Non-IgE Mediated Food Allergy: FPIES, FPIAP, Celiac Disease

Dr. Stacy Silvers

Aspire Allergy & Sinus

ASAP Conference

September 22, 2024

Disclosers

None

Food Protein Induced Enterocolitis Syndrome

- Recognized as a distinct clinical entity in the 1970s
- Diagnostic code didn't come until 2015
- First international consensus guidelines in 2017
- Prevalence is poorly defined
  - Isreal- 0.34% of infants over a 2-year period
  - Australia- 15.4/100,000/year in infants <2 years
  - US- 0.28% incidence
- Atopy is common
  - 11-57% of patients had atopic dermatitis in US and Australian studies.

Presentation

Acute

- Intermittent food exposures
- Vomiting 1-4 hours after ingestion, possible diarrhea 5-10 hours after ingestion
- Lethargy, pallor, hypotension/shock
- No symptoms between ingestion, normal growth

Chronic

- Daily ingestion of food
- Almost exclusively in infants being formula fed
- Intermittent vomiting
- Chronic diarrhea
- Poor weight gain/FTT
- Usually better in 3-10 days after elimination diet started
- Subsequent feed results in acute symptoms

Diagnosis - Acute

Acute FPIES

Major criterion:	Minor criteria:
Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms	1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency department visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5-10 h) 8. Hypotension 9. Hypothermia

The diagnosis of FPIES requires that a patient meets the major criterion and ≥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.

Diagnosis - Chronic

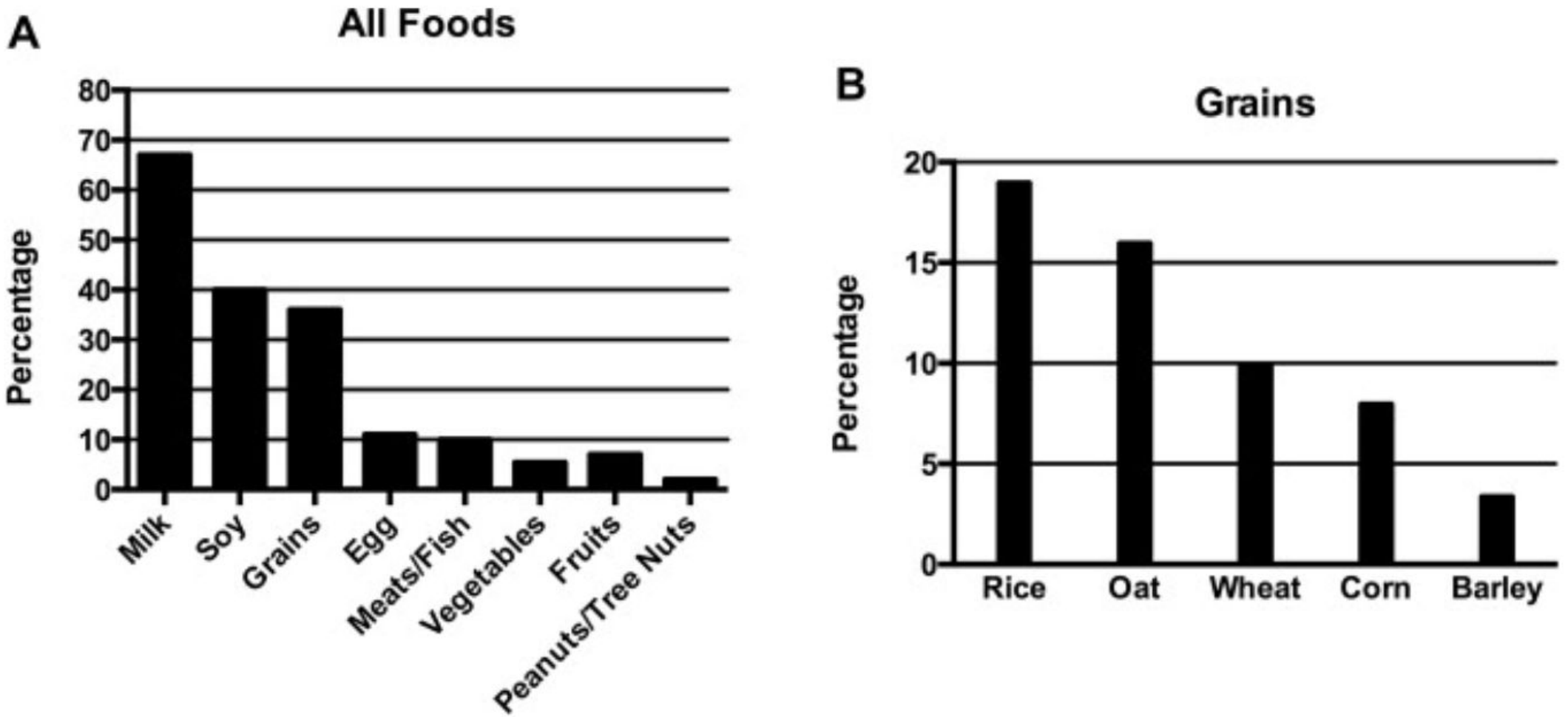
Chronic FPIES	
Severe presentation: When the offending food is ingested on a regular basis (eg, infant formula); intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis. *Milder presentation*: Lower doses of the problem food (eg, solid foods or food allergens in breast milk) lead to intermittent vomiting and/or diarrhea, usually with poor weight gain/FTT but without dehydration or metabolic acidosis.	The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhea in 24 h (usually 5-10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

