

Delayed Food Reaction Unresponsive to Epinephrine: A Difficult Case of FPIES



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INSTRUCTIONS

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Overall Purpose/Goal: To provide excellent case-based reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Joseph Cafone, MD, Matthew Greenhawt, MD, MBA, MSc, and Gita Ram, MD (authors); Scott H. Sicherer, MD (editor)

Learning objectives:

1. To distinguish between immediate- and delayed-type food reaction.
2. To understand the current criteria for the diagnosis of food protein-induced enterocolitis syndrome (FPIES).
3. To recognize the appropriate treatment plan for FPIES.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: M. Greenhawt is a member of Nutricia's specialty advisory board pertaining to Neocate. The rest of the authors declare that they have no relevant conflicts of interest. S. H. Sicherer declares no relevant conflicts of interest.

The Difficult Cases Feature is based on the *Difficult Cases* Course presented at the AAAAI Annual Meeting and coordinated by the AAAAI New Allergist-Immunologist Assembly (NAIA). View the entire presentation and obtain CME or MOC credit by visiting the *JACI: In Practice* homepage www.jaci-inpractice.org.

Key words: Food protein–induced enterocolitis

CASE

A 25-month-old girl with Trisomy 21, repaired Hirschsprung disease, reflux, atrial septal defect, hypothyroidism, hypotonia, strabismus, and feeding difficulties presented for evaluation of immediate emesis after ingestion of multiple formulas, including cow's milk formula. She also had emesis unrelated to feeds and

was diagnosed with reflux. She tolerates Neocate. At 1 year of life, she tried PediaSure and had immediate emesis followed by 3 days of loose stools, on 2 separate occasions.

Her history was significant for tolerating fruits, vegetables, and grains, but she had not been exposed to egg, soy, peanut,

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Conflicts of interest: M. Greenhawt is a member of Nutricia's specialty advisory board pertaining to Neocate. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 4, 2019; revised November 14, 2019; accepted for publication November 15, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.11.015>

TABLE I. Symptom and intervention log

Time	Symptoms	BP	Interventions
0	Active, happy	92/57	First dose
115 min	Active, happy		Last dose
150 min (2.5 h)	Large emesis	119/62	
155 min	Red rash around mouth	131/69	Epinephrine IM
175 min	Large emesis, 4 sneezes	103/69	Cetirizine and ranitidine
185 min (3 h 5 min)	25 sneezes	98/61	Second epinephrine, IV placed, and bolus given
195 min	Gagging, dry heaving	118/83	Ondansetron IV
245 min (4 h 5 min)	Large emesis	151/80	Third epinephrine and second bolus
Transfer to ICU	Hypotensive	75/38	IV bolus and methylprednisolone

BP, Blood pressure; ICU, intensive care unit; IM, intramuscular; IV, intravenous.

tree nut, fish, or shellfish. Allergy testing to milk (given immediate emesis attributed to cow's milk-based formula) revealed a skin prick test wheal of 5×20 mm and specific IgE level of 0.84 kU/L. A cow's-milk food challenge was recommended given mild sensitization and only moderate pretest probability of an IgE-mediated allergy. She completed a 6-step milk-protein challenge (total 8 g) over 115 minutes but developed protracted vomiting 45 minutes after the last dose (150 minutes after the first dose), refractory to multiple doses of epinephrine and 2 intravenous fluid boluses (Table I). The child was transferred to the intensive care unit where she became hypotensive, which resolved following a third fluid bolus.

DISCUSSION

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy, easily missed or misdiagnosed. This atypical case illustrates the importance of considering FPIES in patients with suspected IgE-mediated reaction to a trigger food where vomiting is the primary/solitary symptom. FPIES often presents within the first 6 months of life or at the time of weaning. Given the potential for misdiagnosis and limitations in reporting, the true incidence of FPIES is unknown.¹⁻³ The specific mechanism for FPIES is poorly understood, but likely related to gut inflammation resulting in increased tissue permeability and fluid shift into the gastrointestinal lumen.^{4,5} Patients generally present with protracted vomiting 1 to 4 hours after food ingestion (with/without diarrhea 5-10 hours after ingestion). Other findings may include hypovolemic shock, neutrophilia, thrombocytosis, metabolic acidosis, or methemoglobinemia related to the fluid loss.^{3,6} Many are misdiagnosed with gastroenteritis, sepsis, or metabolic disorders given a common symptom of vomiting. The most common North American triggers include milk, soy, oat, and rice.^{7,8} Skin prick testing is neither helpful nor recommended given no IgE mechanism. The most recent international practice guidelines proposed 1 major and 3 or more minor criteria be met to diagnose FPIES, based on expert opinion.⁹ However, assessment can be challenging emergently or after an episode. Oral food challenge remains the diagnostic criterion standard but is often used only to demonstrate when FPIES has been outgrown. The treatment of acute FPIES reactions is rehydration (oral or intravenous), though there is emerging evidence for ondansetron

as an antiemetic.^{10,11} Long-term management is to avoid triggering allergens. Nutritional consultation may be helpful for monitoring caloric and micronutrient intake. Regular follow-up is essential to review symptoms, growth monitoring, and ongoing food introduction.

