



# FPIES – A Not so Rare Pediatric Food Allergy

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# Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.
- Participant in Biocryst Advisory Board (2020)
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# Objectives

- Identify and classify acute and chronic FPIES
- List common foods implicated in acute FPIES
- Discuss the management options for acute FPIES

# Outline

- Acute and Chronic FPIES
  - Clinical presentation and diagnosis
  - Natural history
  - Commonly implicated foods
  - Food challenges



# Epidemiology of Pediatric Food Allergies

- Up to 10% of children have a reported food allergy
  - ~2-3 per US classroom
- Higher rates in Industrialized/Westernized regions
  - Australia, UK, Netherlands, and US
- Increased risk in males, African Americans, Asians, and in those with a family history of food allergies
  - Children with moderate to severe atopic dermatitis

# Types of Food Allergies

Type of Allergy	Timing of Symptoms	Symptoms
IgE-mediated	Typically immediate (<1 hour)	Urticaria, angioedema, vomiting, wheezing, coughing, hypotension, and potentially death
Acute food protein-induced enterocolitis syndrome (FPIES)	1-4 hours after ingestion	Repetitive vomiting, lethargy, pallor, dehydration, diarrhea, and potentially hypotension
Eosinophilic Esophagitis	Hours to days after ingestion	Food impaction, vomiting, reflux, and difficulty swallowing.
Food protein-induced allergic proctocolitis (FPIAP)	Insidious	Bloody stools
Pollen-food Syndrome (oral allergy syndrome)	Immediate (<30 minutes)	Oral and throat pruritus/tingling. Rare GI or systemic symptoms.

**FPIES – Non-IgE-mediated food allergy**

# FPIES Incidence/Prevalence

- Not known due to limited large-scale epidemiologic studies
  - Selection bias (most cases reported in academic centers)
  - Most reports are retrospective and have variable classification criteria
    - Acute vs Chronic
    - Classic vs Atypical
- Israel: 3 per 1000 (0.34%)
- Italy: 1%
- Australia: 15.4/100,000/year
- US: 0.5%

Mehr, et al. Curr Opin Allergy Clin Immunol, 2014.

Nowak-Wegrzyn, et al. J Allergy Clin Immunol, 2019.

Joshi S, Nicolaidis R, and Bird JA. Acute Food Protein-Induced Enterocolitis Syndrome. Food Protein-Induced Enterocolitis Syndrome – Diagnosis and

Management. Springer Nature Switzerland, Cham, Switzerland; 2019, 1<sup>st</sup> edition.



# Categorizing FPIES

**TABLE I.** Proposed defining features for clinical phenotyping of FPIES

FPIES subtypes	Defining features
Age of onset	
Early	Younger than age 9 mo
Late	Older than age 9 mo
Severity	
Mild-to-moderate	Repetitive emesis with or without diarrhea, pallor, mild lethargy
Severe	Repetitive projectile emesis with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis
Timing and duration of symptoms	
Acute	Occurs with intermittent food exposures, emesis starts usually within 1-4 h, accompanied by lethargy and pallor; diarrhea can follow within 24 hours, with usual onset of 5-10 h. Usual resolution of symptoms within 24 h after elimination of the food from the diet. Growth is normal, and child is asymptomatic during food trigger elimination.
Chronic	Occurs with daily ingestion of the food (eg, feeding with CM- or soy-based formula in an infant); symptoms include intermittent emesis, chronic diarrhea, poor weight gain, or FTT. Infants with chronic FPIES usually return to their usual state of health within 3-10 d of switching to a hypoallergenic formula, although in severe cases temporary bowel rest and intravenous fluids might be necessary. Subsequent feeding of the offending food after a period of avoidance results in acute symptoms.
IgE positivity	
Classic	Food specific, IgE negative
Atypical	Food specific, IgE positive



# Clinical Presentation (Acute FPIES)

Major Criterion:	Minor Criteria:
<b>Vomiting in the 1- to 4-hour period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms</b>	<ol style="list-style-type: none"><li>1. A second (or more) episode of repetitive vomiting after eating the same suspect food</li><li>2. Repetitive vomiting episode 1-4 hours after eating a different food</li><li>3. Extreme lethargy with any suspected reaction</li><li>4. Marked pallor with any suspected reaction</li><li>5. Need for emergency department visit with any suspected reaction</li><li>6. Need for intravenous fluid support with any suspected reaction</li><li>7. Diarrhea in 24 hours (usually 5 to 10 hours)</li><li>8. Hypotension</li><li>9. Hypothermia</li></ol>