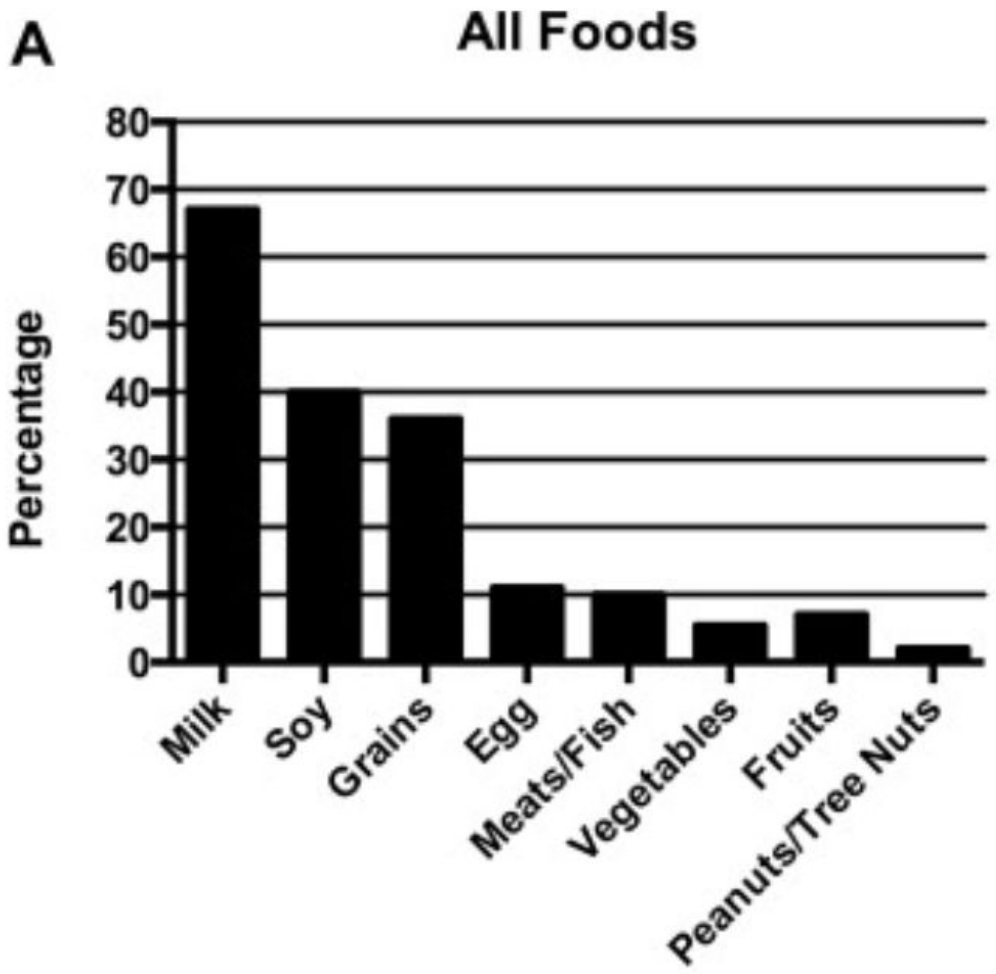
Diagnosis – Atypical FPIES

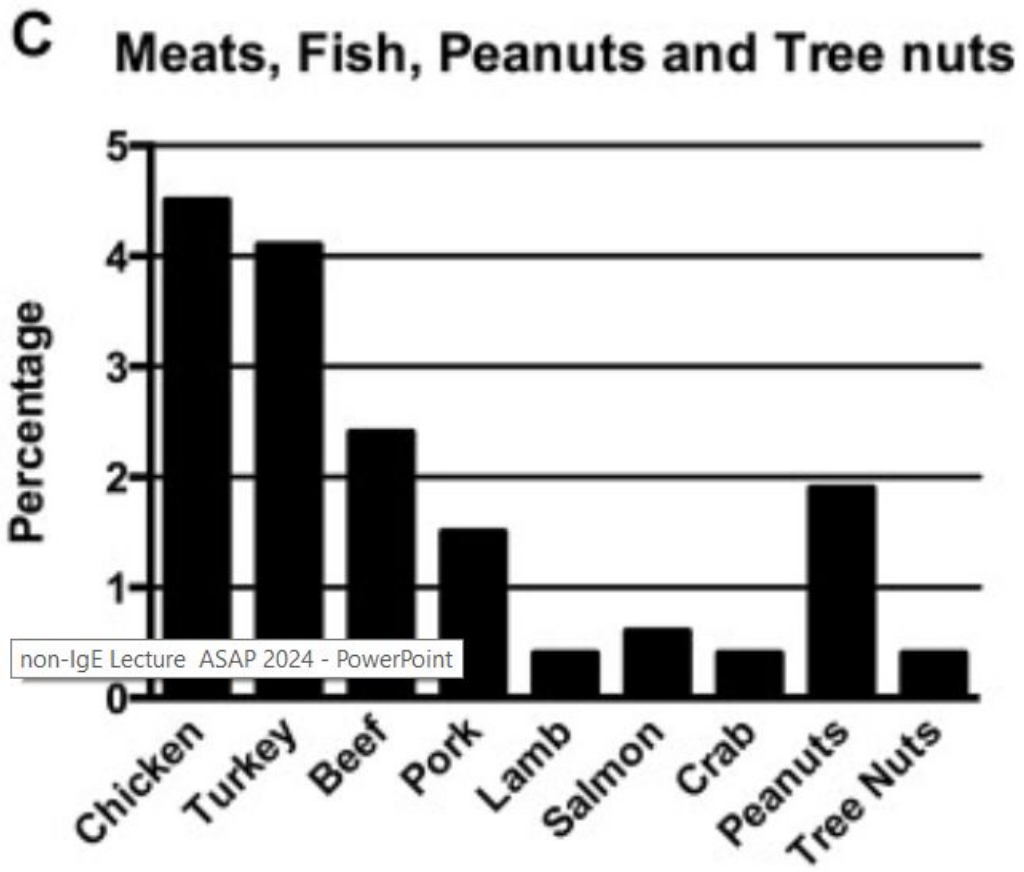
- Pt have serum IgE or positive SPT to the offending food
  - Reported in 8-25% of patients with FPIES
  - These patients may have a more protracted course.
    - In one study, 41% of CM FPIES pateints turned into an IgE-mediated allergy
    - They were more likely to have FPIES persist beyond 3 years.
  - Sensitization to other foods doesn’t seem to impact the FPIES natural history