This case illustrates the importance of considering FPIES reactions in patients with suspected IgE-mediated allergy with a history of vomiting as the presenting symptom who are nonresponsive to epinephrine. There have been occasional case reports in which patients initially demonstrate immediate IgE-mediated reactions and later develop delayed-type reactions consistent with FPIES, though this is uncommon.^{12,13} One small case series from a single large referral center noted that 7 of 17 children who were milk-sensitized had slower resolution of their FPIES, though these data have not been replicated. The recent guidelines suggest that periodic testing for food specific IgE before reintroduction can be considered in children with other atopic conditions although the pretest probability is low and may complicate decision making.⁹ Regardless of the FPIES workup, clinicians should be aware of the rare possibility that FPIES may coexist in a patient with suspected IgE-mediated food allergy. Aggressive hydration with or without ondansetron in patients with persistent vomiting unresponsive to epinephrine should be considered.

Further information and discussion can be obtained by viewing the original Difficult Cases presentation in this article's Online Repository at www.jaci-inpractice.org.

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Difficult Cases: Food Protein-Induced Enterocolitis Syndrome

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Disclosures

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- ▶ I have not had a financial interest or other relationship with the manufacturers of the products that will be discussed in my presentation.

Matthew Greenhawt M.D., MBA, MSC

- ▶ I am a member of Nutricia's specialty advisory board pertaining to Neocate, but otherwise have not had a financial interest or other relationship with the manufacturers of the products that will be discussed in my presentation.

Case #1

25 month old F with Trisomy 21
Hirschsprung's disease s/p pull-through surgery
GERD
ASD
Feeding difficulties requiring GT
Hypothyroidism
Hypotonia
Strabismus

Case #1

> Newborn

- ▶ Given cow's milk formula in NICU (poor suck, unable to breastfeed)
- ▶ Immediate emesis
- ▶ Also had emesis unrelated to feeds, later thought to be GERD
- ▶ Several formulas tried, immediate emesis with all
- ▶ Tolerated Neocate

> Age 1 year

- ▶ Pediasure given via G-tube
- ▶ Immediate emesis
- ▶ Dad says also had loose stools x 3 days
- ▶ Pediasure offered again few weeks later, same reaction

Case #1

- ▶ Now on Neocate Jr. via G-tube
- ▶ Tolerates fruit/vegetable purees, grains
- ▶ No exposure to
- ▶ Allergy Testing

	22 months of age
SPT	5 x 20
slgE	0.84 kU/L

- ▶ Food Challenge to cow's milk recommended

Case #1

- ▶ 25 months old
- ▶ Completed 6 doses of milk protein– 8 g protein

Time	Symptoms	Treatment	BP
0	Active, happy	First Dose	92/57
115 mins	Active, happy	Last Dose	
150 mins (2.5 hours)	Large Emesis		119/62
155 mins	Red rash around mouth	Epinephrine IM	131/69
175 mins	Large emesis, 4 sneezes	Cetirizine & ranitidine	103/69
185 mins (3 hrs, 5 mins)	~25 sneezes	2 nd Epi , IV placed & bolus given	98/61
195 mins	Gagging, dry heaving	setron IV	118/83
245 mins (4 hrs, 5 mins)	Large emesis	3 rd Epi, 2 nd bolus	151/80

- ▶ Transferred to ICU for monitoring: BP dropped to **75/38** -92/48 x 30 mins
 - ▶ IV bolus, methylprednisolone, BPs normalized

Question 1

What is the appropriate initial treatment for this reaction

- ▶ A. Epinephrine
- ▶ B. Steroids
- ▶ C. Ondansetron
- ▶ D. IV hydration
- ▶ E. All of the above

Answer 1

What is the appropriate initial treatment for this reaction

- ▶ A. Epinephrine
- ▶ B. Steroids
- ▶ C. Ondansetron
- ▶ **D. IV hydration**
- ▶ E. All of the above

What type of reaction was this?

IgE-mediated reaction

- ▶ Hx: immediate emesis with each ingestion
- ▶ Hives/Rash
- ▶ Sneezing

FPIES reaction

- ▶ Multiple emesis starting 2+ hours after ingestion of trigger
- ▶ Emesis not responsive to epinephrine
 - ▶ Requiring multiple boluses/IVF
- ▶ Low sIgE to milk

Food Protein-Induced Enterocolitis Syndrome

- Non IgE-mediated food allergy
- Typically occurs within first 6 months of life
- Protracted vomiting & lethargy: 1-4 hours after ingestion
- Diarrhea may follow: 5-10 hours after ingestion
- Other signs/symptoms: Hypovolemic shock, neutrophilia, thrombocytosis, metabolic acidosis, methemoglobinemia
- Symptoms often non-specific
 - ▶ Often misdiagnosed

Even allergists not always proficient with FPIES

Trends in Provider Management of Patients with Food Protein–Induced Enterocolitis Syndrome



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23-question online survey to AAAAI members

470 respondents

64% reported “full understanding” of FPIES diagnosis/management

FPIES vs. infantile colic: 82.5%

FPIES vs. proctocolitis: 71.3%

Providers currently managing FPIES patients

- ▶ 47.5% soy formula appropriate substitute for patient’s with CM FPIES

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



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Proposed FPIES Diagnostic criteria

