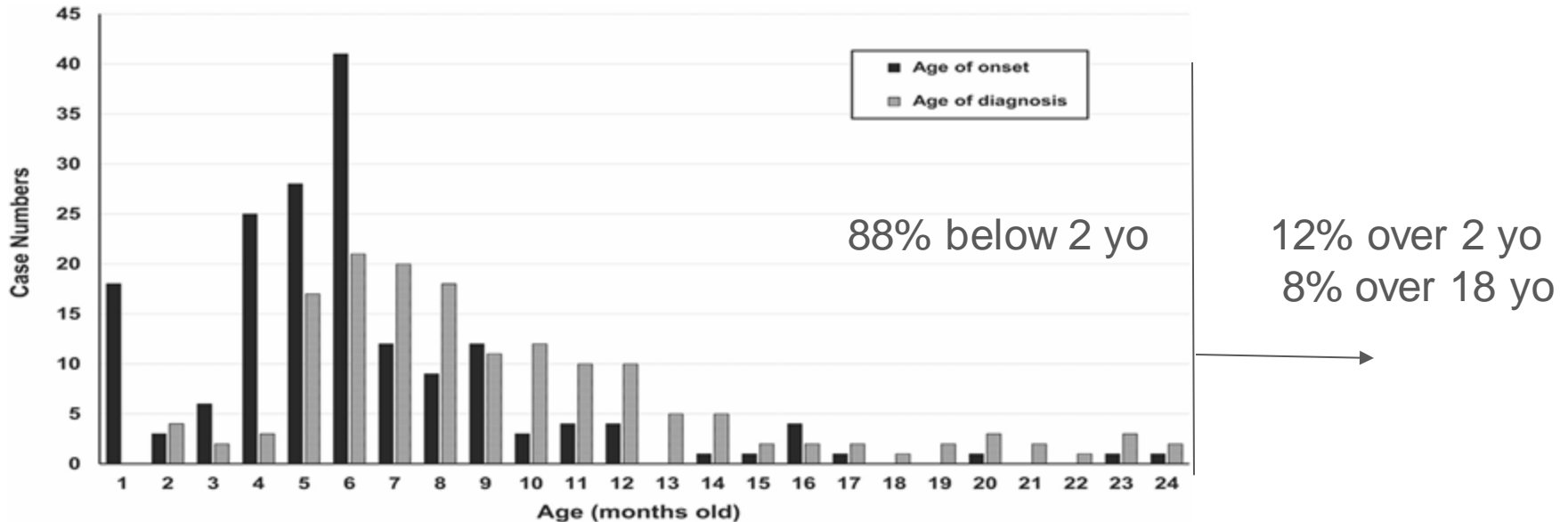
The first descriptions of FPIES in the medical literature emerged in the 1960s





# Prevalence of FPIES

- Prevalence in US = 0.51% in children
- Occurs 1st year of life



# Acute FPIES diagnostic criteria

## *1 Major*

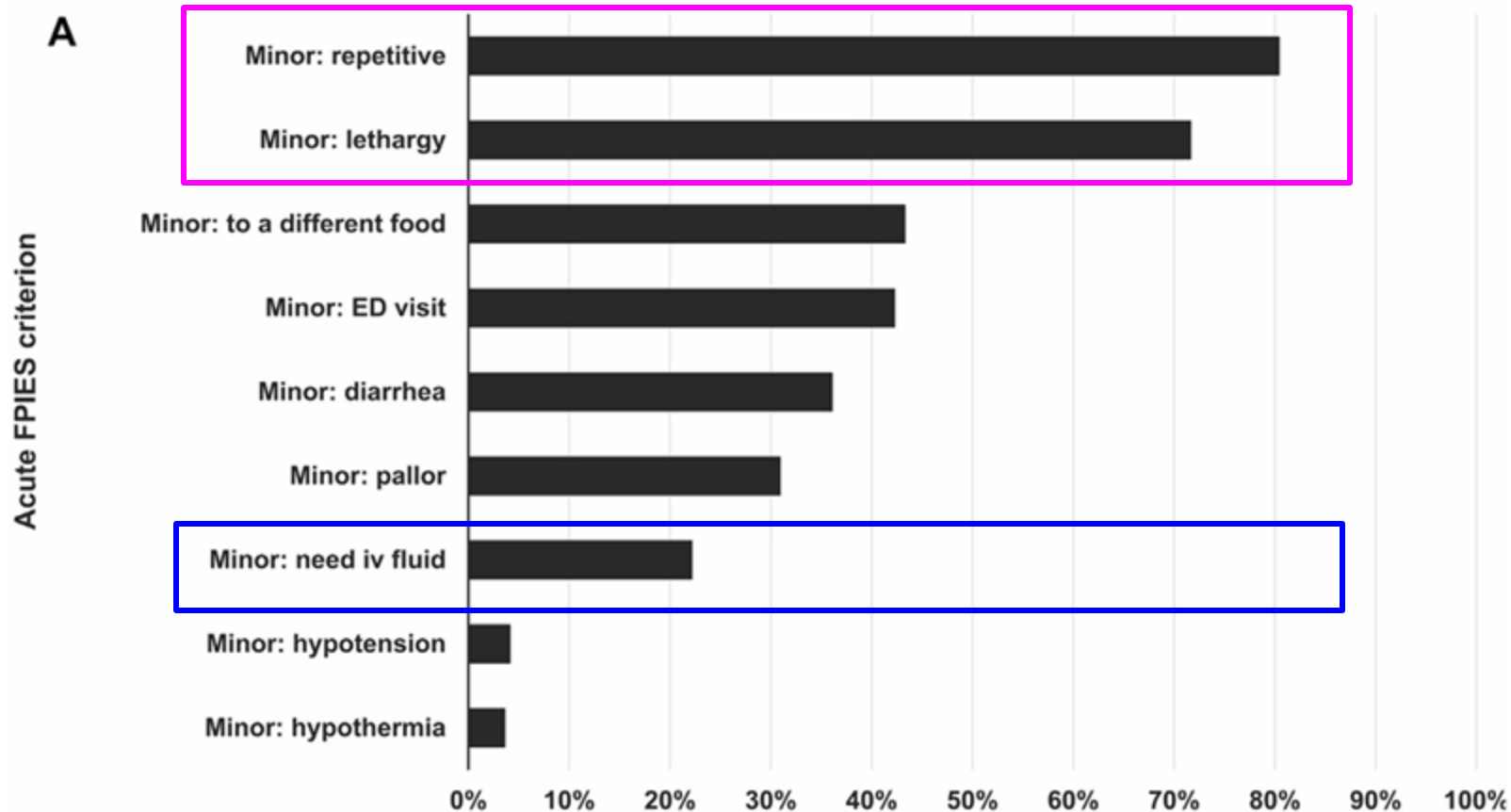
**Vomiting** 1-4 hr  
No IgE allergic rxn



## *Any 3 of the following minor criteria*

- Past hx of repetitive vomiting with **other** food
- Repetitive vomiting
- Diarrhea w/in 24 hr
- Lethargy
  
- ED
- IVF
- Low BP
- Low temp

# Acute FPIES symptoms



# Acute FPIES diagnostic criteria

## *1 Major*

**Vomiting** 1-4 hr  
No IgE allergic rxn



## *Any 3 of the following minor criteria*

- Past hx of repetitive vomiting with **other** food
- Repetitive vomiting (**80%**)
- Diarrhea w/in 24 hr
- Lethargy (**70%**)
  
- ED
- IVF
- Low BP
- Low temp

# A case study

- Extensively breastfed till 4 month old
- Recurrent projectile vomiting 2 hours after 1st ingestion cow's milk formula
- No hives, no fever
- Abby looks lethargic
- Hypotension at ED, recover with IVF, Zofran and Steroids

# A case study

- Extensively breastfed till 4 month old
- **Recurrent** projectile **vomiting 2 hours** after 1st ingestion cow's milk formula
- **No hives**, no fever
- Abby looks **lethargic**
- **Hypotension** at **ED**, recover with **IVF**, Zofran and Steroids

Diagnosis is **acute FPIES = 1 Major (yellow) + 5 minors (blue)**

# Acute FPIES diagnostic criteria

## 1 Major

**Vomiting** 1-4 hr  
No IgE allergic rxn



## Any 3 of the following minor criteria

- Past hx of repetitive vomiting with **other** food
- **Repetitive vomiting**
- Diarrhea w/in 24 hr
- **Lethargy**
  