Pathophysiology

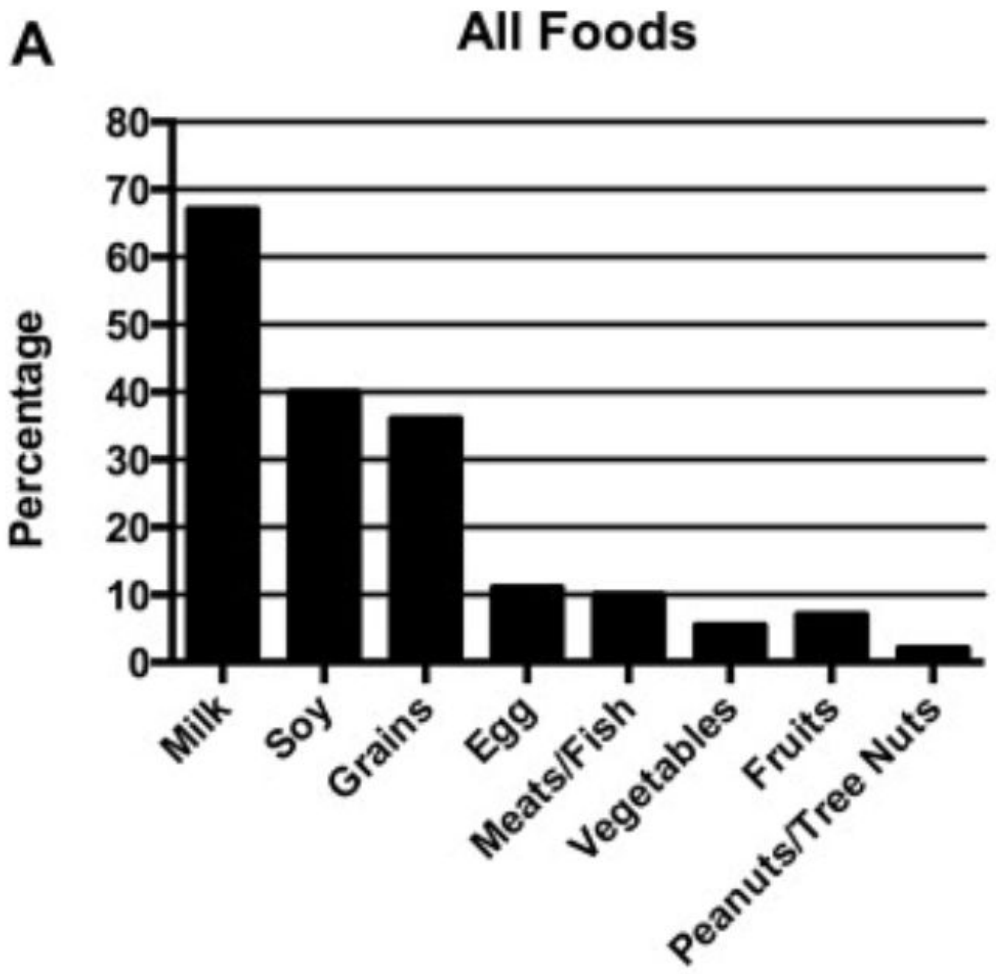
- Not well understood
- Food ingestion results in gut inflammation
  - Increased intestinal permeability and fluid shift
    - Vomiting
    - Diarrhea
    - Shock
- Ag-specific T cells and inflammatory cytokines have been found
- Serum IL-8 and tryptase has been reported in reactions (neutrophil and mast cell involvement)
- No evidence of humoral response