Major +
3 minor

Major Criterion	Minor Criterion
- Vomiting 1-4 hrs after ingestion - Absence of classic IgE-mediated allergic skin or respiratory symptoms.	- A 2nd (or more) episode of repetitive vomiting after eating same suspect food - Repetitive vomiting episode 1-4 hours after eating a different food - Extreme lethargy with any suspected food - Marked pallor with any suspected reaction - Need for ED visit with any suspected reaction - Need for IVF support with any suspected reaction - Diarrhea in 24 h (usually 5-10h) - Hypotension - Hypothermia

Diagnosis

Clinical history of typical signs/symptoms & resolution of symptoms with avoidance

SPT/APT not recommended

Reproducible if exposure to trigger

Timing of symptoms after ingestion

Delay in diagnosis

- ▶ Non-specific symptoms
- ▶ Lack of familiarity with FPIES
- ▶ Some of the solid foods not typically considered

Misdiagnosis: gastroenteritis, sepsis, metabolic disorders, etc.

OFC may be helpful but consider risk/benefit, and necessity given the clinical history

Do Phenotypes Exist in FPIES?

Age of onset

- ▶ Early: < 9 months of age
- ▶ Late: > 9 months of age
- ▶ Consider age of true onset, vs. age of this being brought to a provider's attention

Severity

- ▶ Mild to moderate
 - ▶ Repetitive emesis with or without diarrhea, pallor (watery diarrhea, can be bloody)
- ▶ Severe
 - ▶ Repetitive emesis with or without diarrhea, pallor, dehydration, shock, hypotension, methemoglobinemia, metabolic acidosis, behavior change

IgE positivity

- ▶ Classic: IgE testing negative
- ▶ Atypical: IgE testing positive (somewhat controversial and not universally observed)

ncidence

Not 100% known

May not present to allergist- pediatrician, gastroenterologist

Misdiagnosis common

Some may never seek medical attention: mild reactions, nonessential food trigger, parent assumes viral illness

Major limitation is reporting—case series/reports from tertiary centers vs. true observational cohorts at a population level

ncidence

- ▶ Large birth cohort study > 13,000 patients born 2004-2006 in Israel¹
 - ▶ 44 patients identified (0.34%) to cow's milk
 - ▶ 0.5% of same cohort had IgE FA to cow's milk
 - ▶ Only study to date that can address cumulative incidence
- ▶ Retrospective study over 16 years in Sydney, Australia ²
 - ▶ 1992-1995: 6 cases
 - ▶ 2004-2007: 14 cases
- ▶ Multicenter study in Italy ³
 - ▶ 2004: 4 cases
 - ▶ 2010: 13 cases
- ▶ Cause: Increased awareness vs true increase in number of cases

1. Katz Y, et al. JACI 2011
2. Mehr S, et al. Pediatrics 2012
3. Sopo SM, et al. Clin Exp A 2012

Pathophysiology

Exact mechanism unclear, more research needed in this area

Reaction against food protein that leads to gut inflammation

- ▶ ↑ intestinal permeability
- ▶ Fluid shift into GI lumen → vomiting, diarrhea, and resulting potential for hypovolemic shock