- **ED**
- **IVF**
- **Low BP**
- Low temp

# Patients' characteristics

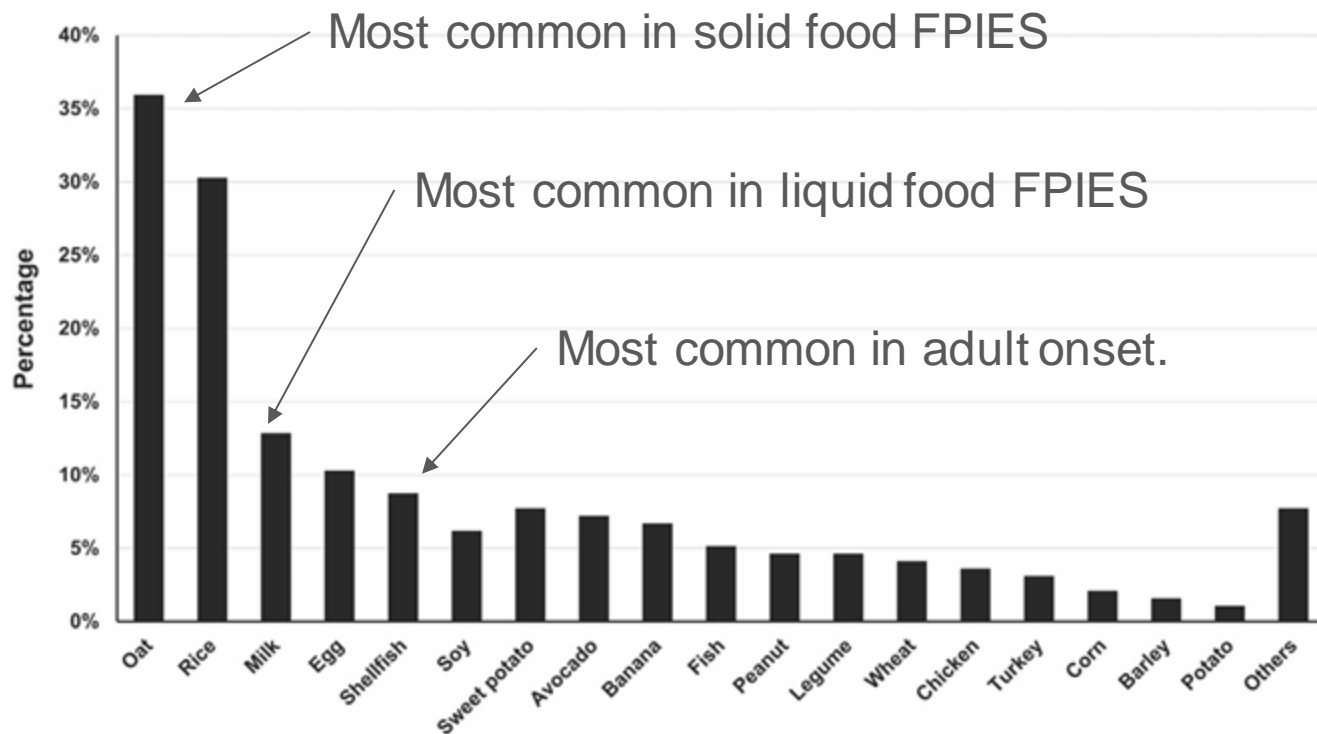
**TABLE I.** Characteristics of patients with FPIES

Characteristic	Case no.	Percentage
Total	203	
Sex: male	107	52.7%
Race		
White	174	85.7%
Black	4	2.0%
Asian	5	2.5%
Hispanic	5	2.5%
Others or unrecorded	15	7.4%
Birth and breast-feeding		
Delivery mode, cesarean section	53	26.1%
Prematurity	6	3.0%
Perinatal antibiotics	18	8.9%
Breast-feeding ever	152	74.9%

Characteristic	Case no.	Percentage
Personal history		
Allergic proctocolitis	47	23.2%
Gastroesophageal reflux	73	36.0%
IgE-mediated food allergy	23	11.3%
Eczema	82	40.4%
Asthma	27	13.3%
Hay fever/allergic rhinitis	29	14.3%
Family history		
FPIES	3	1.5%
Food allergy	63	31.0%
Other atopic diseases	94	46.3%
Gastroesophageal reflux	34	16.7%
IBD	19	9.4%
Celiac disease	15	7.3%
Eosinophilic esophagitis	1	0.5%

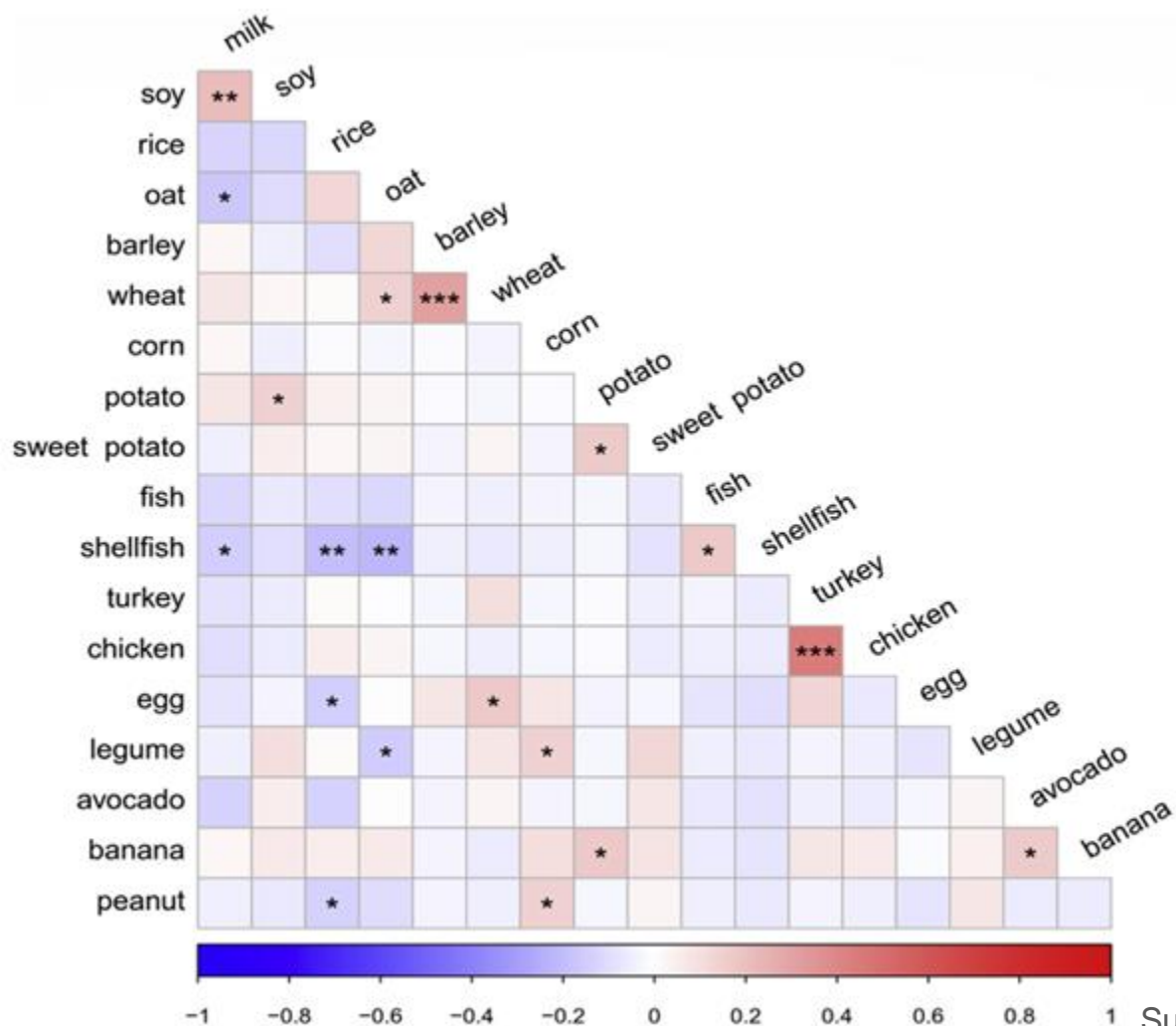


# Common FPIES Food triggers



**FIG E4.** Foods causing acute FPIES, expressed as a percentage of patients with FPIES reaction to the trigger food.

# Co-allergies



**Boston  
Specialists**  
Dr. John Leung

# FPIES evaluation

- No biomarkers
- Ddx = viral gastroenteritis, GI anaphylaxis, obstruction, EGID, IBD
- PMN is elevated
- Chronic FPIES is a diagnosis of exclusion
- FPIES may be missed due to
  - No typical allergic symptoms
  - Delayed onset
  - Unusual IgE-hypoallergic food triggers: oat, rice, fruit, veggies, avocado
- Guideline does not recommend SPT, IgE and patch testing
- A subset of FPIES patients have IgE FA and IgE/SPT is helpful

# FPIES evaluation: OFC

- OFC is usually not necessary for diagnosis, but helpful in checking for resolution (6-24 m).
- Wait 6-24 months prior to OFC of trigger food(s)
- Pre-OFC: check SPT and IgE level
- Facility: Expert center, with IV capacity (50% needs IVF), airway
- Med: Steroids + Zofran IV/IM (shown to be effective in 2 case series)
- OFC protocol varies
  - 2017 guideline = 0.3 g food protein/kg of body weight (max 3g), in 3 equal doses over 30 mins, and observe for 4-6 hr
  - Severe hx, smaller dose, 3 hr obs, then full serving and obs for 4 hr
  - For atypical FPIES, graded OFC like IgE food allergy, obs for 4 hr

# What do you recommend for Abby in outpatient settings?

- **Diagnostics**

- IgE level and SPT? **No**
- Patch testing? **No**
- OFC? **No**

- **Management**

- Does mom have to avoid cow's milk if she breastfeeds? **No**
- Steroids? Zofran? Antihistamine? **Y+Y+N**
- Avoid CM only? Or Soy too? **Consider both**
- What kind of formula? **Extensively hydrolyzed**, not Amino acid
- Other solid food(s) avoidance: **6 month per guideline**
- How do I reintroduce the food group back?
- When should we reintroduce soy or CM again?
- Baked milk challenge first?