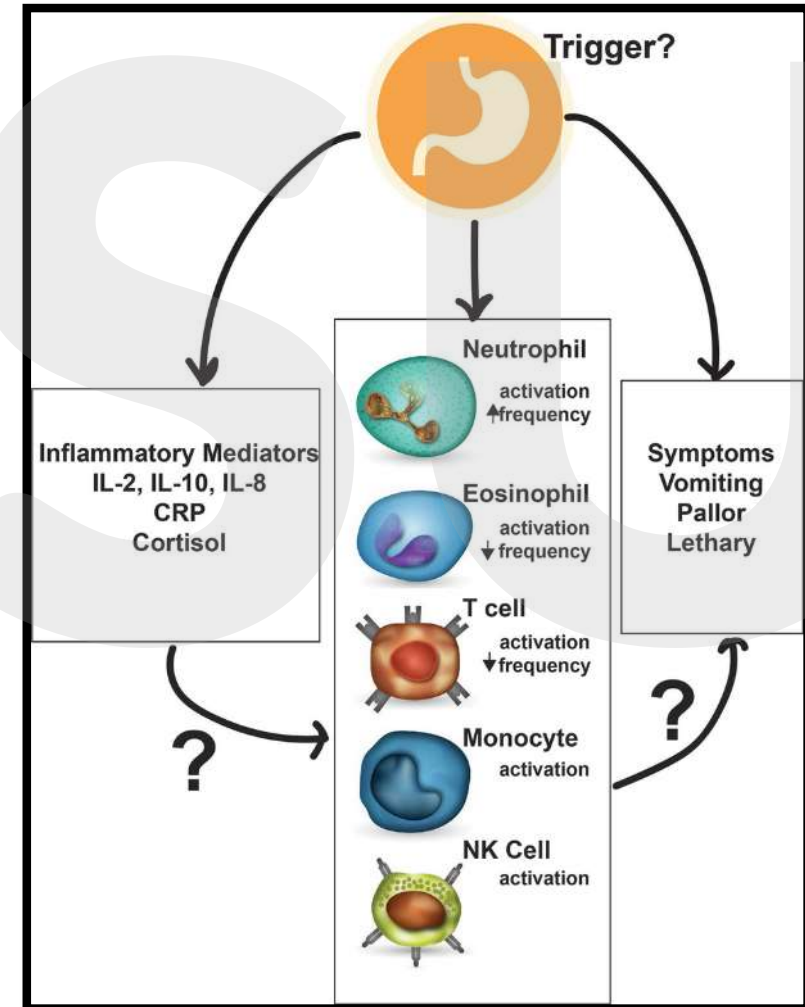
The diagnosis of FPIES requires that a patient meets the major criteria and  $\geq 3$  minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group. Furthermore, although not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