Non-specific inflammation found in colon/ileum by endoscopy & biopsy

Cell-mediated food hypersensitivity

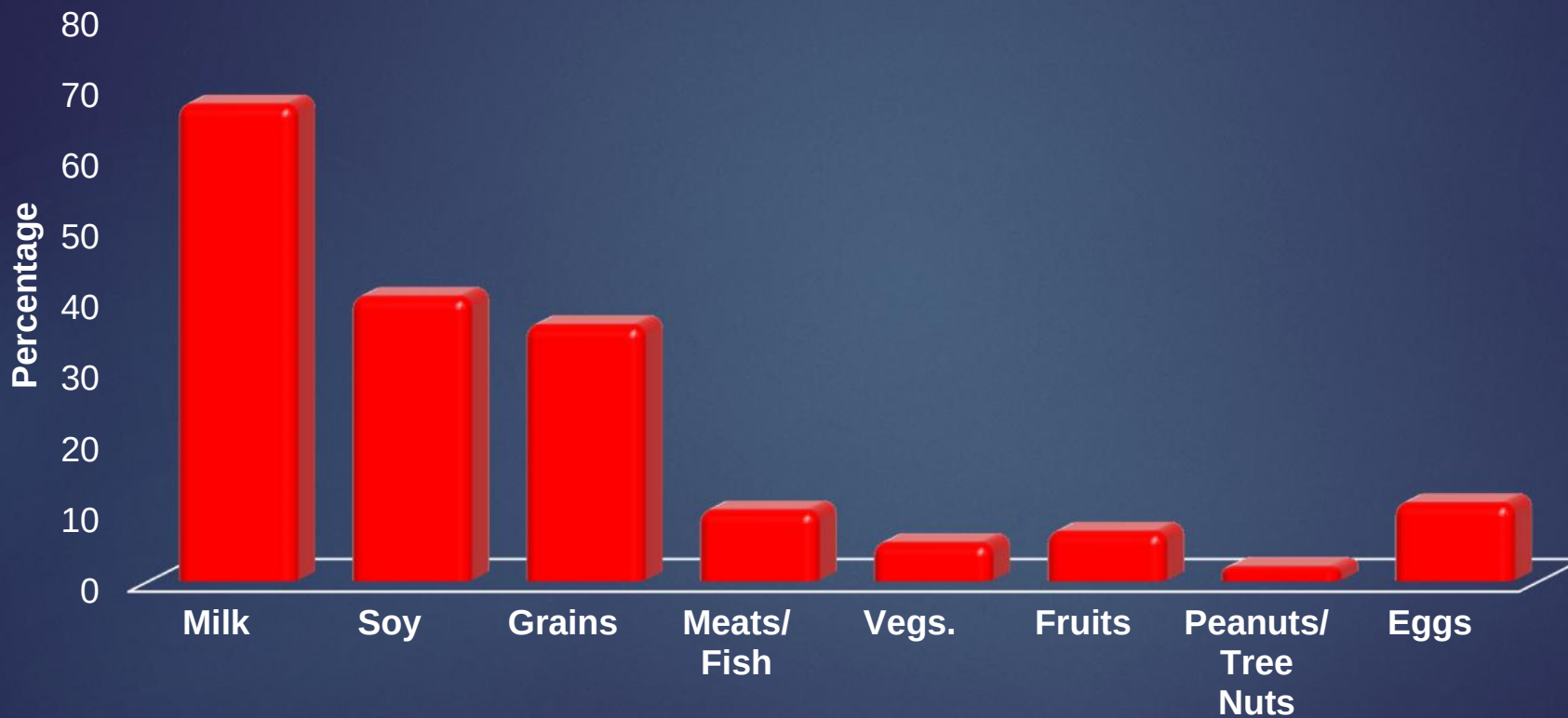
- ▶ SPT negative
- ▶ Delayed onset

TNF may be involved (hypotension, fever) ¹

Relative lack of expression of TGF ²