**TABLE IX.** Empiric guidelines for selecting weaning foods in infants with FPIES

Ages and stages	Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*
<p>4-6 mo (as per AAP, CoN)</p> <p>If developmentally appropriate and safe and nutritious foods are available:</p> <ul style="list-style-type: none"> <li>● Begin with smooth, thin purees and progress to thicker purees</li> <li>● Choose foods that are high in iron</li> <li>● Add vegetables and fruits</li> </ul>	<p>Vegetables</p> <p>Broccoli, cauliflower, parsnip, turnip, pumpkin</p>	<p>Squash, carrot, white potato, green bean (legume)</p>	<p>Sweet potato, green pea (legume)</p>
<p>6 mo (as per WHO)</p> <p>Complementary feeding should begin no later than 6 mo of age:</p> <ul style="list-style-type: none"> <li>● In the breast-fed infant, high-iron foods or supplemental iron (1 mg/kg/d) are suggested by 6 mo of age</li> <li>● Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.</li> </ul>	<p>Fruits</p> <p>Blueberries, strawberries, plum, watermelon, peach, avocado</p>	<p>Apple, pear, orange</p>	<p>Banana</p>
<p>8 mo of age or when developmentally appropriate:</p> <ul style="list-style-type: none"> <li>● Offer soft-cooked and bite-and-dissolve textures from around 8 mo of age or as tolerated by infant.</li> </ul>	<p>High-iron foods</p> <p>Lamb, fortified quinoa cereal, millet</p>	<p>Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal</p>	<p>Higher-iron foods: fortified, infant rice and oat cereals</p>
<p>12 mo of age or when developmentally appropriate:</p> <ul style="list-style-type: none"> <li>● Offer modified tolerated foods from the family: table-chopped meats, soft cooked vegetables, grains, and fruits</li> </ul>	<p>Other</p> <p>Tree nuts and seed butters* (sesame, sunflower, etc.)</p> <p>*Thinned with water or infant puree for appropriate infant texture and to prevent choking</p>	<p>Peanut, other legumes (other than green pea)</p>	<p>Milk, soy, poultry, egg, fish</p>

# Natural history

- Generally good prognosis
- Self-limiting in childhood
- Most outgrow by 3-5 yo
- Atypical FPIES tends to ? linger longer
- CM-induced FPIES resolved in all children by age 2 years, and soy-induced FPIES resolved by age 14

# What do you recommend for Abby in outpatient settings?

- **Diagnostics**

- IgE level and SPT? **No**
- Patch testing?
- OFC? **No**

- **Management**

- Does mom have to avoid cow's milk if she breastfeeds? **No**
- Steroids? Zofran? Antihistamine? **Y+Y+N**
- Avoid CM only? Or Soy too? **Consider both**
- What kind of formula? **Extensively hydrolyzed**, not Amino acid
- Other solid food(s) avoidance: **6 month per guideline**
- How do I reintroduce the food group back? Per protocol
- **When should we reintroduce soy or CM again?** **Most outgrow by age 2**
- **Baked milk challenge first?** **No consensus**



# Milk triggered acute FPIES in 4 months old

## My approach:

- Avoid soy formula till 6-12 months
- At 12 months, consider soy milk OFC in office with 4 hours observation
  - I will check SPT for soy and CM
  - If SPT +, OFC protocol will be modified to graded challenge
  - If SPT -, 2 step challenge.
- A baked milk challenge in selected cases (no guideline)
- OFC for CM at 2 year of age (guideline = 6-24 months)

# Food aversion (it is real)

- 22% has food aversion
- Risk factor:  $\geq 3$  food triggers (10%)
- No data on prognosis/outcome

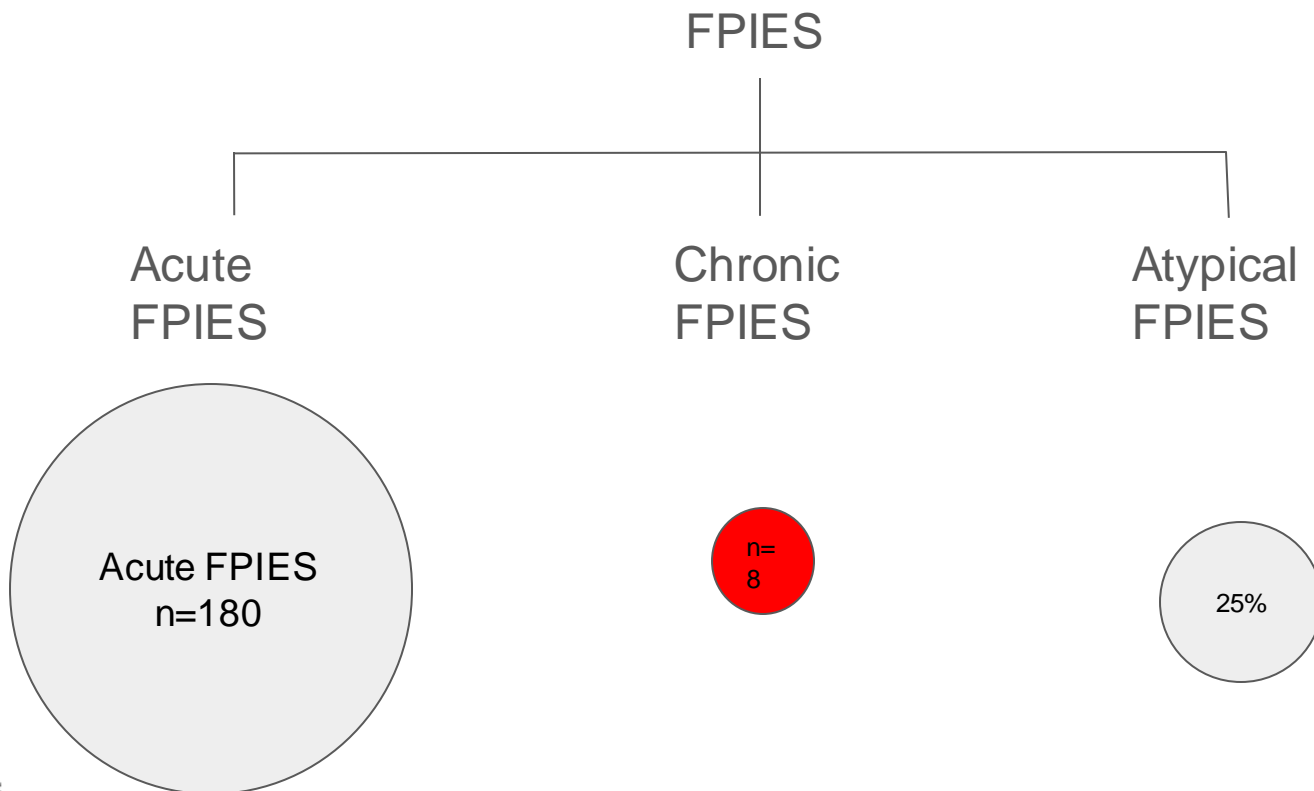
## My approach:

- Offer in office OFC during reintroduction phase
- Frequent follow up and monitoring by dietitian

# Summary of acute FPIES

- Acute FPIES = 0.5%, rare
- 1 major + 3 minors (repetitive vomiting & lethargic)
- Diagnosis = no biomarkers, keeps ddx board, hinges on history
- OFC is not necessary for diagnosis, but for reintroduction
- SPT is not usually in diagnosis, but can guide OFC
- Food triggers
  - CM & soy for liquid triggers, oat and rice for solid triggers
  - Shellfish is most common in adult FPIES, less likely to outgrow and usually a solo-trigger
- For infant CM FPIES, avoid soy, breastfeed/extensively hydrolyzed formula, soy OFC at 1y, milk OFC at 2y
- Baked milk OFC considered
- Food aversion - frequent follow up and OFC in selected cases

