Guidelines for Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome

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Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

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Learning Objectives

- Recognize the clinical presentation of FPIES
- Identify medical and nutritional strategies using current FPIES guidelines

MODULE 1: INTRODUCTION

- Discuss what is Food Protein-Induced Enterocolitis Syndrome (FPIES)
- Review common symptoms and food triggers
- Distinguish FPIES from other major non-IgE-mediated food allergies

Food Protein-Induced Enterocolitis Syndrome

- **FPIES** is a non-IgE, cell-mediated food allergy† which manifests as delayed, repetitive vomiting after ingestion (sometimes with diarrhea), primarily in infants.
  - One of several immunologic reactions to dietary proteins
- FPIES can lead to shock and dehydration.
- Chronic FPIES can lead to failure to thrive.
- Pathophysiology is poorly understood.
- FPIES awareness remains low.

†Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol.* 2017;27:1-18. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2015;135:1114-24.

Immunologic Reaction to Dietary Proteins

- Classification helps put FPIES in perspective
  - IgE mediated
  - Non-IgE mediated (T cell)
  - Mixed: IgE and T-cell mediated

Natural History: Prevalence and Food Triggers

- Prevalence—little data available:
  - Israeli study: CM-FPIES 0.34% in infants born at a single hospital over a 2-year period[1]
  - Australian study: estimated 15.4/100,000/year in infants <2 years old, CM, rice, egg[2]
  - Spanish Prevale study: 0.7% <1 year old, CM-0.35%, Fish-0.26%, egg yolk 0.09%[3]
- Onset typically occurs during the first year of life[4]
- Symptoms appear usually 1 to 4 hours after ingestion[4]

*Seafood-induced FPIES may start in older children and adults

1. Katz Y, et al. *J Allergy Clin Immunol.* 2011;127(3):647–53. e641–643;
2. Mehr S, et al. *J Allergy Clin Immunol.* 2017;
3. Bellón S,et al . *J Allergy Clin Immunol*. 2018; pii: S0091-6749(18)31331-9.
4. Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol.* 2017;27:1-18.

Natural History: Resolution

- Generally favorable prognosis
- Self-limiting disorder of childhood
- Majority outgrow FPIES by age 3-5 years
- Atypical FPIES (positive skin or blood test for food IgE) tends to be more persistent

International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology

- **First international evidence-based consensus guidelines**
  - 9 countries represented
  - Published 2017 https://www.fpies.org/fpies-guidelines/
  - *J Allergy Clin Immunol.* 2017 Apr;139(4):1111-1126.e4. doi:10.1016/j.jaci.2016.12.966 **Open Access**
- Recommendations
  - Epidemiology and diagnosis
  - Specific diagnostic criteria for acute and chronic FPIES
  - Guidance on managing FPIES emergencies and long-term

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4; Leonard SA, et al. *World Allergy Organ J*. 2018;11:4.

FPIES Clinical Phenotypes

- FPIES phenotype depends on dose and frequency of food allergen ingestion.
- Phenotype provides guidance for diagnosis and management.

Phenotypes influenced by		
Age of onset	early (<9 months)	late (>9 months)
Severity	mild-to-moderate	severe
Timing and duration of symptoms	acute (symptoms resolve in 24 hrs)	chronic (resolution may take days to weeks)
Associated IgE-mediated food allergy	IgE negative	IgE positive

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.

Acute FPIES with Soy—case vignette

14-month-old girl, who is breastfed, avoids soy (all legumes), milk (all dairy), most proteins; she eats fruits, vegetables, grains, and hypoallergenic, amino-acid-based solid food

- She was born at term, via NSVD; mother GBS+
- She was breastfed without any symptoms
- @ 3 mo, on a 2nd feeding with soy infant formula (3 oz)—violently vomiting in 2 hours; lethargy pale; rushed to the ER—hypotensive, elevated WBC with left shift, sepsis work-up, admitted to ICU for management

Since then, she has avoided concentrated soy strictly, but has been eating foods with soy as a minor ingredient

ICU, intensive care unit; NSVD, normal spontaneous vaginal delivery; GBS, Group B streptococcus; WBC, white blood count.

Chronic vs Acute Presentation: Determined by frequency and dose of the ingested food

- Acute FPIES
  - Manifests within 1 to 4 hours after ingestion
  - Repetitive emesis
  - Pallor
  - Lethargy progressing to dehydration
  - Hypovolemic shock in 15% of cases

- Chronic FPIES
  - Manifests with watery diarrhea
  - Emesis is intermittent but progressively worsening
  - Poor growth, progressing to dehydration
  - Dehydration, metabolic acidosis, hypovolemic shock after a period of days to weeks

Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol.* 2017;27:1-18.

FPIES Phenotypes (continued)

Acute	Chronic
Ingestion following a period of avoidance (at least several days)	Young infants fed continuously with milk or soy formulas
Onset of emesis: 1–4 hours	Watery diarrhea
Lethargy, limpness (“septic appearance”)	Mucous, blood in stools
15% go into shock	Intermittent emesis
15% with methemoglobulinemia	Low albumin and total protein
6–8 hours later: diarrhea	Failure to thrive, poor growth
Onset: usually under 12 months; Fish/Shellfish: children, adults	Onset: first 1–3 months of life
Symptoms resolve within 24 hrs	Symptoms resolve within days–weeks, may require TPN
Cow’s milk, soy, rice, oat, vegetables	Cow’s milk, soy

Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol*. 2017;27:1-18.