1. Nowak-Wgrzyn A, et al. C
Opin Allergy Clin Immuno
2. Chung HL, et al. JACI 200

Common Triggers: CHOP



Common Triggers: Mt. Sinai

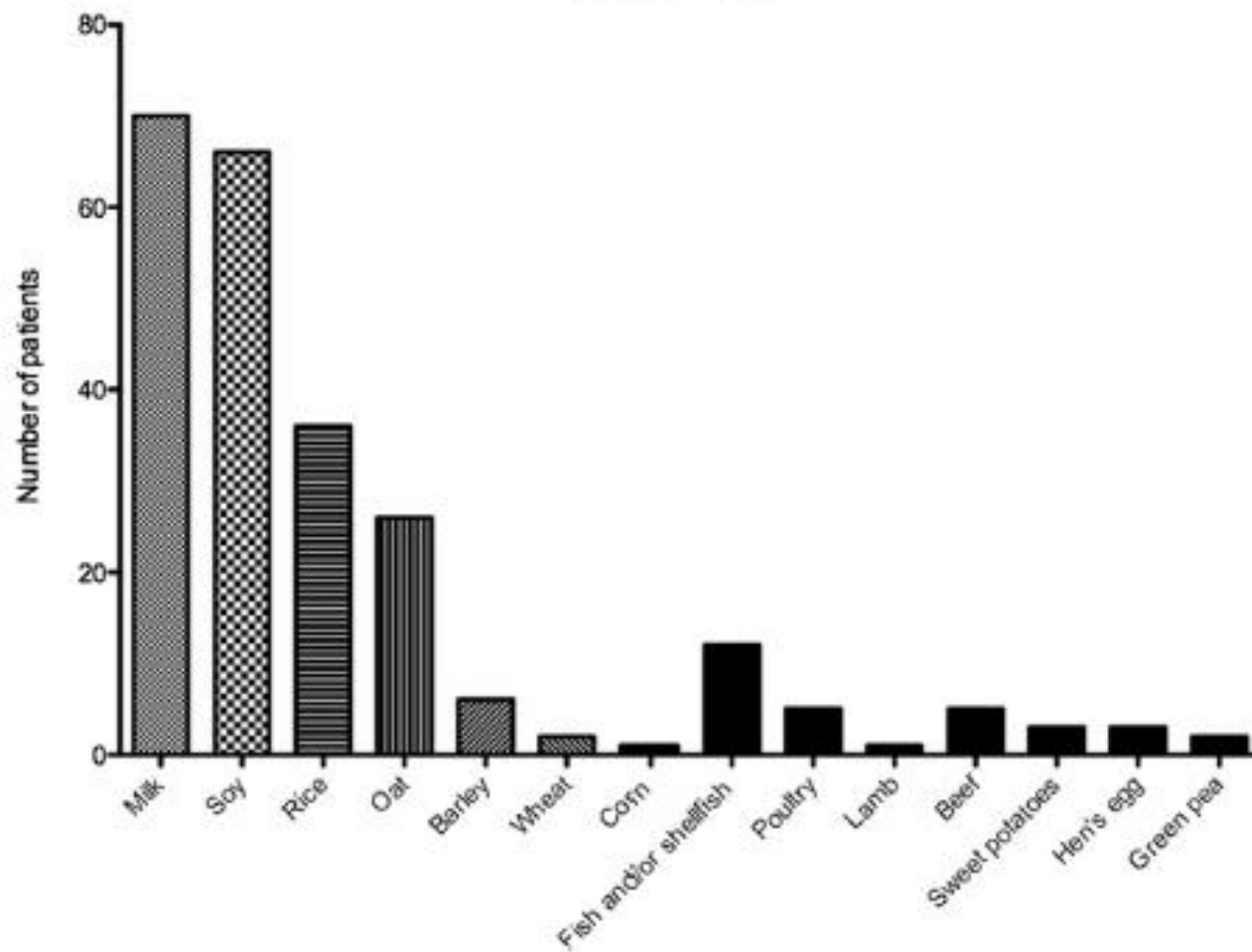
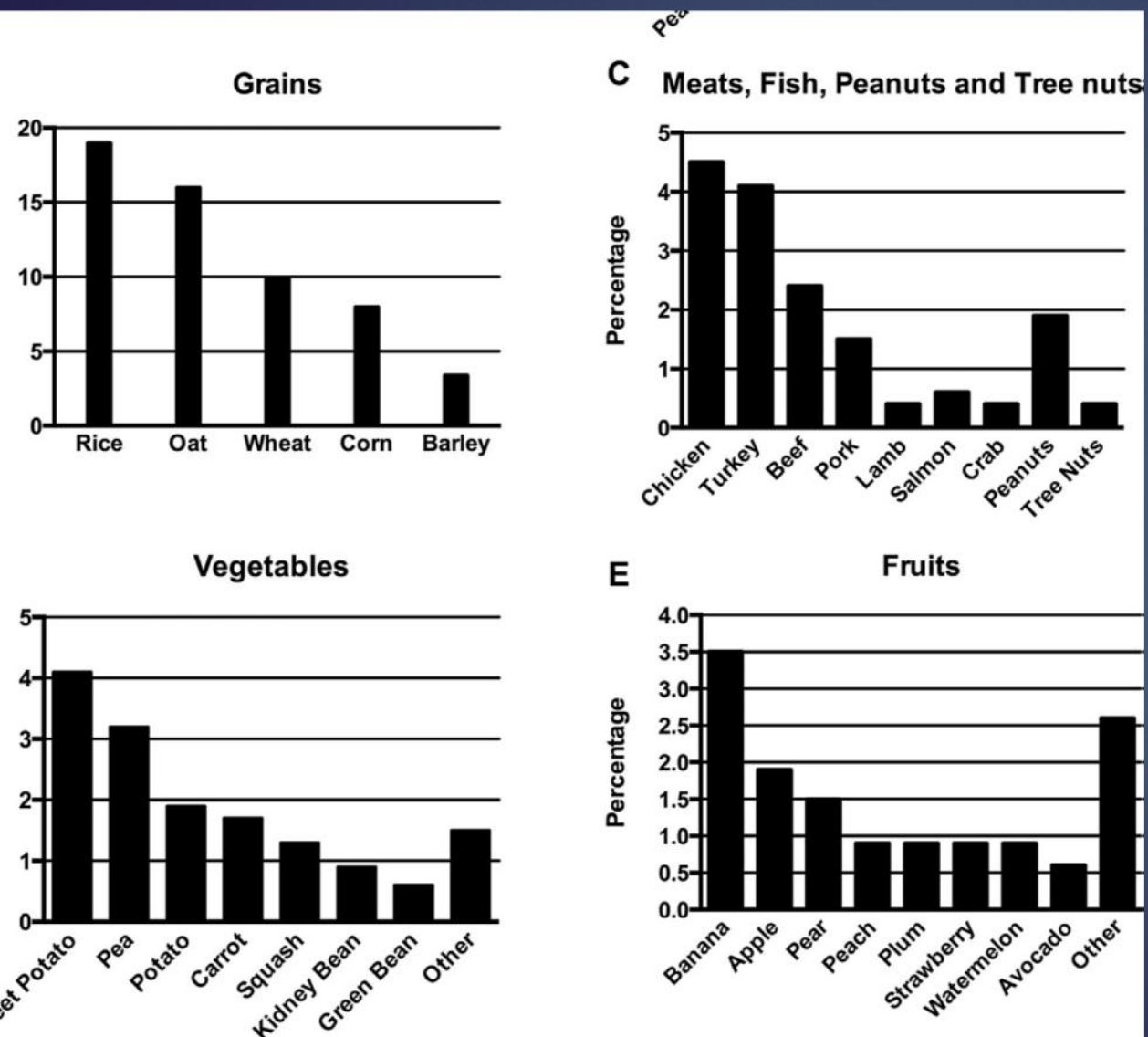


FIG 1. FPIES food triggers.