# Onset Characteristics

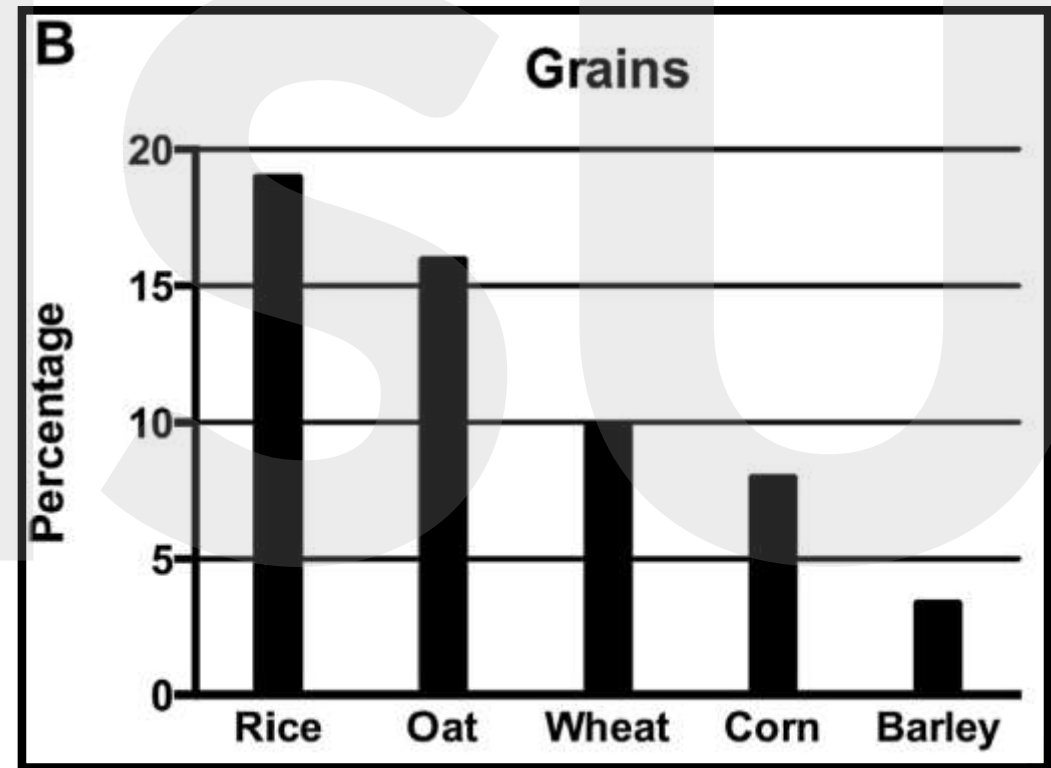
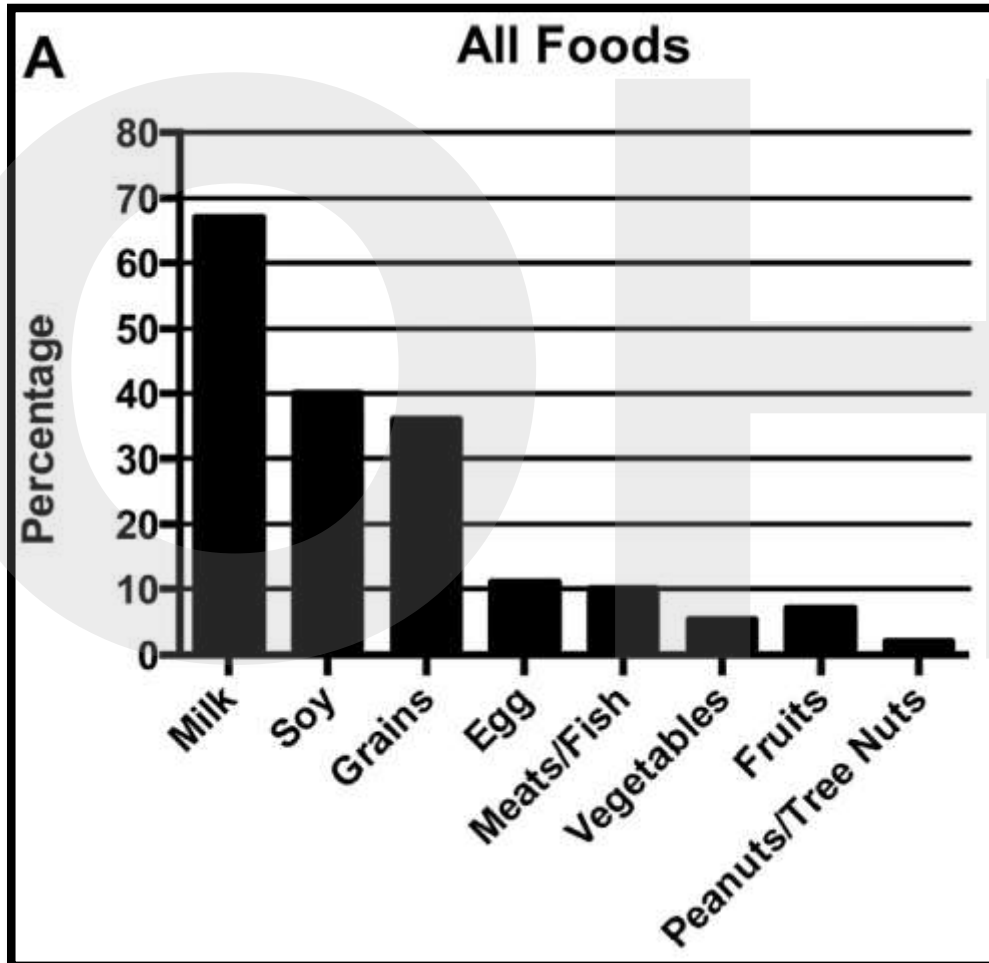
- Slight male predominance (50-60%)
- Concurrent atopic disease is frequent (20-77%)
- 75% of cases occur with 1<sup>st</sup> or 2<sup>nd</sup> ingestion of culprit food
- Age of symptom onset correlates with age of food introduction
  - CM or soy: <1 month to 12 months (median is 3-5 months)
  - Solid food-induced FPIES: median is 4-7 months