# Concept # 2: Type of FPIES



# Chronic FPIES diagnostic criteria

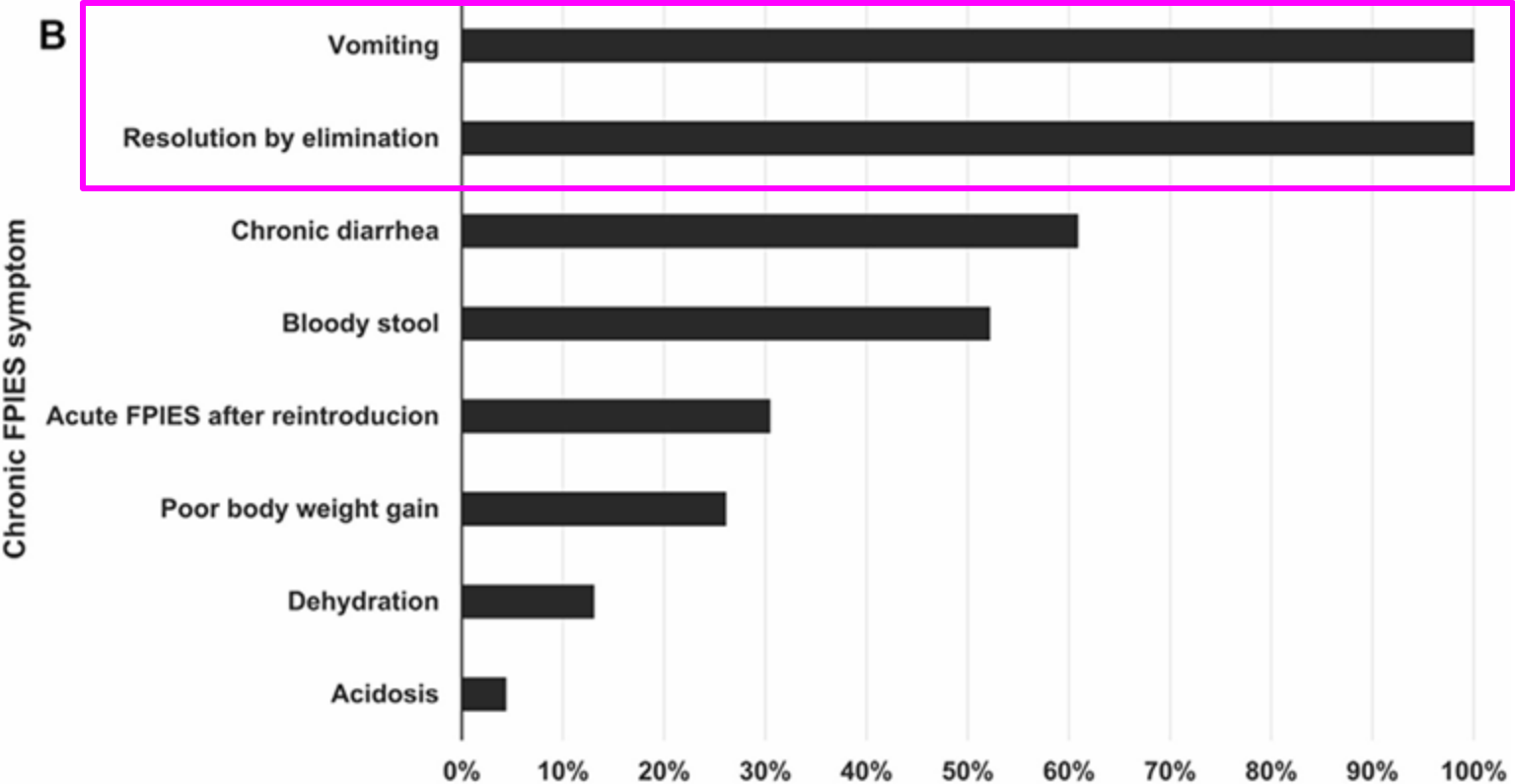
The most important criteria for chronic FPIES diagnosis is the resolution of the symptoms within days, following elimination of the offending food, and acute recurrence of symptoms when the food is reintroduced, with the onset of vomiting in 1 to 4 hours, with diarrhea in 24 hours, but usually 5 to 10 hours

**Without a confirmatory challenge, diagnosis of chronic FPIES remains presumptive.**

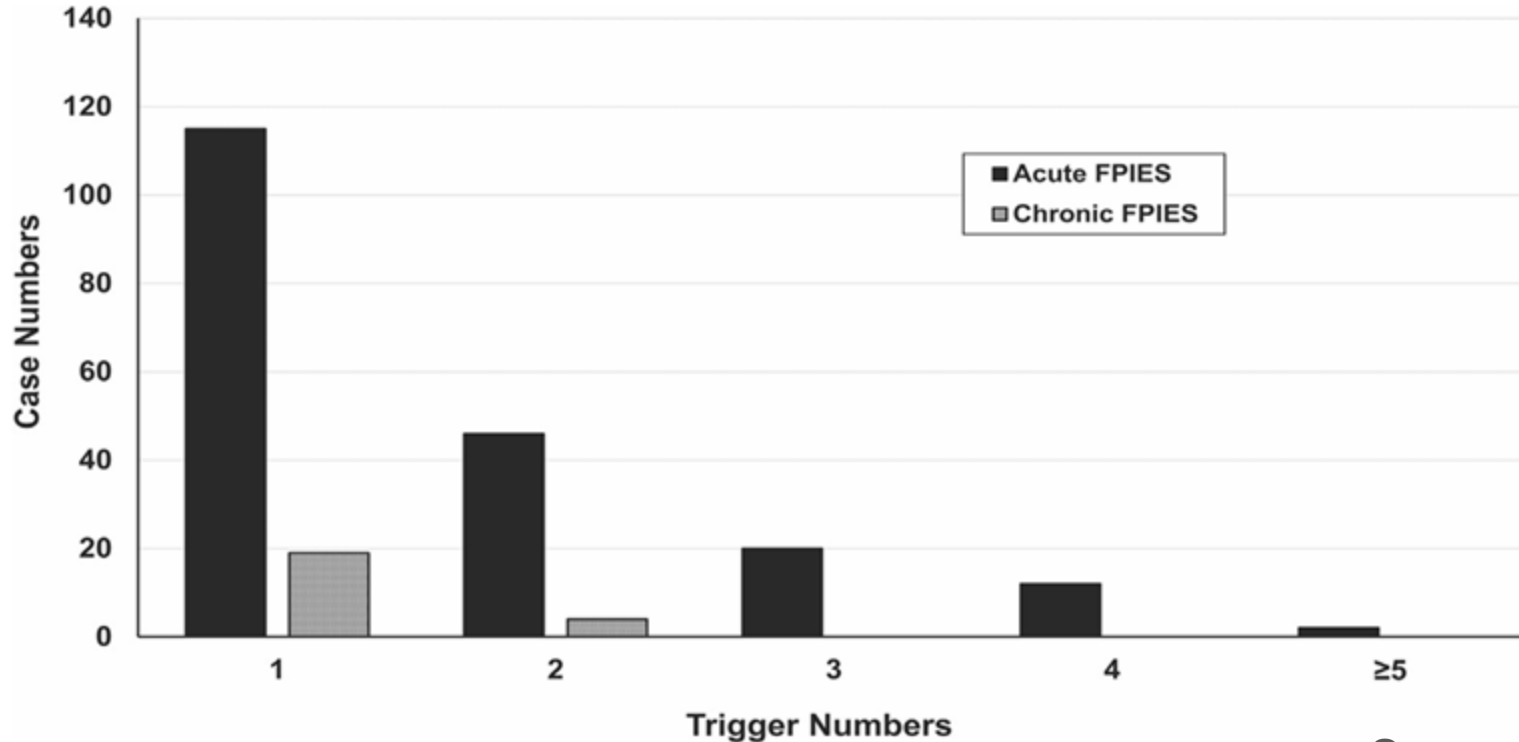
# Acute versus Chronic

<b>Acute FPIES</b>	<b>Chronic</b>
“Acute”	“Chronic”: FTT
Repetitive vomiting + diarrhea + ED	Int. vomiting + water diarrhea
Age of onset: 6 months	0.4 month (formula fed)
0.5% prevalence	Much lower