Common Triggers



- Most patients (65-80%) react to 1 food
- 5-10% react to > 3 foods
- 5% may react to > 6 foods

Potential for Cross-reactivity in FPIES

FOOD GROUP	COW MILK	SOY	EGG	NUT	FISH	MEAT	FRUIT	VEGE	GRAIN	OTHER
COW MILK	1.00									
SOY	0.25	1.00								
EGG	-0.20	-0.05	1.00							
NUT	-0.05	-0.02	0.18	1.00						
FISH	-0.12	-0.06	-0.09	-0.02	1.00					
MEAT	-0.13	0.03	-0.03	-0.02	0.12	1.00				
FRUIT	-0.10	-0.09	-0.12	-0.02	-0.08	-0.01	1.00			
VEGE	0.00	-0.02	-0.06	-0.02	-0.07	0.07	0.35	1.00		
GRAIN	-0.31	-0.08	-0.27	-0.07	-0.09	-0.10	0.05	-0.01	1.00	
OTHER	-0.06	-0.04	-0.06	-0.01	-0.04	-0.05	0.13	-0.05	-0.01	1.00

This was based on national-level reporting in Australia, which differs from earlier published reports of co-emergent FPIES triggers observed in smaller case-reports/series at individual centers

True rates and relative risks cannot be determined from present data—this is a knowledge gap

Nutritional Guidance

Age and stage	Lower risk foods	Moderate risk foods	Higher risk foods
4 to 6 months	Vegetables: broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean	Sweet potato, peas
6 monthss	Fruits: blueberries, plums, watermelon, peach, avocado, strawberries	Apple, pear, orange	banana
8 months of age	High iron foods: lamb, quinoa, millet	Beef, grits, corn, wheat, barley	Rice and oat cereals
12 months of age or when appropriate	Tree nuts, seed butter	Peanut, other legumes	Milk, soy, poultry, egg, fish

Importantly, this does not mean DELAY the introduction of peanut but it emphasizes that in an individual with FPIES, early introduction of peanut must be PRIORITIZED along with other nutritional considerations

FPIES & IgE FA

Summary Statement 4

- ▶ **Consider** specific IgE-testing of children with FPIES **to their trigger food** because comorbid IgE-mediated sensitization to triggers, such as CM, can infer a greater chance of persistent disease [**Strength of recommendation: Moderate; Evidence strength: IIb-III; Evidence grade: C**]

Summary Statement 9

- ▶ **Do not** routinely perform testing for food sIgE **to identify food triggers** of FPIES because FPIES is not an IgE-mediated process. However, because some patients with FPIES can exhibit coexisting IgE-mediated allergies, testing can be considered in patients with certain comorbid conditions. [**Strength of recommendation: Moderate; Evidence strength: IIb-III; Evidence grade: C**]

gE → FPIES

Barni et al. ¹

- ▶ 2 case reports: very young infants with IgE mediated reaction to cow's milk who developed FPIES reaction upon food challenges
 - ▶ Initially with positive SPT and sIgE
 - ▶ 2 months later: negative SPT, essentially negative sIgE
 - ▶ OFC: Multiple emesis requiring IVF & ondansetron 2-4 hours after milk

Banzato et al. ²

- ▶ 15 day old male with diffuse urticarial and edema of hands/feet minutes after first ingestion of cow's milk formula
 - ▶ SPT positive, sIgE 13.7
 - ▶ 3 months: SPT negative, sIgE not done
 - ▶ OFC: 2 hours later, lethargy, pallor, hypotonia, vomiting, diarrhea. Treated with IVF, methylprednisolone

FPIES → IgE

Onesimo¹

- ▶ 2 case reports of infants with typical FPIES to cow's milk who later developed IgE reactions upon OFCs
 - ▶ Young infants with negative SPT & sIgE initially
 - ▶ OFCs performed after >12 months avoidance:
 - ▶ Vomiting, edema of glottis, lethargy, shock- corrected by epinephrine
 - ▶ Contact urticarial, cough, vomiting with milk ingestion at home after passing in office OFC

FPIES & IgE FA

Coexisting IgE sensitization to FPIES reported in 8-25% of patients in US/Australia
1 Japanese cohort of CM FPIES, 47% with detectable milk-specific IgE levels

Caubet ¹

- ▶ At one single center, 41% of patients with CM-FPIES transformed into IgE-mediated phenotype over time
- ▶ Those with CM sensitization in this sample were more likely to have FPIES persist beyond 3 yrs of age

2017 consensus guidelines

Depending on the center, 2-20% might eventually become sensitized to the suspect FPIES-related food/foods, though the significance of this is unclear

20-40% may be sensitized to other common food allergens

Atypical FPIES

- ▶ Children with sIgE to their trigger food
- ▶ Slower resolution of FPIES
- ▶ Periodic testing for food sIgE can be considered in patients with comorbid conditions
 - ▶ IgE to other foods, AD influence by food
- ▶ NOT to be done with initial evaluation, best to be done at time of considering OFC

In patients with CM-induced FPIES, some centers consider measuring CM sIgE levels before performing a food challenge

- ▶ This is largely based on a single center's experience with reports of evolution of FPIES to IgE mediated allergy symptoms upon OFC

Treatment of acute FPIES

Mild (1-2 emesis, no lethargy)

- ▶ Attempt oral rehydration
- ▶ If ≥ 6 mos, consider ondansetron IM 0.15 mg/kg/dose (max 16 mg/dose)
- ▶ Monitor for 4-6 hrs

Moderate (> 3 emesis, mild lethargy)

- ▶ If ≥ 6 mos, administer ondansetron IM
- ▶ Consider IV placement
- ▶ Transfer to ED or ICU
- ▶ Monitor VS
- ▶ Monitor for 4-6 hrs
- ▶ Discharge if able to tolerate clear liquids