# Pathophysiology of FPIES

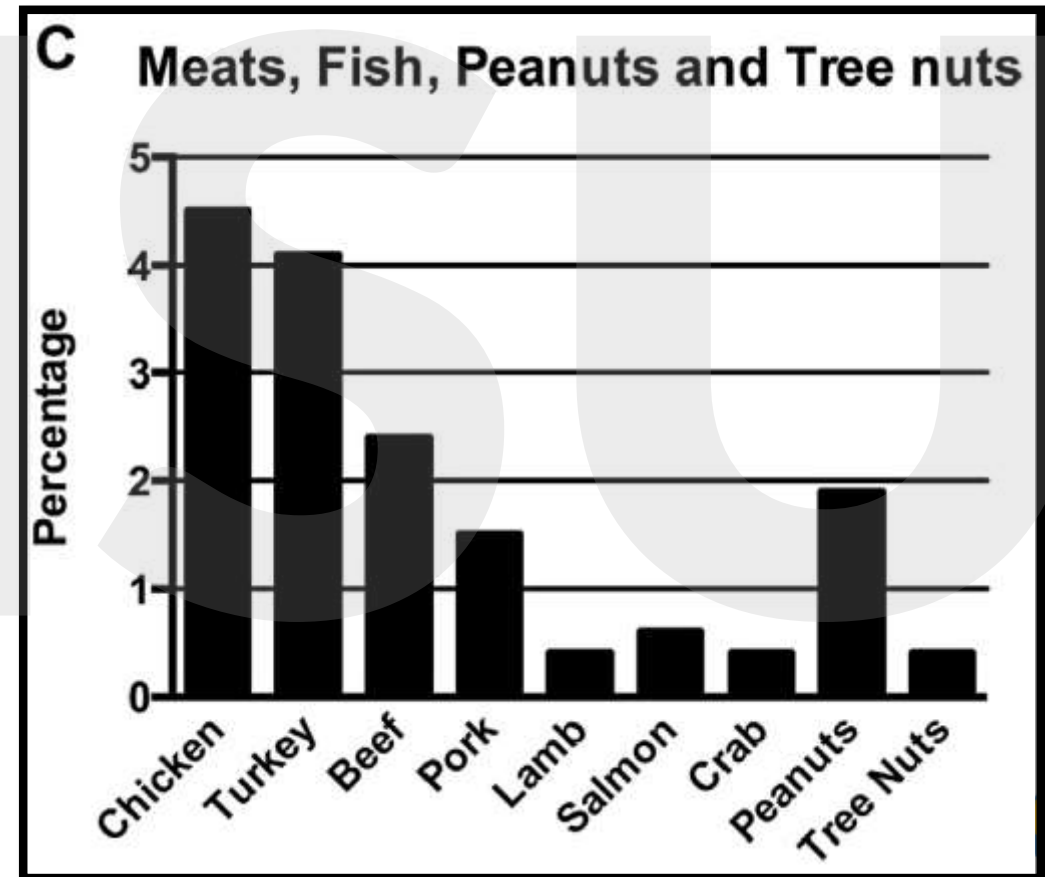
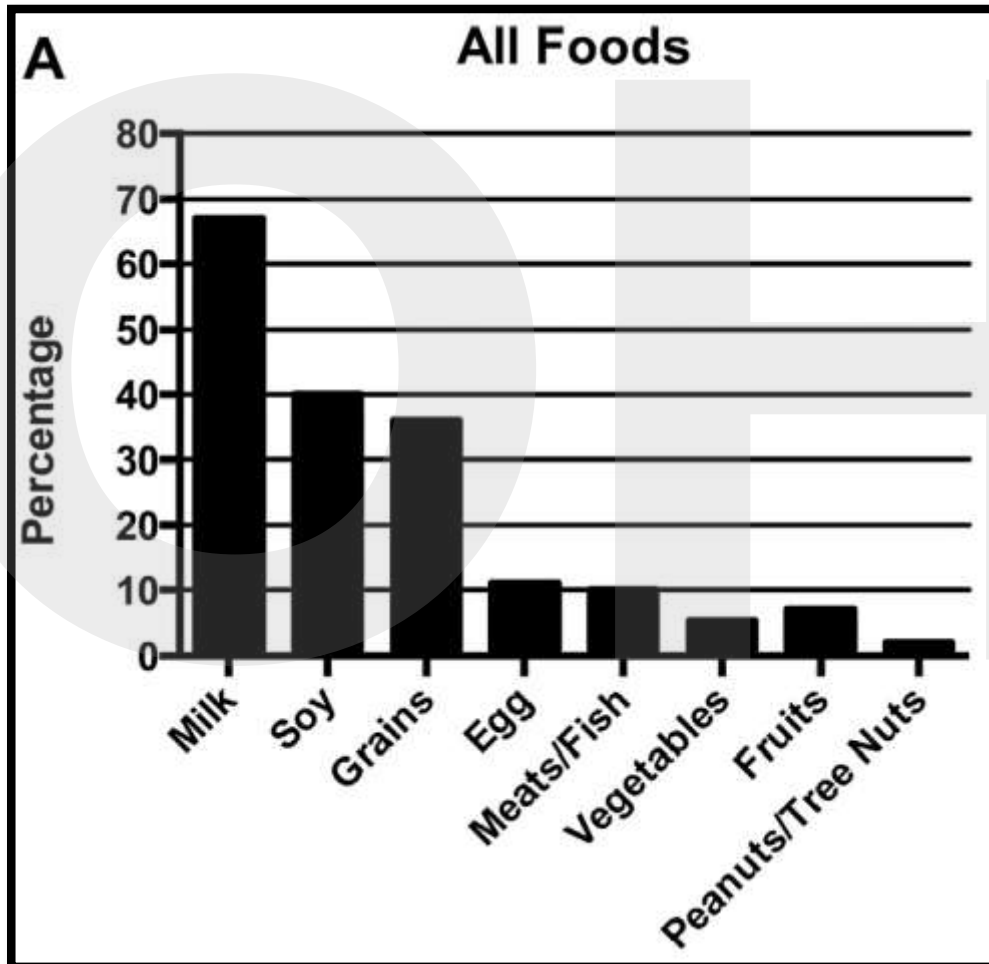
- Not currently well understood
- Nonspecific gut inflammation leading to increased permeability
  - Macrophages, neutrophils, and eosinophils
  - Elevated IL-8 and tryptase
- Antigen-specific T cells have been reported
- Humoral immune system has minimal involvement