Clinical Vignette with Twins: Chronic vs Acute FPIES Presentation

3-year-old identical twins, born via CS; no perinatal complications
Current avoidance: cow's milk/dairy, soy, egg, avocado
Fed with CMF at 3 weeks of age:

Alice: diarrhea, dehydration, managed outpatient IV hydration [**Chronic FPIES**]
Ana: diarrhea, dehydration, admitted to PICU [**Chronic FPIES**]

- Both improved when fed an elemental formula; Thriving

Age 11 months, both girls ingested 3-oz yogurt; within 4 hours developed repetitive, projectile vomiting, diarrhea, dehydration.

- Treatment with IV formula and ondansetron in the pediatric ER [**Acute FPIES**]

CMF, cow's milk formula; CS, Caesarean section; PICU, pediatric intensive care unit

MODULE 2:
DIAGNOSIS AND MANAGEMENT

- Discuss the most prominent clinical features of FPIES
- Distinguish from other major non-IgE-mediated food allergies
- Incorporate the latest FPIES guidelines on how:
  - To improve the diagnosis
  - To proceed with an oral food challenge

Misdiagnosis is Common

- Misdiagnosis is common, delaying diagnosis for months
- Usually 2 or more acute FPIES reactions before diagnosis is considered

- Most common FPIES masqueraders:
  - Acute viral gastroenteritis
  - Sepsis
  - Anaphylactic reactions
  - Other non-IgE mediated food allergic disorders: Eosinophilic esophagitis (EoE), food protein-induced allergic proctocolitis (FPIAP) and enteropathy (FPE)
  - Intestinal obstruction

Differential Diagnosis

- Extensive differential diagnosis
- Determine infection vs obstruction vs metabolic
- Allergic vs nonallergic
  - Infection, surgical, GI disorders
  - Other non-IgE, enteropathy
- Necrotizing enterocolitis (NEC)

Distinguishing FPIES, FPIAP, and FPE

	Main clinical features
FPIES	Delayed repetitive vomiting, pallor, lethargy
FPIAP	Benign blood in stool, baby thriving Average age at onset lower: 2 months vs 4-6 months in FPIES, no acute symptoms upon food ingestion
FPE	Chronic diarrhea, malabsorption, low weight gain, no acute symptoms upon food ingestion

FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced enteropathy.

Leonard SA. *Curr Allergy Asthma Rep*. 2017;17:84. Arik Yilmaz E, et al. *Allergy Asthma Proc*. 2017;38:54-62.

Diagnostic Strategies

- Understanding FPIES specific features
  - Diagnosis of exclusion
  - Currently, no diagnostic tests or biomarkers
- Recognize pattern of clinical symptoms
- FPIES may be missed due to
  - Absence of typical allergic symptoms (eg, urticaria, wheezing)
  - Delayed onset (1–4 hours) in relation to food ingestion
  - Unusual food triggers, eg, rice, oat, sweet potato that are considered as hypoallergenic foods for IgE-mediated food allergy

Leonard SA. *Curr Allergy Asthma Rep*. 2017;17:84.

Oral Food Challenge: What You Need to Know

- Oral food challenge (OFC) can confirm the diagnosis
- OFC is the *only* currently available diagnostic test
- FPIES diagnosis is based on consistent clinical features with improvement following withdrawal of suspected causal protein
- Physician-supervised OFC is necessary to evaluate for FPIES resolution
- Keep child away from food until challenge is done
- OFC is standardized

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.

Oral Food Challenge (continued)

- At-home OFCs are not recommended, given the potential for severe reactions
- Intravenous fluids must be available for rehydration, if needed
  - Attempt oral rehydration by breastfeeding or with clear fluids
- Recommended to be done at centers with expertise in managing food allergy and performing oral food challenges
- Repeat OFC usually between 1 and 2 years or longer from the most recent reaction, depending on nutritional and social importance of food

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.

MODULE 3: MANAGEMENT STRATEGIES

- Discuss treatment and strategies
- How to address acute reaction management
- Examine nutritional management:
  - When breastfeeding
  - When breastfeeding is not possible

Treatment Strategies & Management

- According to FPIES Guidelines… eliminate food trigger(s) from diet
  - Food avoidance risks nutritional deficiencies in long term
  - Involve nutritionist
  - Introduce food without unnecessary delays
- Acute management of FPIES emergencies
- Long-term management of FPIES

Acute Management

- Severe reaction—Have emergency treatment plan
  - Go to the Emergency Room
  - Call 911
  - Child needs fluids to recover
- Mild reaction—Can manage at home, except in a child with prior severe FPIES reaction to the trigger food

ER Letter—Individualized Allergy Action Plans

- Letter every parent should carry (see Resources)
  - Provide letter to ER—What to do with accidental exposure
  - Letter includes:
    - Clinical features (it is this)
    - How this child is being treated for FPIES
    - Avoid medicine (eg, do not give antihistamine or epinephrine)
    - Foods this child has FPIES reaction(s) to
- How to Treat—Best treatment is rehydration in ER
  - Rehydration [with intravenous fluids]
  - Single dose of intravenous methylprednisone given in severe reactions
  - Ondansetron iv/im/po may be useful in mild-moderate reactions

IV, intravenous; IM, intramuscular; PO, Per os (orally).