# Chronic FPIES symptoms

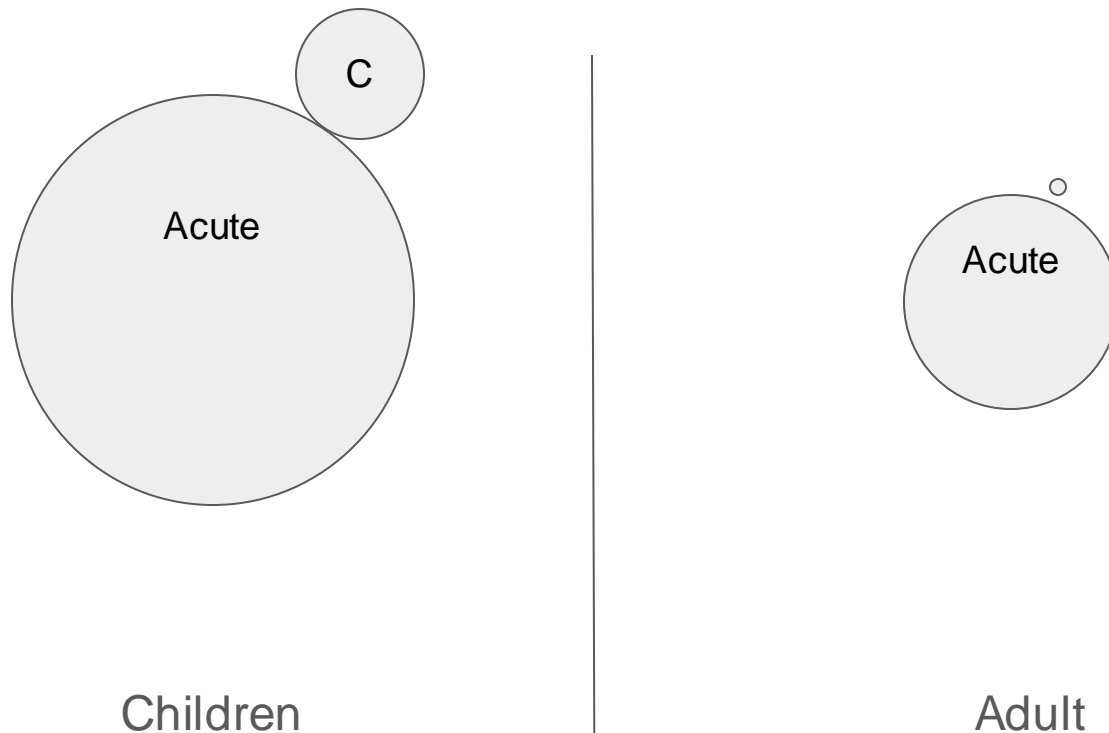


# Acute FPIES often has more triggers

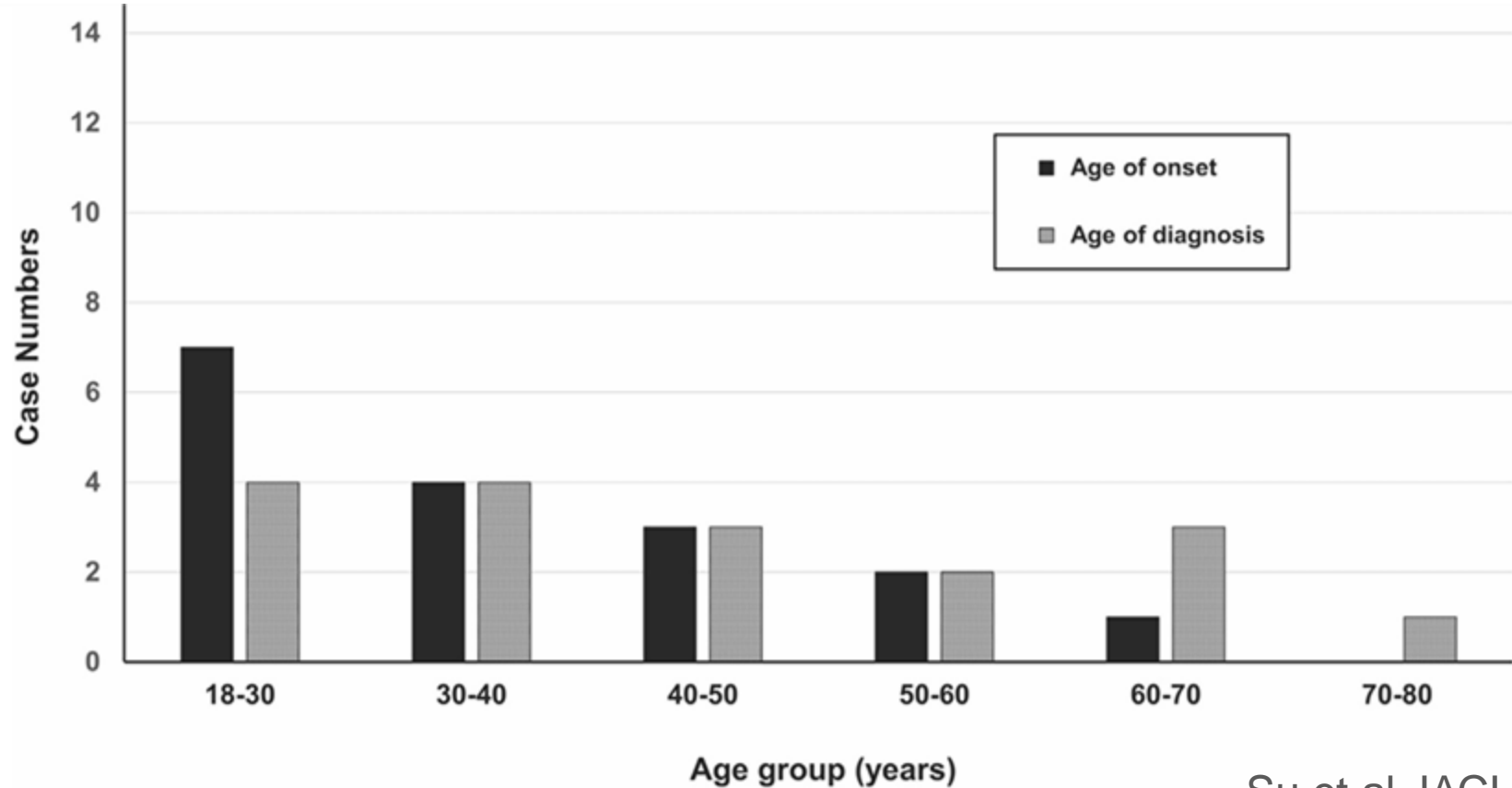




# Concept # 3: Adult versus pediatric FPIES

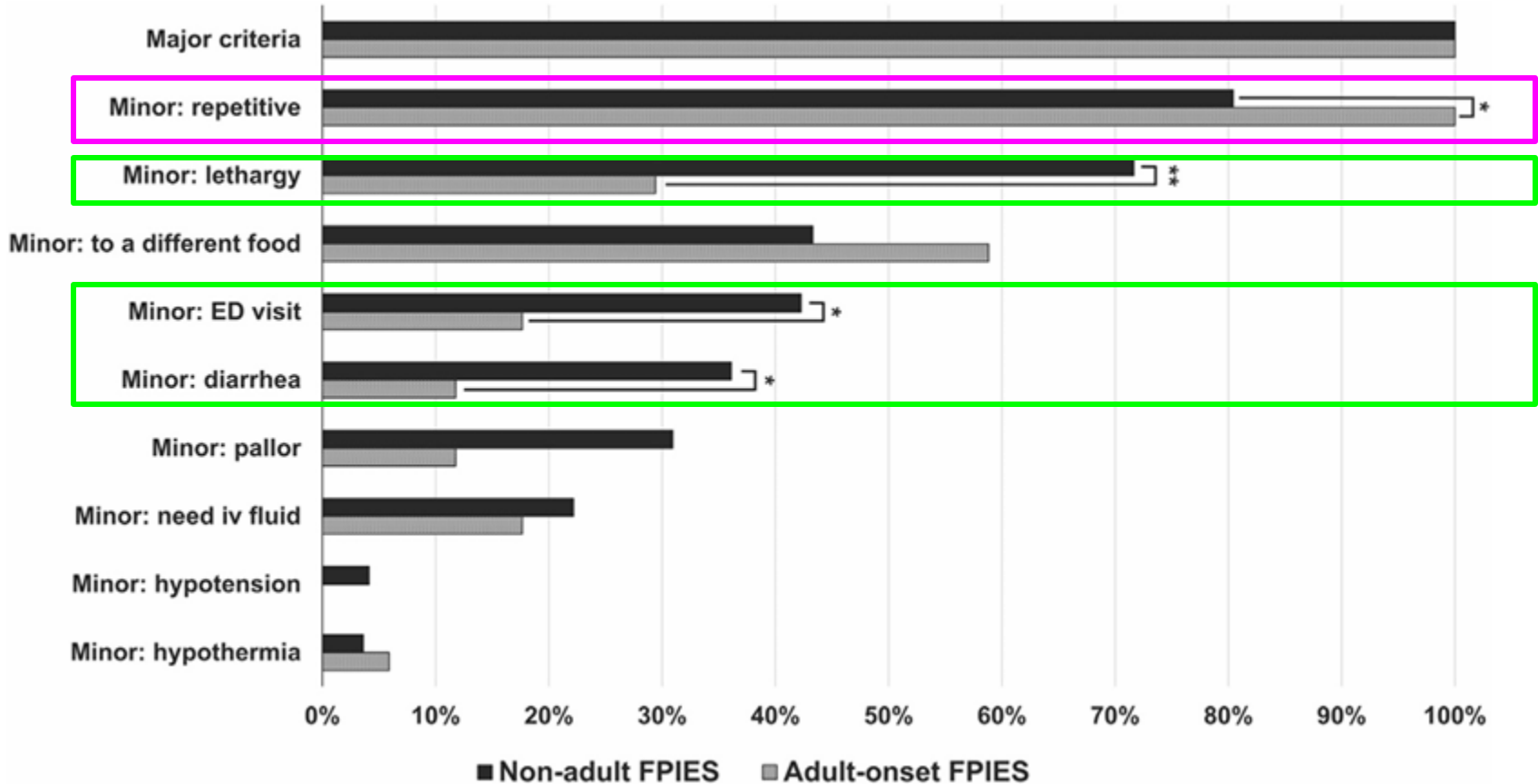


# FPIES can occur in older patients



	Adults		Children	
	Acute	Chronic	Acute	Chronic
Prevalence	0.22%	1 case	0.51%	0.05%
Most common trigger	Seafood	N/A	Liquid: CM Solid: oat, rice and avocado	CM
Age	40	N/A	Liquid: < 6m; Solid: 4-7m	< 3m
Natural hx	Persistent		2-3 yrs	
Atypical	N/A		25%	
Atopic	Common			
Gender	No major difference			