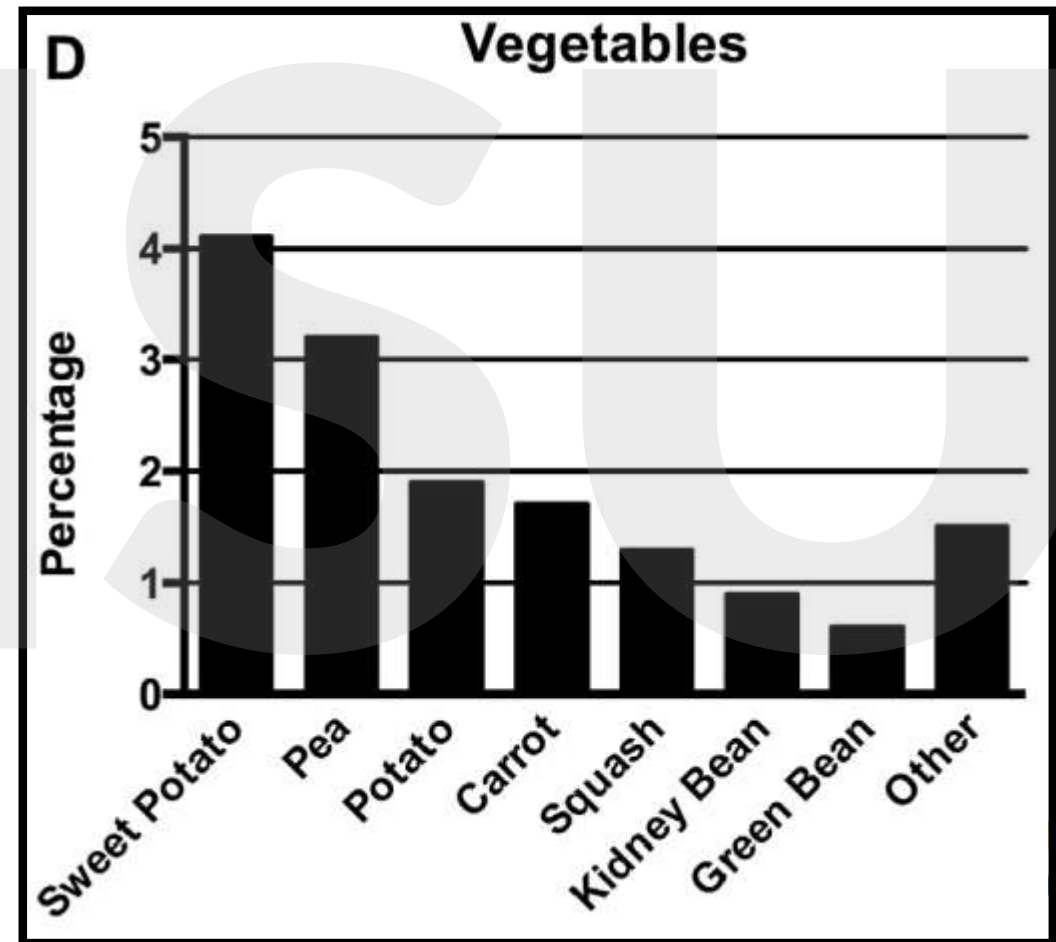
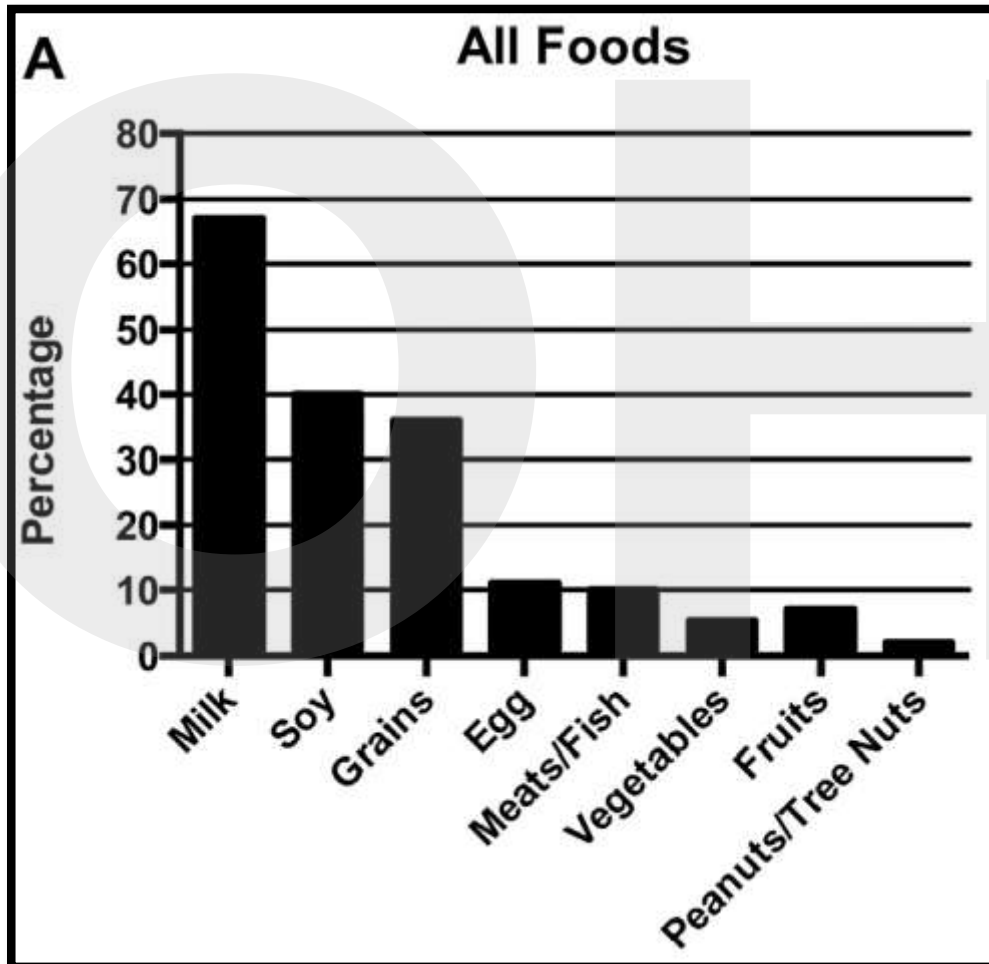
# Foods Associated with Acute FPIES