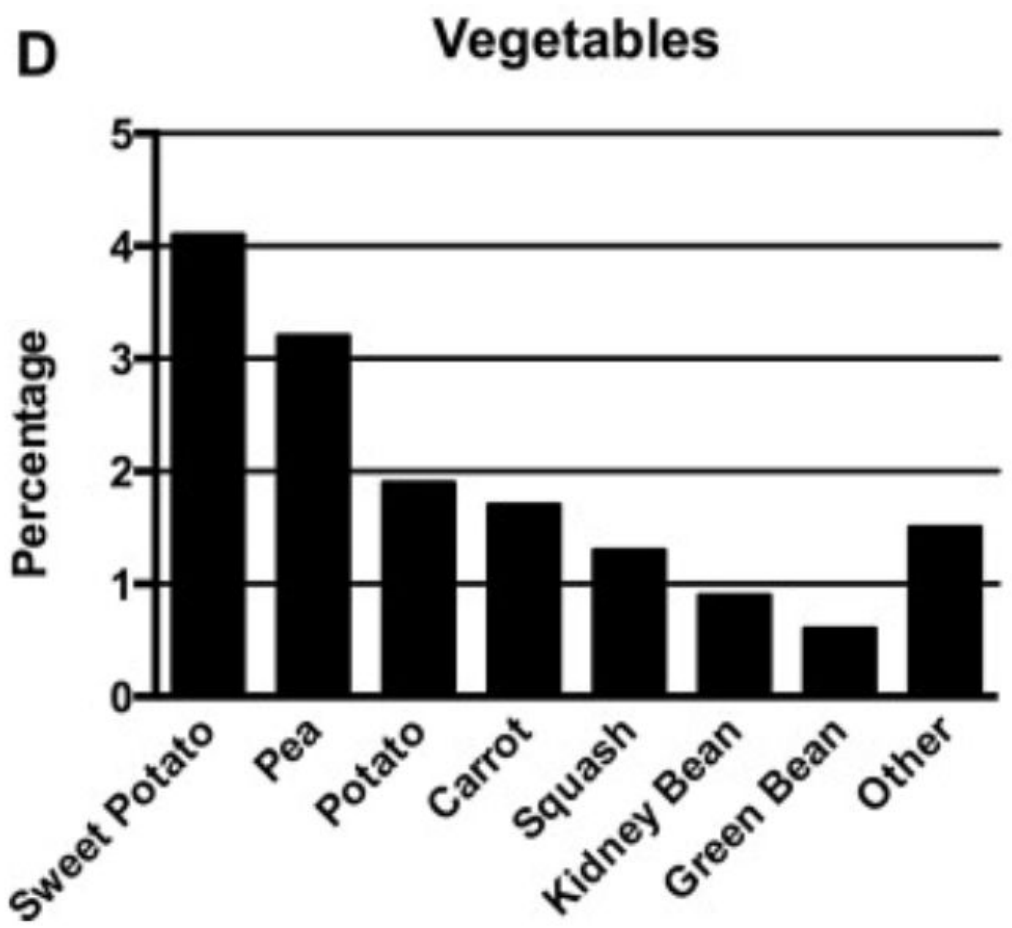

A
All Foods
Percentage
80
70
60
50
40
30
20
10
0
Milk
Soy
Grains
Egg
Meats/Fish
Vegetables
Fruits
Peanuts/Tree Nuts
B
Grains
Percentage
20
15
10
5
0
Rice
Oat
Wheat
Corn
Barley