# Adult FPIES has more repetitive vomiting, less lethargy, ED visit & diarrhea



## Case 2

25 yo man presents with intermittent nausea and nonspecific abdominal pain, as well as bloating. He self-eliminates food items one by one, and found that avoiding eggs actually helps with his symptoms. His symptoms associated with eggs do not occur immediately and has never been associated with hives or wheezing. The improvement is gradual over days/weeks after he avoids eggs.

He paid out of pocket to obtain a panel of IgG intolerance tests and it shows elevated IgG levels for eggs, along with 12 other food items. He feels fine as long as he is avoiding eggs and wants to know if he needs to other the other 12 foods.

### He wants to know:

- 1) What is the diagnosis?
- 2) Is eating eggs from time to time do any damage to his body?
- 3) Does he need to avoid foods that have elevated levels of IgG levels.
- 4) Does he need any EpiPEN?
- 5) Can he do OIT?

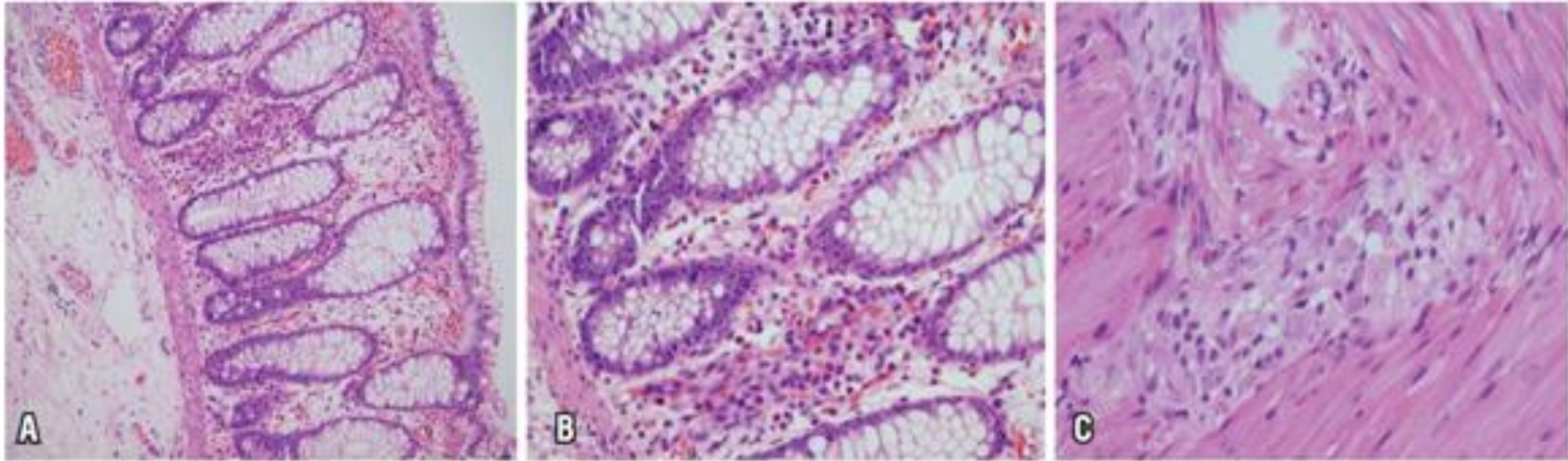
# Case 2

## 1) What is the diagnosis?

- a) EGID, chronic FPIES, MGID, ~~IgE-mediated~~
- b) Confirmation of diagnosis requires pan-endoscopies.
- c) Diagnosis will not change management

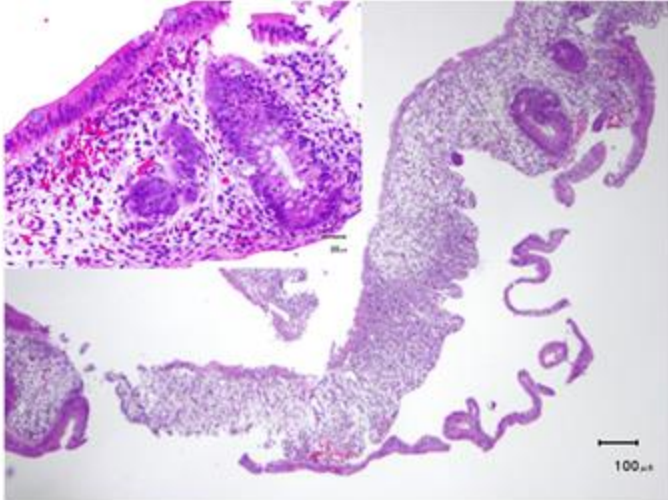
But, what will endoscopies show if we chose to do endoscopies and if he has FPIES?

# Pathology of FPIES

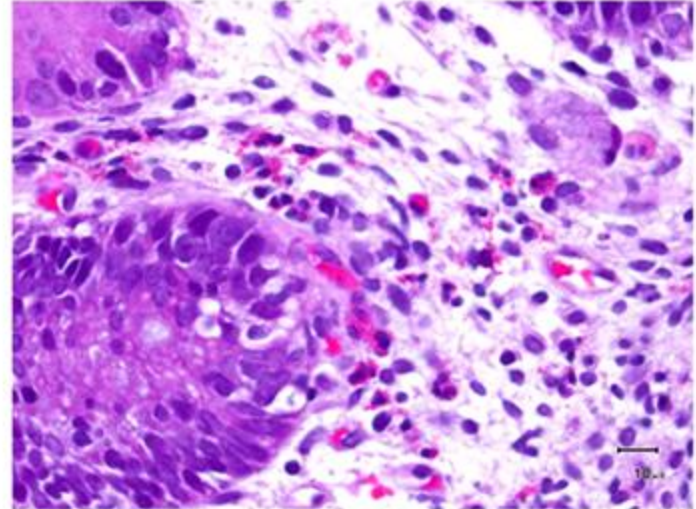


**Figure 1.** A. Histopathology with hematoxylin – eosin staining. B. Marked eosinophil infiltrate, formation of micro abscesses with damage in the crypts, aggregation by erosion in the surface mucus. C. Occasional eosinophil permeating other layers, some in the sub-mucus which is also edematous, and there are even eosinophils in the mesenteric plexus. (40x).

# Pathology of FPIES



**Fig. 2.** Colon (composite). Contiguous areas of lamina propria with crypt loss (lower and right), prominent cryptitis and crypt apoptotic bodies (upper left), H &E.



**Fig. 3.** Rectosigmoid with prominent eosinophils in lamina propria, with reactive crypt epithelial changes and crypt apoptotic bodies, H&E.



# Case 2

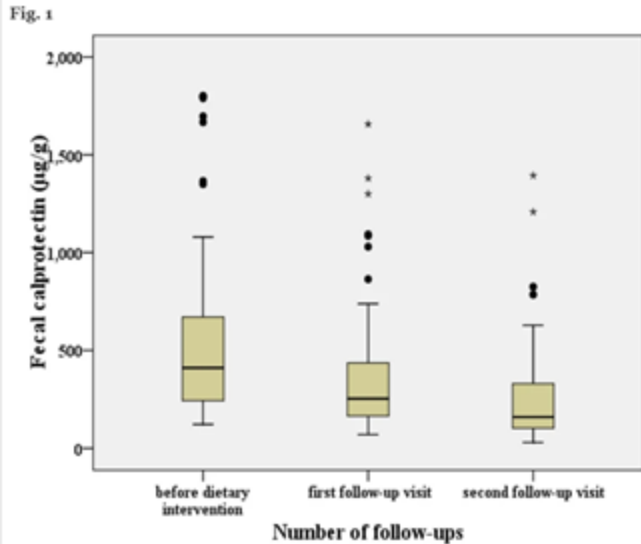
## 1) What is the diagnosis?