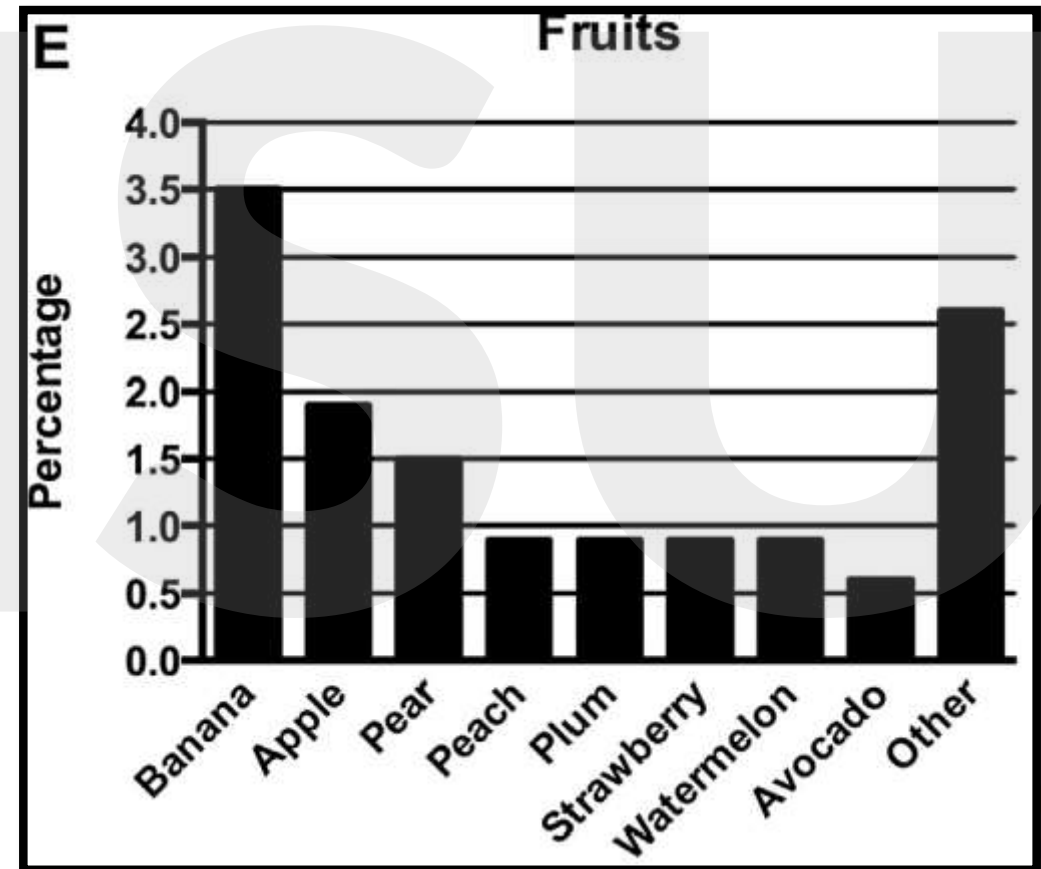
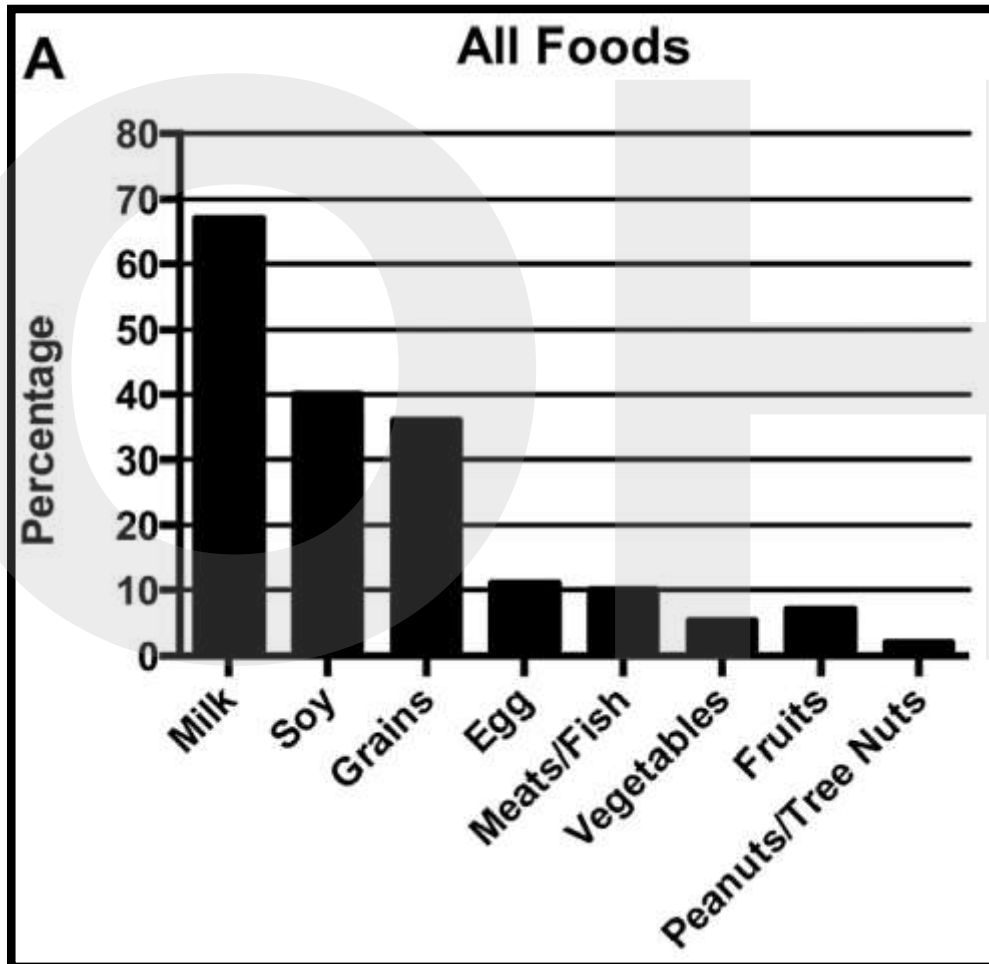
# Foods Associated with Acute FPIES