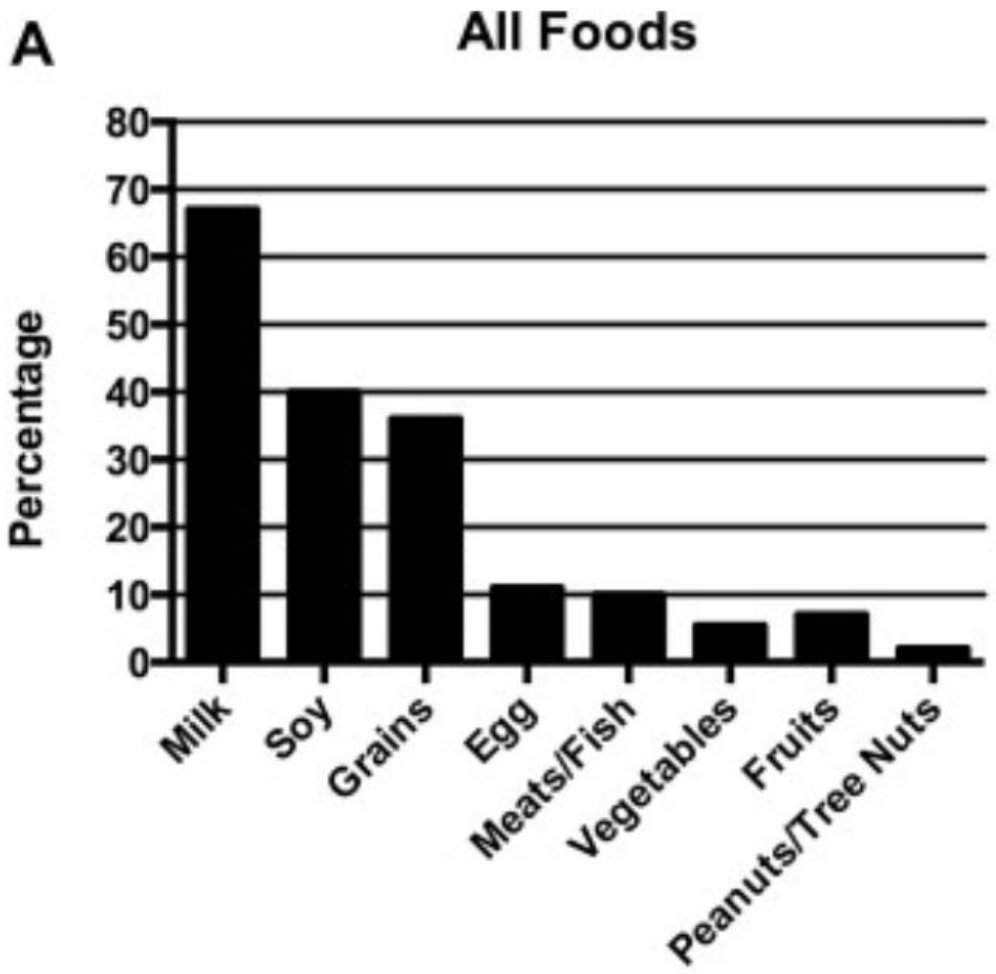


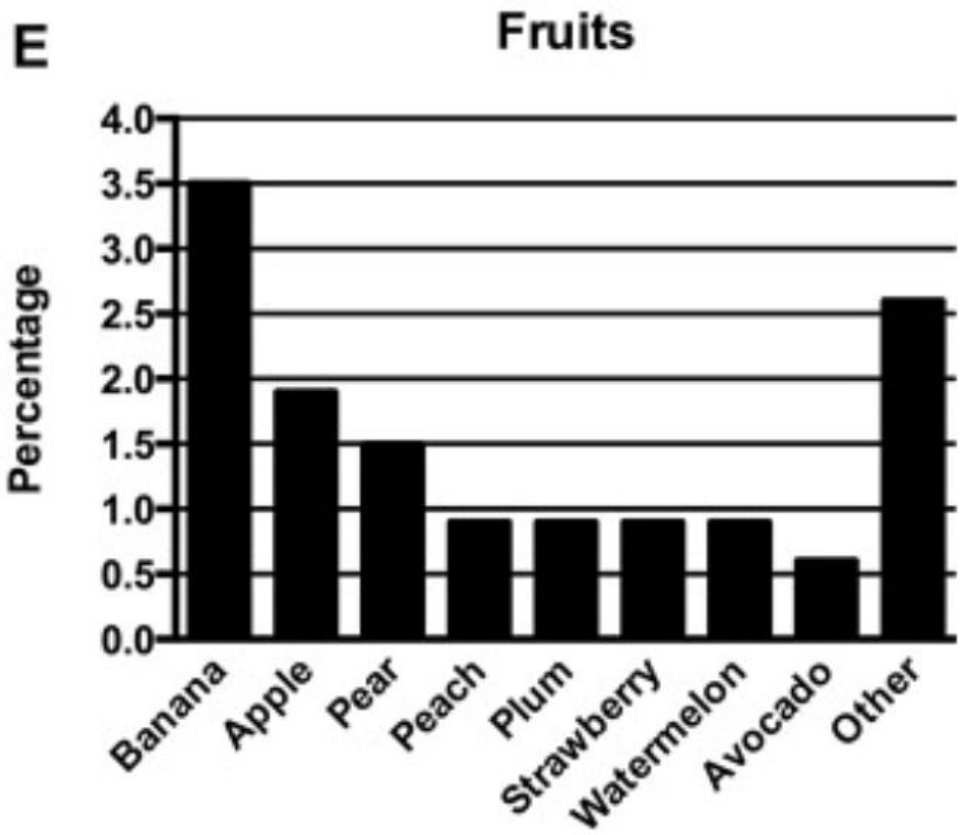


non-IgE Lecture ASAP 2024 - PowerPoint


A
All Foods
Percentage
80
70
60
50
40
30
20
10
0
Milk
Soy
Grains
Egg
Meats/Fish
Vegetables
Fruits
Peanuts/Tree Nuts


D
Vegetables
Percentage
5
4
3
2
1
0
Sweet Potato
Pea
Potato
Carrot
Squash
Kidney Bean
Green Bean
Other