He agrees that endoscopy will not change the outcome, but he is curious if a fecal calprotectin may be helpful

# Calprotectin

- Calprotectin is a calcium- and zinc-binding protein of the S-100 protein family which is mainly found within neutrophils.
- The presence of calprotectin in faeces is a consequence of neutrophil migration into the gastrointestinal tissue due to an inflammatory process
- Faecal calprotectin is a very sensitive marker for inflammation in the gastrointestinal tract
- May not be helpful in diagnosis, elevated in both enterocolitis & FPIES
- May be helpful in food reintroduction/monitoring
- Not proven, personal opinion, helpful elective cases

# Calprotectin in FPIES



Comparison of fecal calprotectin levels of infants with a milk protein allergy before dietary intervention and at the first and second follow-ups

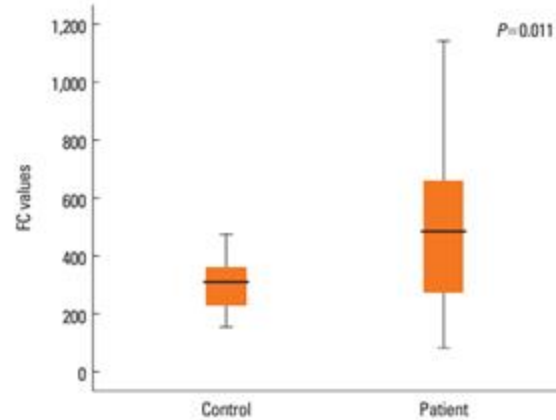


Fig. 2. Comparison of fecal calprotectin levels before diet in CMPA patients with those in the control group.

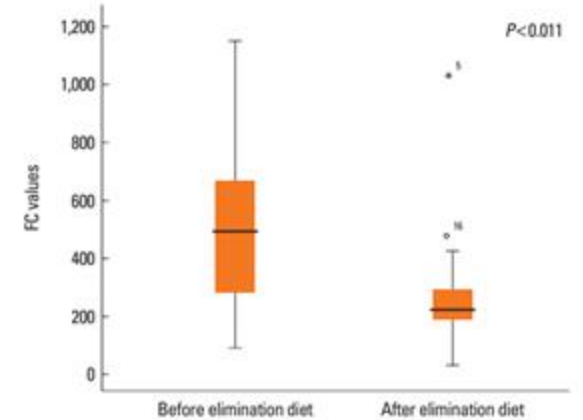


Fig. 3. Comparison of fecal calprotectin levels before and after diet in patients with CMPA.

## Case 2

1. **What is the diagnosis?** Non-IgE egg allergy
2. **Is eating eggs from time to time do any damage to his body?** No
3. **Does he need to avoid foods that have elevated levels of IgG levels?** No
4. **Does he need any EpiPEN?** No (esp if SPT is negative)
5. **Can he be desensitized?** Not that we know of

# Summary of FPIES

- FPIES = rare, life-threatening, poorly understood, avoidance
- Acute >> Chronic, Pediatric >> adult
- Acute (a major + 1 minor); chronic (sx resolves with food elimination)
- 40% ED, 25% IVF, Zofran, IVF, Steroid
- Most kids outgrow, less for adult FPIES
- Co-allergy and protocol for reintroduction
- Food aversion, frequent follow-up/supervised OFC
- FPIES can occur in older patients
  - Repetitive vomiting (100%)
  - Overlap of EGID, MGID, food intolerance, IBS

# Gap of knowledge

- **Diagnosis:**
  - No biomarkers. Role of fecal calprotectin
  - Chronic FPIES actually a subset of EGID. How to differentiate?
- **Pathogenesis**
  - rare
  - majority of cases are infants, presented to ED very sick
  - self-limiting, quick resolution
- **Treatment:**
  - Reintroduction is based on expert opinion
  - Access to dietitians trained with FPIES are very limited
  - Access to food aversion therapists are even harder
  - ? Th2 blockers, esp for multi-trigger
  - ? Oral immunotherapy

# The END

## Search Results

Viewing 1 result

Card View

Showing results for: **Food protein-induced enterocolitis syndrome** | Enrolling by invitation studies

+ [Synonyms of conditions or disease \(2\)](#)

None Selected



ENROLLING BY INVITATION

NCT04644783

Novel Blood Test to Predict Safe **Foods** for Infants and Toddlers With **Food Protein-induced Enterocolitis Syndrome (FPIES)**

Conditions

Food Protein-Induced Enterocolitis Syndrome

Allergies

Pediatric Disorder

Locations

Ann Arbor, Michigan, United States

Asthma has 4651 active trials  
Eczema has 1381 active trials  
FPIES has 1 active trial in US