Treatment of acute FPIES

Severe (3 emesis, severe lethargy, hypotonia, ashen/cyanotic appearance)

- ▶ Place IV + give 20 ml/kg bolus; repeat PRN
- ▶ If ≥ 6 mos, administer ondansetron
- ▶ If IV placement difficult, administer ondansetron IM **IV**
 - ▶ ODT is an acceptable alternative
- ▶ Consider IV methylprednisolone 1 mg/kg
- ▶ Monitor/correct acid base abnormalities
- ▶ Correct methemoglobinemia
- ▶ Monitor VS
- ▶ Discharge after 4-6 h from onset of reaction, patient back to baseline, tolerating oral fluids
- ▶ Transfer to ED/ICU for persistent symptoms

Clinical Pearls: Case 1

Mixed presentations are rare, but can occur. Be observant and ready to treat either reaction type. Must consider potential for FPIES or IgE presentation with any OFC.

How to balance not delaying introduction of other allergenic solids given a G-tube?

Testing for sensitization, even to milk, in established FPIES still has only level C evidence

- ▶ Prospective study across multiple centers is needed to better validate this
- ▶ Consider changing challenge dosing strategy/duration as an alternative approach

Cross-reactivity patterns vary and are not fully established

- ▶ Notable differences among US centers with milk/soy, as well as limited soy FPIES internationally

Emerging role for ondansetron use to halt vomiting progression to hypovolemia

FPIES diagnostic criteria are not validated but offer a way to better specify definition

Case #2

Full term male

Similac Advance formula

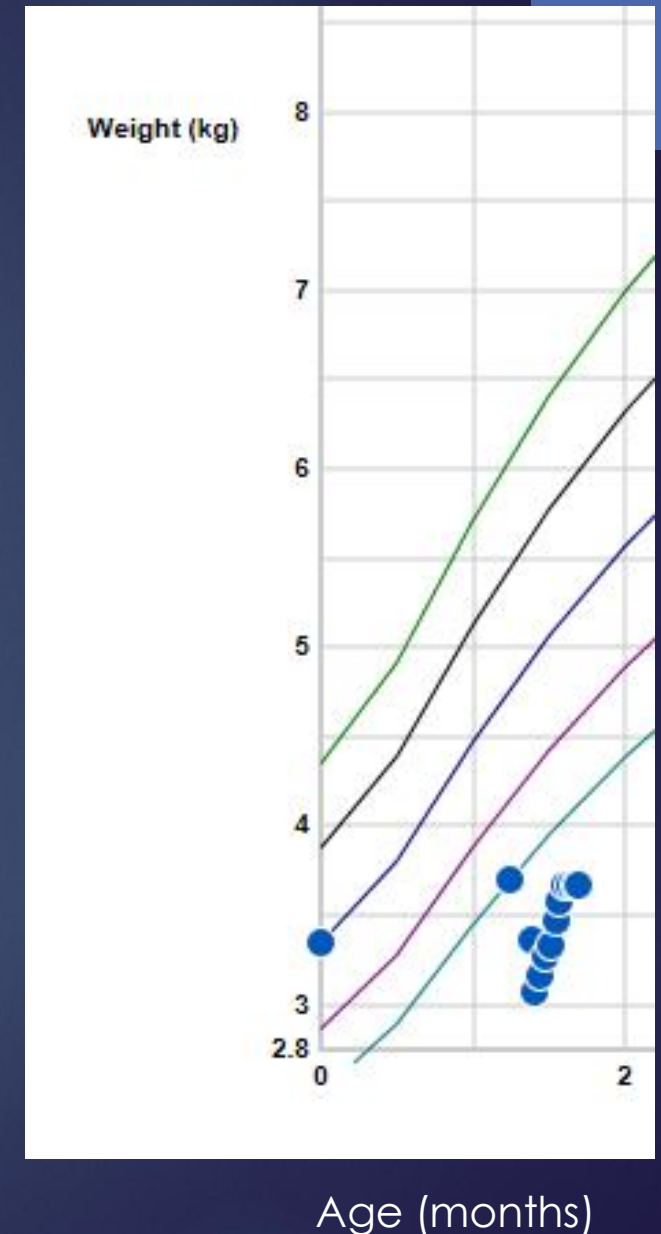
Intermittent spit-up, vomiting

4.5 weeks of age, increased vomiting and crying

- ▶ Discharged with diagnosis of GERD

Follow-up with PCP: persistent vomiting, growth chart reviewed

- ▶ Diagnosis: "milk protein allergy."
- ▶ Switched to Alimentum



Case #2

Few days later, projectile vomiting, lethargy, watery diarrhea

Brought to ED again

DDx: Sepsis, Pyloric Stenosis



Case #2: Transferred to CHOP

SH Labs
2: 27.9 > 15.4 < 643, 17% bands
1:
36 | 104 | 18 /
----- 126
7 | 10 | 0.35 \

2
36 | 106 | 4 /
----- 126
| 12 | 0.23 \

ST 20, ALT 32, Tbili 1.4, Dbili 0.8, alk phos 183, albumin 3.3
Ammonia 100
28/25

SF: glucose 61, protein 56, RBC <1, WBC 2, gram stain no WBCs rare RBCs no organisms
A: spec grav >1.030, neg ketones, 100 protein, neg nitrite, neg leuk esterase, 0-2 WBCs