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# Foods Associated with Acute FPIES

<b>Milk</b>	<b>Legumes</b>
Cow's Milk	Soy
Goat's Milk	Green peas
<b>Hen's Egg</b>	Kidney beans
Egg white	Green beans
Egg yolk	Lentils
<b>Grains</b>	<b>Vegetables</b>
Rice	Sweet potato
Oat	Potato
Wheat	Carrot
Corn	Squash
Barley	Other**
Quinoa	<b>Fruit</b>
<b>Meats</b>	Banana
Chicken	Apple
Turkey	Pear
Beef	Peach
Pork	Plum
Lamb	Strawberry
<b>Seafood</b>	Melon
Hake, tuna, salmon	Other***
Shellfish (shrimp, crab, lobster, prawn)	<b>Peanut</b>
Mollusks	<b>Tree Nuts</b>
Other*	<b>Tapioca</b>

\*Other fish include sole, monkfish, swordfish, sea bass, mackerel, gilthead sea bream, and megrim.

\*\*Other vegetables include tomato, spinach, cauliflower, cucumber, and pumpkin.

\*\*\*Other fruits include avocado, blueberry, apricot, grape, cherry, coconut, mango, pineapple, orange, kiwi, and raspberry.

Number of food triggers	Percentage of children with acute FPIES reporting reactions
1	60-70%
2-3	20-30%
≥ 4	10%

Joshi S, Nicolaidis R, and Bird JA. Acute Food Protein-Induced Enterocolitis Syndrome. [Food Protein-Induced Enterocolitis Syndrome – Diagnosis and Management](#). Springer Nature Switzerland, Cham, Switzerland; 2019, 1<sup>st</sup> edition.





# Co-Allergy with Acute FPIES

FPIES to:	Clinical Cross-reactivity or Co-allergy	Observed Occurrence
Cow's Milk	Soy	<16%-40%
	Other animal milk	Unknown*
	Lactose-free milk	100%
	Extensively hydrolyzed casein-based formula	<10%-21%
	Amino-acid based formula	<4%
	Any solid food	<16%-28%
Soy	Cow's milk	<30%-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow milk or soy	<25%
Legumes	Soy	<80%
Rice	Oats	<42%
	Wheat	5%
	Corn	9%
Poultry	Other poultry	<40%
Fish	Other foods (not fish)	42%

Abbreviation: FPIES, food protein-induced enterocolitis syndrome.

\*While the cross-reactivity/co-allergy is unknown between cow's milk and milk from other animals, goat's milk and sheep's milk should be avoided due high homology of protein sequences. Milks from donkey, camels or both might be better options as they are typically well tolerated in IgE-mediated CM allergy.

This summary should be interpreted with caution as much of this data is derived from single center studies with more severe phenotypes likely over-estimating the risk of co-allergy.