A
All Foods
Percentage
80
70
60
50
40
30
20
10
0
Milk
Soy
Grains
Egg
Meats/Fish
Vegetables
Fruits
Peanuts/Tree Nuts


E
Fruits
Percentage
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Banana
Apple
Pear
Peach
Plum
Strawberry
Watermelon
Avocado
Other

Number of Food Triggers

Number of Food Triggers	% of Children with Acute FPIES
1	60-70%
2-3	20-30%
>4	10%

Management

- Generally, involves avoidance of the offending food

- Cow's milk
  - Breast feed
  - Extensively hydrolyzed formula
    - 10-20% may need an amino acid-based formula
  - Consider soy formula
  - Avoid goat/sheep milk
  - ?Baked milk?
  - More likely to have FPIES to a solid food
    - Rice and oat
    - Consider this when introducing solids

Management

- Maternal avoidance of FPIES trigger generally not required
  - Only if there a history of reacting to breast milk or failure to thrive
- Should attempt to expand diet
  - New food every 4 days
  - May need supervised introduction if family is hesitant
  - Tolerating one food in a group suggests tolerance to others in the same group
  - Risk of nutritional deficiencies. Consider dietician referral
- Ondansetron and ED Letter

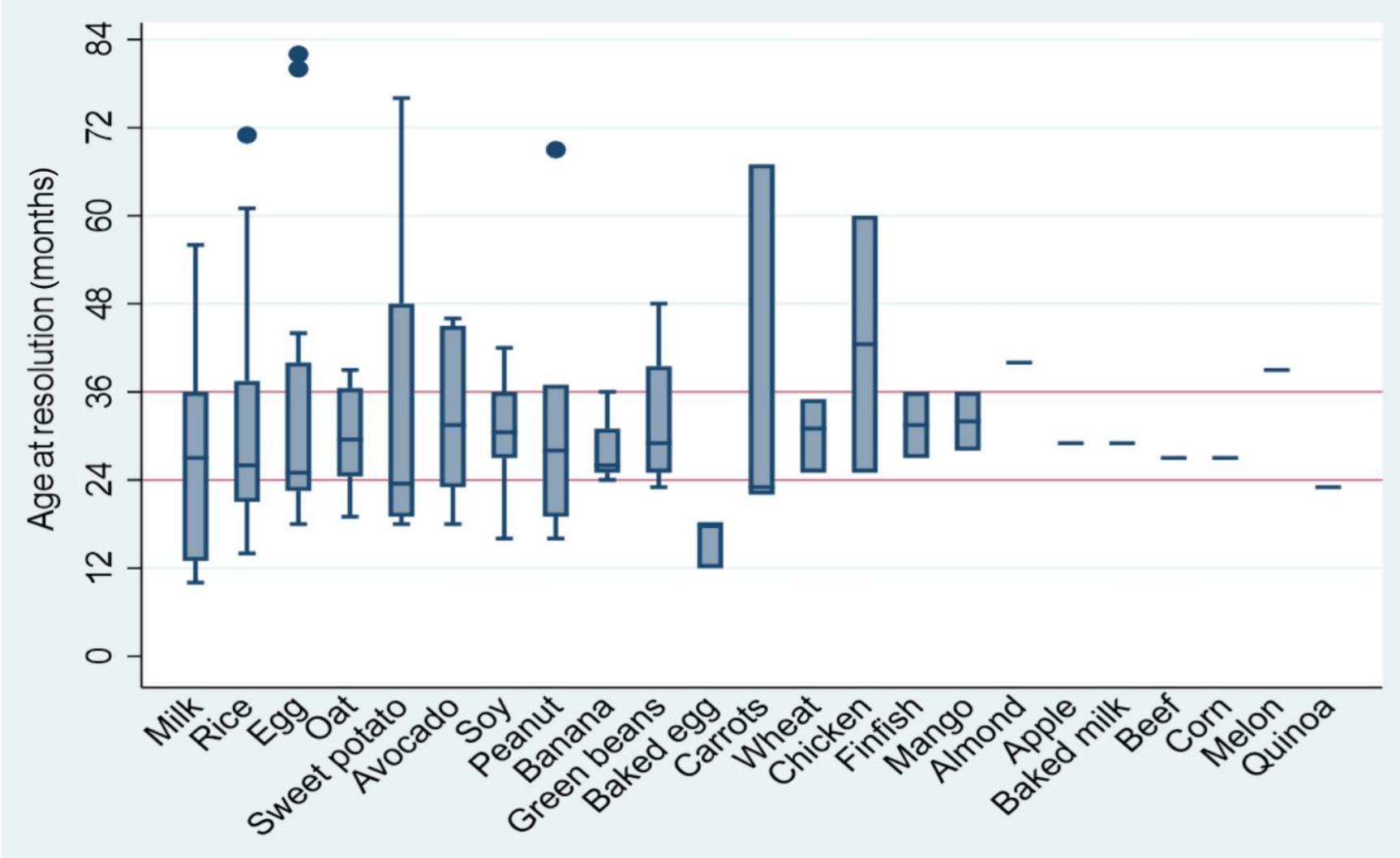
Management

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

Ages and stages	Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*
4-6 mo (as per AAP, CoN)	Vegetables		
If developmentally appropriate and safe and nutritious foods are available: ● Begin with smooth, thin purees and progress to thicker purees ● Choose foods that are high in iron ● Add vegetables and fruits	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
6 mo (as per WHO)	Fruits		
Complementary feeding should begin no later than 6 mo of age: ● In the breast-fed infant, high-iron foods or supplemental iron (1 mg/kg/d) are suggested by 6 mo of age ● Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
8 mo of age or when developmentally appropriate:	High-iron foods		
● Offer soft-cooked and bite-and-dissolve textures from around 8 mo of age or as tolerated by infant.	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher-iron foods: fortified, infant rice and oat cereals
12 mo of age or when developmentally appropriate:	Other		
● Offer modified tolerated foods from the family: table-chopped meats, soft cooked vegetables, grains, and fruits	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

Resolution/Natural History

- Cow's milk
  - 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


Age at resolution (months)
0
12
24
36
48
60
72
84
Milk
Rice
Egg
Oat
Sweet potato
Avocado
Soy
Peanut
Banana
Green beans
Baked egg
Carrots
Wheat
Chicken
Finfish
Mango
Almond
Apple
Baked milk
Beef
Corn
Melon
Quinoa

Allergic Proctocolitis