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4; Miceli Sopo S, *Allergy.* 2017;72(4):545-551.

Long-term Management of FPIES

- Eliminate food trigger(s) from diet
- Periodic reassessment for tolerance (every 12–24 months)
- Attention to feeding skills
- Timely introduction of complementary solid foods
- Provide emergency plan for potential acute reaction
- Be aware of issues associated with long-term management:
  - Avoidance
  - Breastfeeding

Long-term Nutritional Management

- Nutritional management is most important (once diagnosed)
- Long-term management of food avoidance
  - Potential for nutritional deficiencies
- Anticipatory guidance of complementary feeding
  - Unnecessary delay of solid food introduction, how to reduce this risk

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Nutritional Daily Management

- No need to avoid traces or foods with “may contain” labels
- Avoid baked milk/egg (unless tolerance to baked products is documented by a challenge, or is frequent at large ingestions)
- Consider dietary consult
- Be aware of co-reactivity (eg, milk-soy, rice-oat)
- Introduce solids in a timely manner
- Monitor growth

CM, cow’s milk; eHF, extensively hydrolyzed formula; AA, amino acid.

Management While Breastfeeding

FPIES can happen in exclusively breastfed infants, although rarely

- Do not restrict maternal diet unless infant is symptomatic (acute or chronic), or is not thriving
- Majority are asymptomatic and thriving during breastfeeding
- Rarely have acute or chronic symptoms been reported in breastfed infants, attributed to foods in maternal diet
- Maternal dietary avoidance vs stopping
- Substitute for breast milk: Hypoallergenic formula
    - Extensively hydrolyzed casein or amino acid formula [up to 40%]

Selecting Safe Nutritional Alternatives

Ages and Stages	Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*

<u>4 to 6 months (per AAP, CoN)</u>
• 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)

<u>6 months (per WHO)</u> • Complementary feeding should begin no later than 6 months of age. • In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months 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

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.

Selecting Safe Nutritional Alternatives

Ages and Stages	Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*
8 months of age or when developmentally appropriate • Offer soft-cooked and bite-and-dissolve textures around 8 months 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 months of age or when developmentally appropriate • Offer modified tolerated foods from the family table: chopped meats, soft cooked vegetables, grains, and fruits.	Tree nuts and seed butters* (sesame, sunflower, etc)	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.

Future Investigations are Needed

- Pathophysiology of FPIES is poorly understood
- Currently, no diagnostic biomarkers
- No therapies to accelerate resolution

Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol.* 2017;27:1-18.

FPIES Takeaways

- ✓ FPIES is a delayed food allergic reaction and can be *very* serious
- ✓ FPIES misdiagnosis is common, delaying diagnosis for months
- ✓ Pathophysiology is an unmet need [we are not sure what is causing it]
- ✓ Favorable prognosis: FPIES often resolves in 1 to 5 years
- ✓ Management relies on avoidance of the food trigger and periodic re-evaluations for resolution during a supervised oral food challenge
- ✓ Nutritional consultation is recommended

Nowak-Węgrzyn A, et al. *J Investig Allergol Clin Immunol.* 2017;27:1-18.

FPIES Resources

- FPIES.org https://www.fpies.org
- FPIES Guidelines https://www.fpies.org/fpies-guidelines/
- FPIES Emergency Room Letter example
  https://www.fpies.org/wp-content/uploads/2017/12/IFPIES-ER-Letter.pdf

- Help track frequency of FPIES occurrence
  - ICD-10 code: K52.2

  https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Management/finances-coding/FPIES-Codes-ICD-10.pdf

American Academy of Allergy Asthma & Immunology
www.aaaai.org

Food Protein-Induced Enterocolitis Syndrome for ICD-10

K52.2 is a new, approved ICD-10 code for **Food Protein-Induced Enterocolitis Syndrome** (FPIES). FPIES is a non-IgE gastrointestinal food hypersensitivity that manifests as delayed, profuse vomiting, often with diarrhea, acute dehydration, and lethargy. The most common triggers are milk and soy, but any food, even those thought to be hypoallergenic (e.g., rice and oat), can cause an FPIES reaction.

According to the International Association for Food Protein Enterocolitis (IAFFPE), hundreds of patients suffer from FPIES, a rare non-IgE form of food allergy. The new code **K52.2** will take effect when ICD-10 implementation is completed in 2015. ***The new code is the result of advocacy efforts by the International Association for Food Protein Enterocolitis, a lay organization and partner of the AAAAI.***

https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Management/finances-coding/FPIES-Codes-ICD-10.pdf