Joshi S, Nicolaidis R, and Bird JA. Acute Food Protein-Induced Enterocolitis Syndrome. Food Protein-Induced Enterocolitis Syndrome – Diagnosis and Management. Springer Nature Switzerland, Cham, Switzerland; 2019, 1<sup>st</sup> edition.



# Diagnosis and Management

- Clinical diagnosis
  - Skin prick and sIgE testing is only helpful to diagnose concomitant IgE-mediated allergy
  - OFC is not typically needed for diagnosis
- Acute Management
  - Oral hydration or IVF +/- Ondansetron
  - Epinephrine not typically prescribed
- Long-term Management
  - Avoidance, avoidance, avoidance (including cross-reactive foods)
  - Systematic introduction of other foods to expand patient's diet
  - Oral food challenge to evaluate for tolerance

# Food Introduction

**Table 7** Empiric guidelines for selecting weaning foods in infants with FPIES [1]

Ages and Stages	Lower risk foods <sup>c</sup>	Moderate risk foods <sup>c</sup>	Higher risk foods <sup>c</sup>
<p><b>4–6 months (as per AAP, CoN)</b> 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>Broccoli, cauliflower, parsnip, turnip, pumpkin</p>	<p><b>Vegetables</b> Squash, carrot, white potato, green bean (legume)</p>	<p>Sweet potato, green pea (legume)</p>
<p><b>6 months (as per WHO)</b> Complementary feeding should begin no later than 6 months of age.</p> <ul style="list-style-type: none"> <li>➤ In the breast fed infant, high iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age.</li> <li>➤ Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated.</li> </ul>	<p>Blueberries, strawberries, plum, watermelon, peach, avocado</p>	<p><b>Fruits</b> Apple, pear, orange</p>	<p>Banana</p>
<p><b>8 months</b> 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 months of age or as tolerated by infant.</li> </ul>	<p>Lamb, fortified quinoa cereal, millet</p>	<p><b>High iron foods</b> 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><b>12 months of age</b> 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>Tree nuts and seed butters<sup>c</sup> (sesame, sunflower, etc.) <sup>c</sup>Thinned with water or infant puree for appropriate infant texture and to prevent choking</p>	<p><b>Other</b> Peanut, other legumes (other than green pea)</p>	<p>Milk, soy, poultry, egg, fish</p>

Leonard SA, Pecora V, Fiocchi AG, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a review of the new guidelines. World Allergy Organ J. 2018 Feb 7;11(1):4.



# Tolerance to Culprit Food(s)

- Tolerance to CM
  - US: 35% by age 2, 70% by age 3, 85% by age 5
  - Australia: 88% by age 3
  - South Korea: 72% by 14-16 months, 100% by 18-20 months
- Solid food-induced FPIES typically develop tolerance later in childhood
- No guidance on frequency of OFCs to evaluate for tolerance
  - US: Generally challenge 1 year after last reaction
  - Korea: Challenge every 2 months after last reaction

# Chronic FPIES

- Offending foods is ingested in the diet on a regular basis
  - Cow's milk or soy-based infant formula (no solid foods have been reported)
- Clinical presentation
  - Early infancy
  - Intermittent and progressive emesis
  - Watery diarrhea (mucus and occasional blood)
  - Failure to thrive, hypoalbuminemia, metabolic derangements, dehydration
- Management
  - Elimination of the food leads to improvement within 3-14 days
    - Switch to eHCF or AAF
  - Subsequent ingestions after a period of elimination may lead to an acute FPIES episode



# Acute vs Chronic FPIES

## Acute FPIES

- Intermittent food exposure
- Variety of foods
- Emesis starts 1-4 hours after ingestion of the food
- Resolution of symptoms within 24 hours

## Chronic FPIES

- Daily ingestion of culprit food
- CM and soy-based formulas
- Intermittent emesis, chronic diarrhea, and FTT
- Returns to usual state of health within 3-14 days with avoidance

# Breastfeeding and FPIES

- Rare case reports of both acute and chronic FPIES in exclusively breastfed infants
- Cow's milk protein passed through breast milk
  - Elimination of food in maternal diet resolves symptoms

# When to Refer to Allergy?

- Any patient with confirmed or suspicion of food allergies (IgE-mediated, FPIES, pollen-food allergy syndrome)
  - Evaluation (confirmation testing, challenges, OIT)
  - Regular follow up and repeat testing (to determine if a challenge is possible)
  - Education
    - Food avoidance measures
    - Spend time with parents to reduce anxiety associated with food allergies
    - Discuss cross-reactivity and contamination possibilities
    - Nutritional assistance (CM replacement)



# Take Home Points

- Food allergies are seen in up to 10% of children
- Acute FPIES is NOT a rare food allergy and the diagnosis is typically made by history alone
  - Skin testing and blood allergy testing are not helpful
- Culprit foods are different than those seen in IgE-mediated allergies
  - Soy, rice, oat, banana, sweet potato
- Most children will outgrow their FPIES allergy by 5 years of age
- Food challenges are vital in the long-term management of acute FPIES



# Thank You and Questions?