- A non-IgE mediated allergy causing inflammation in the distal colon
- Seems common in infants
  - Symptoms start in the first months of life
  - Up to 0.16% of healthy children
- Often linked to cow's milk
  - Cow's milk – 65%
  - Egg – 19%
  - Corn – 6%
  - Soy – 3%
  - Multiple foods – 5%

Allergic Proctocolitis

- Often resolves by 1-3 year of age
- Can affect both breastfed and formula-fed infants
  - Maternal dietary proteins in breastfed infants
  - 50% of cases of FPIAP reported are in exclusively breast-fed infants
  - <10% of cases, extensively hydrolyzed formula's cause symptoms

Allergic Proctocolitis

- Blood-streaked stools
- Currant-jelly stools (blood mixed with mucus)
- May have irritability
- No other signs of illness
  - No fever
  - No failure to thrive/poor weight gain
- Generally, no vomiting or severe diarrhea

Allergic Proctocolitis

- Exact immunologic mechanisms is unknown
  - Non-IgE mediated!!!!
- Involves immune cells in the colon reacting to dietary proteins
  - Focal aggregates of eosinophils in intestinal epithelium, lamina propria, crypt epithelium, and muscularis mucosa
  - Edema
  - Erosions
- Causes inflammation and irritation of the colon lining

Allergic Proctocolitis

- Diagnosis is based on symptoms and exclusion of other causes
  - Infection
  - Inflammatory bowel disease
  - Anal fissures
  - Intussusception
  - Necrotizing enterocolitis
- No specific diagnostic tests
  - Must see resolution after removal of the offending food
  - Start with milk and/or soy, then egg if needed
  - Symptoms typically resolve within 72 hours after dietary elimination
    - May take 1-2 weeks

Allergic Proctocolitis

- Serum IgE or IgG testing has not been found to be helpful
- Patch testing has contradictory data, not recommended
- May find peripheral eosinophilia
- Fecal Occult Blood Test
  - Good negative predictive value (84%)
  - Poor positive predictive value (68%)
    - Up to 1/3 of normal infants can have a positive FOBT
- Stool smear for eosinophilic granules, poor validity
- Fecal calprotectin, no significant correlation
  - Can be elevated, no diagnostic

Allergic Proctocolitis

- Consider dietician if more than 1 food trigger
- Most infants outgrow FPIAP by 12-36 months of age
- Gradual reintroduction of the offending food is often successful
  - For milk, start with 1 ounce/day
  - Increase to full feeding over ~2 weeks
- Recurrence is uncommon after resolution

Allergic Proctocolitis

- Close monitoring of growth and nutrition
- Guidance for breastfeeding mothers or guide formula changes
- Support for food reintroduction
- Consider percutaneous testing prior to reintroduction
  - To ensure no concurrent IgE-mediated allergy

Celiac Disease

NOT MY PROBLEM!