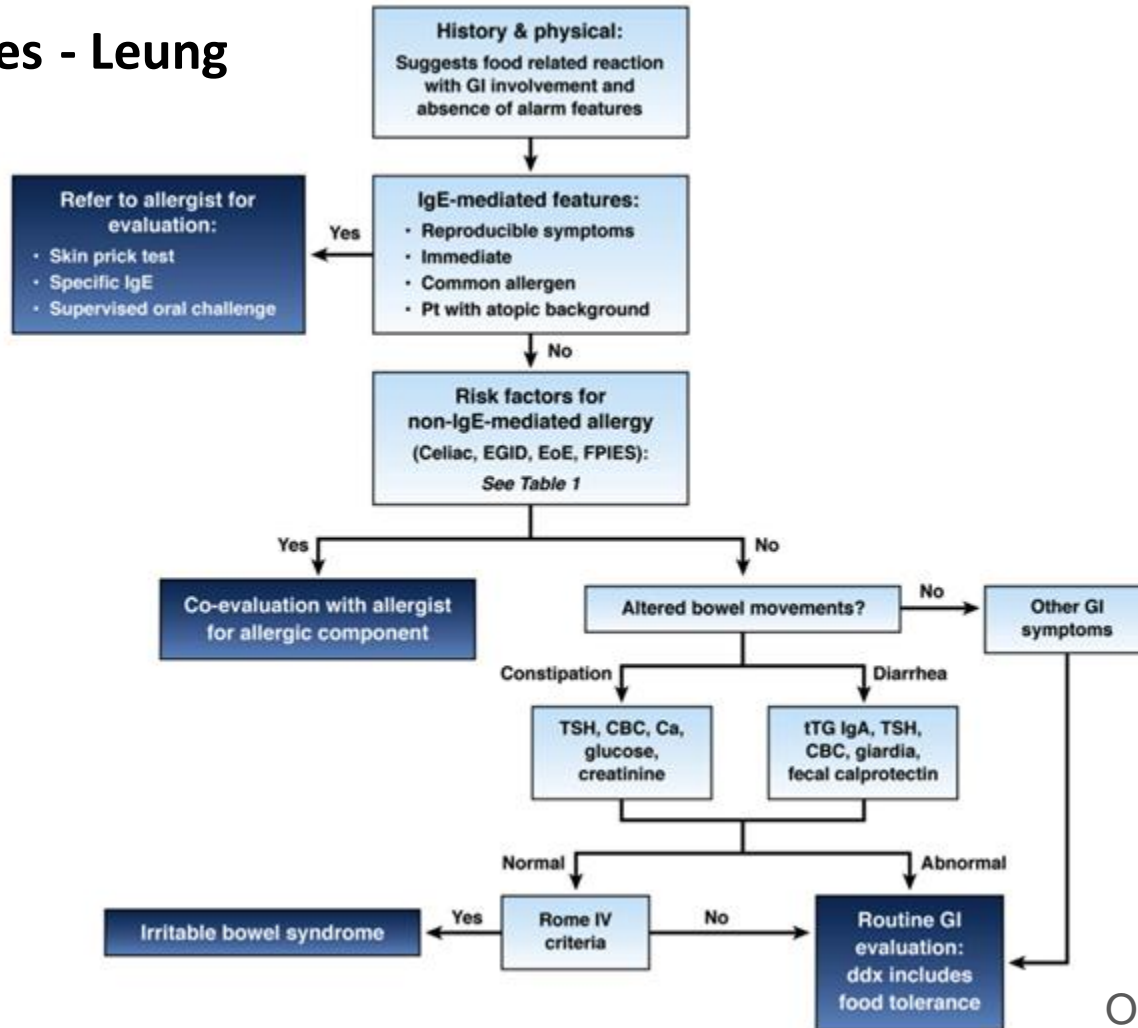


# Useful references

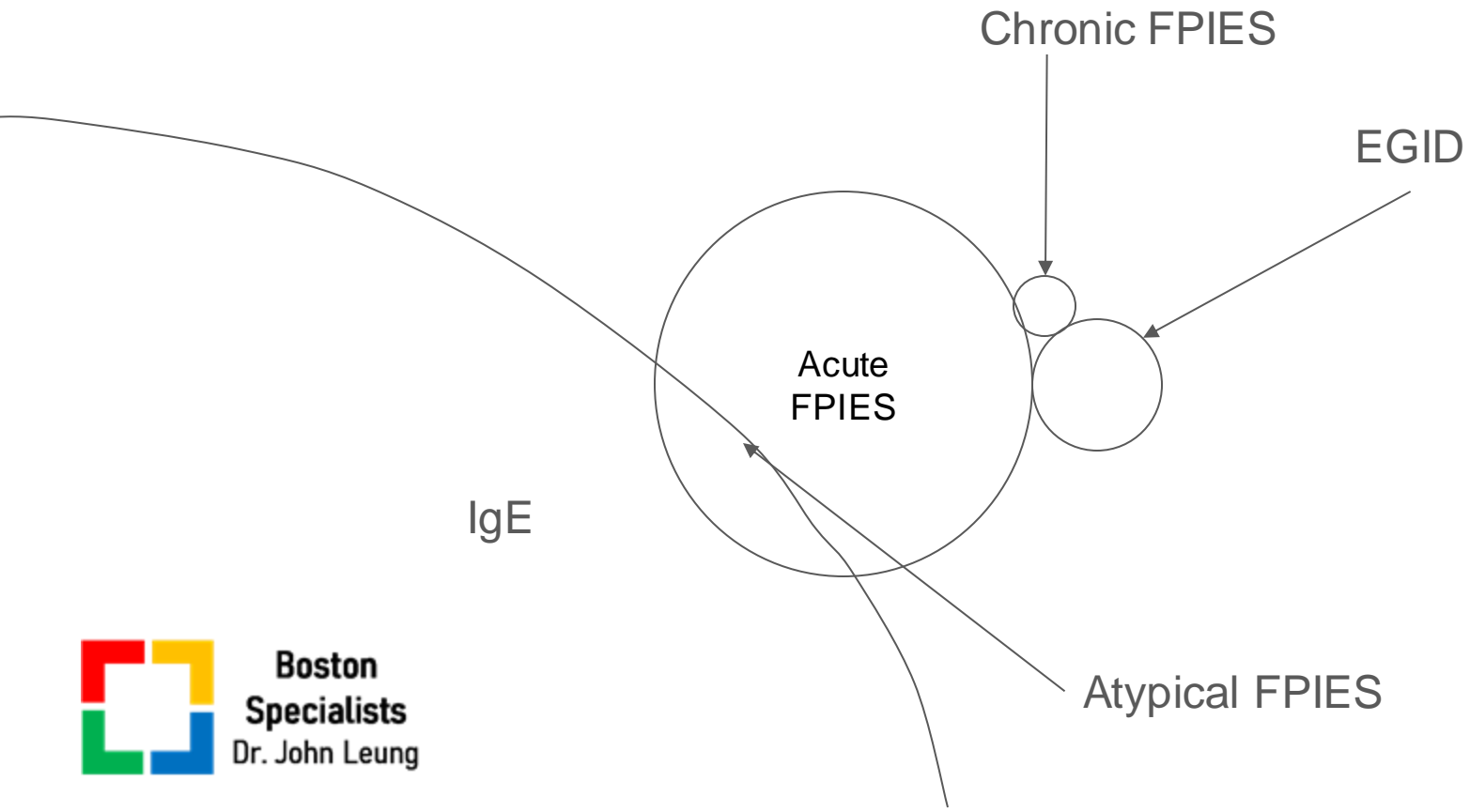
**Table 1.** Symptoms of Adverse Reactions to Food by System

Disease	Signs/Symptoms	Crohn's	UC	IBS	SIBO	GERD	Celiac	EoE	FPIES	OAS	IgE—Food Allergy
<b>Gastrointestinal</b>	Abdominal pain	X	X	X	X	X	X	X	X		X
	Bloating			X	X		X		X		X
	Blood in stool	X	X								
	Chest pain					X		X			X
	Constipation			X							
	Diarhea	X	X	X	X		X		X		X
	Dysphagia	X				X		X			
	Fecal incontinence	X	X								X
	Fecal urgency	X	X								X
	Flatulence	X	X	X	X		X				
	Food impaction							X			
	Heartburn/reflux					X		X			
	Nausea/vomiting	X				X		X	X		X
	Regurgitation					X		X			
<b>Skin</b>	Angioedema/urticaria										X
	Pruritus										X
	Oral ulcers	X	X								
	Oral itching + swelling									X	X
	Ocular pruritus/periorbital edema										X
	Nasal congestion/rhinorhea/sneezing										X
	Wheezing, dyspnea										X
<b>Miscellaneous</b>	Hypotension		X						X		X
	Fatigue	X	X				X		X		
	Weight loss/FTT	X	X				X	X	X		
	Joint pain	X	X				X				

# Useful references - Leung



# Concept # 3



# What food trigger is more prevalence in multi-trigger FPIES?

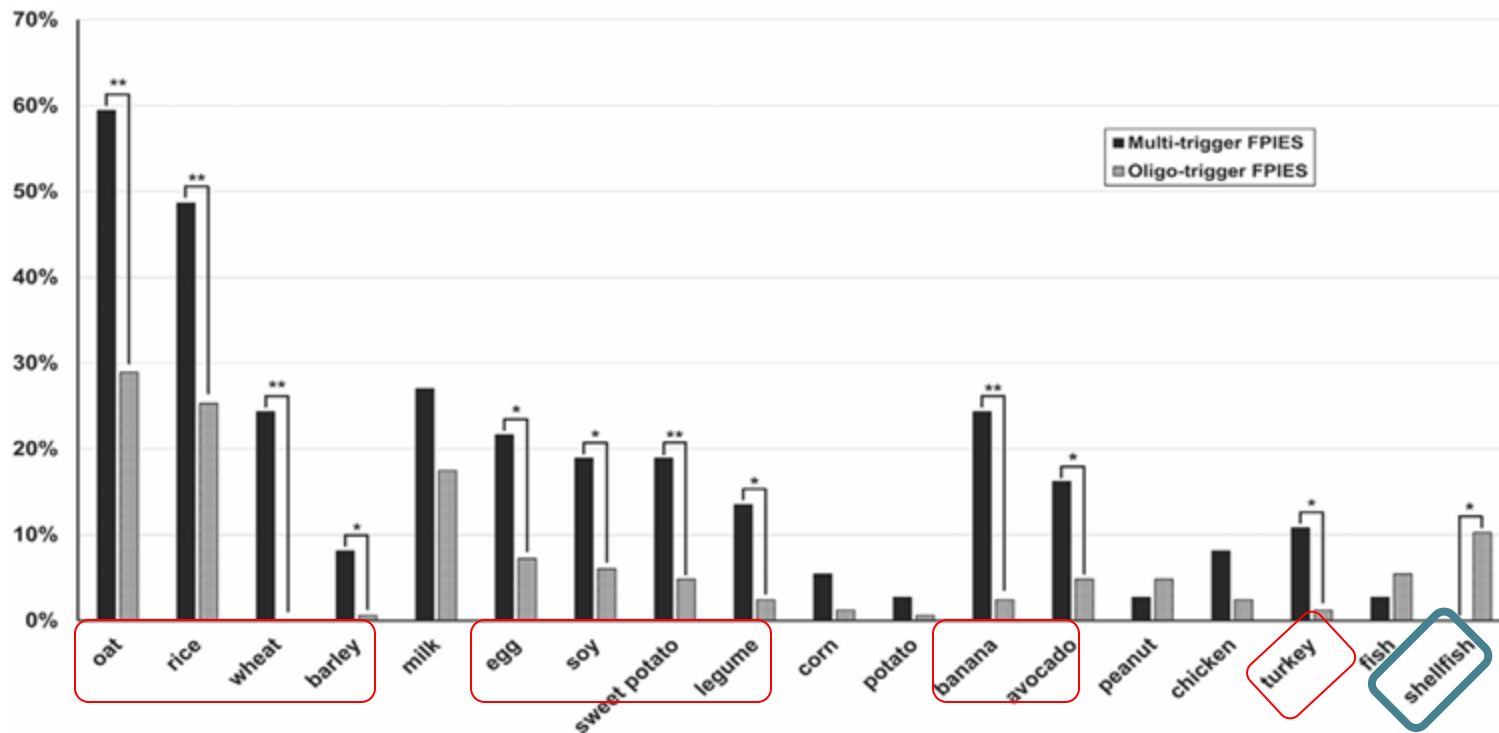


FIG E6. The comparison of the trigger foods between multiple and oligo FPIES (\* $P < .05$ ; \*\*  $P < .01$ ).

# Chronic versus acute food triggers

Condition	FPIES triggers
Chronic FPIES	>99% of cases <sup>9,11,12,14,15,30</sup> Cow's milk-based formula Soy-based formula <1% of cases Food triggers in breast milk
Acute FPIES	United States <sup>13,26,31,34,36</sup> Cow's milk Soy Grains Egg Fruits and vegetables

# Co-allergies

<b>FPIES to:</b>	<b>Clinical cross-reactivity/ coallergy</b>	<b>Observed occurrence*</b>
CM	Soy	<30% to 40%
	Any solid food	<16%
Soy	CM	<30% to 40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	CM or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	About 50%
Poultry*	Other poultry	<40%

**Thus, avoid CM & soy**