Celiac Disease

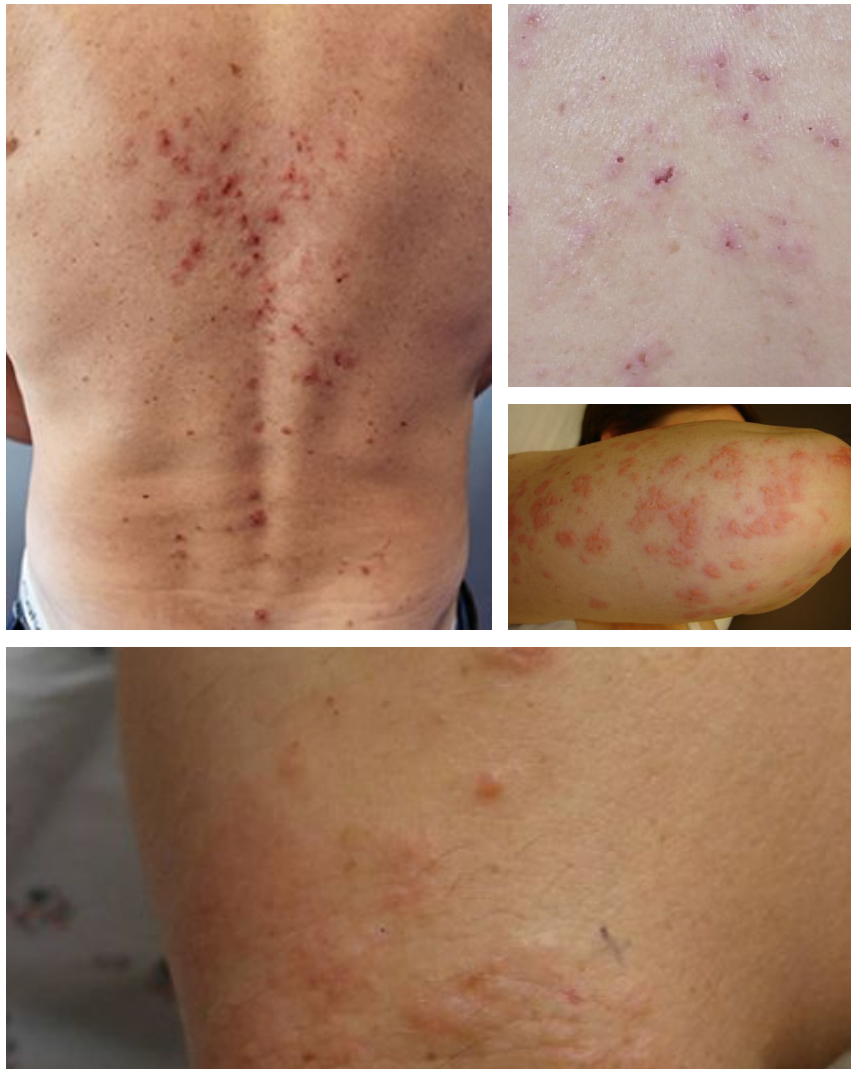
- An autoimmune disorder triggered by the ingestion of gluten
  - Found in wheat, barley, and rye
- Small Bowel disease
  - Villous atrophy
  - Intra-epithelial lymphocytes
  - Crypt hyperplasia
- Women:Men – 2:1
- Worldwide prevalence of 1%
- One of the most common causes of malabsoption

Celiac Disease

- Gluten- storage protein, enriched in glutamines and prolines
  - Incompletely digested
  - Large peptides left behind
- Peptides encounter tissue transglutaminase (TG2) and APCs that express DQ2 or DQ8
- APCs present peptides to CD4+ T cells
  - Mediators released (IFN-gamma)
  - B cells produce anti-tissue transglutaminase Abs (TG2Ab)
  - Lymphocyte infiltration
  - Tissue injury

Celiac Disease

- Diarrhea
- Bloating
- Gas
- Abdominal pain
- Weight loss and fatigue
- Children- decreased growth and delayed puberty
- Anemia
- Joint Pain
- Skin rash (dermatitis herpetiformis)



Celiac Disease

- Dermatitis Herpetiformis
  - Pruritic
  - Papules/blisters
  - Often excoriations
  - 10-15% of those with Celiac Disease
  - Elbows, knees, buttocks, back, scalp

Celiac Disease

- Diagnosis
  - Testing for antibodies*
    - tTG-IgA/IgG
      - High sensitivity (up to 97%) and specificity (96-98%)
      - 1st line test
    - Anti-endomysial IgA antibodies (EMA)
      - 2nd line test, high specificity (almost 100%), sensitivity of ~94%
    - Deaminated gliadin peptide IgA/IgG
      - Can help in IgA-deficiency
      - 2-3% of normal population is IgA deficient (total IgA is usually sent when sending tTG-IgA)
  - Biopsy of small intestine to assess villi damage*
    - Required for definitive diagnosis
  - *While on gluten-containing diet

Celiac Disease

- Genetic testing
  - HLA-DQ2 and/or HLA-DQ8
  - Can confirm predisposition, but not the disease
  - However, high sensitivity
    - Almost 100% of patients exhibit this specific genetic profile
    - Negative test rules out disease

Celiac Disease

- Strict gluten-free diet
  - Avoid all forms of gluten
  - Requires lifelong avoidance
- Monitoring
  - Regular follow-ups and nutritional assessments to ensure healing and prevention of complications
  - Non-responsive disease is rare, but has been reported

Celiac Disease

- Complications of Untreated Celiac Disease
  - Malnutrition
  - Osteoporosis
  - Intestinal lymphoma
  - Infertility
- Associated conditions
  - Type 1 diabetes
  - Autoimmune thyroid disorders
  - Autoimmune hepatitis

Questions?

Dr.Silvers@aspireallergy.com