Cx pending
CX pending

rapid meningitis/encephalitis panel: HSV and enterovirus negative

- ▶ Vitals: T 37.1, others wnl (after resuscitation)
- ▶ Weight < 1% ile
- ▶ U/S: normal
- ▶ Elevated WBC: bandemia
- ▶ Acidotic
- ▶ Hyper-ammonemia
- ▶ Sepsis evaluation
 - ▶ Negative

Case#2: CHOP PICU

- Acidosis: attributed under-resuscitation, normalized after continued IV fluids
- Metabolic workup: reassuring
- Stool studies negative
- Started Pedialyte (tolerated), transferred to floor

Presumed diagnosis: infection



Case #2: Hospital Course

Feeds slowly restarted: Alimentum

Recrudescence of severe vomiting and watery diarrhea

GI consult:

- ▶ Bowel rest/TPN
- ▶ Transition to Elecare

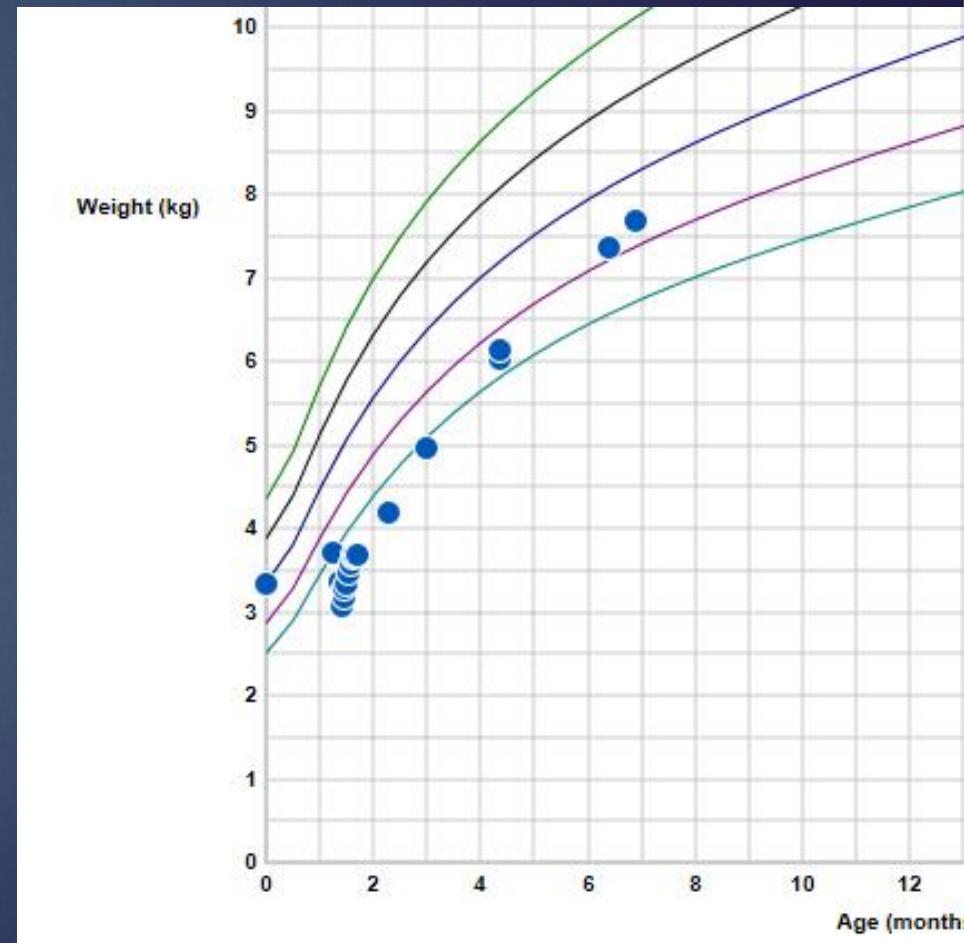
Discharged home well, tolerating Elecare



Case #2: Follow-Up



- ▶ Several months of milk elimination
- ▶ Tolerating many fruits & vegetables.
- ▶ Growth chart



Question 2

What is the correct diagnosis for this patient

- ▶ A. Milk Protein Allergy
- ▶ B. Acute on Chronic FPIES
- ▶ C. Gastro-esophageal reflux disease
- ▶ D. Acute FPIES

Answer 2

What is the correct diagnosis for this patient

- ▶ A. Milk Protein Allergy
- ▶ **B. Acute on Chronic FPIES**
- ▶ C. Gastro-esophageal reflux disease
- ▶ D. Acute FPIES

Diagnosis of chronic FPIES

Daily ingestion of food (feeding with CM- or soy-based formula)

Symptoms

- ▶ Intermittent emesis
- ▶ Chronic diarrhea
- ▶ Poor weight gain
- ▶ FTT

Usually return to usual state of health within 3-10 d of switching to hypoallergenic formula (severe cases may need temporary bowel rest, IVF).

Subsequent feeding of offending food after period of avoidance → acute symptoms

Diagnosis of chronic FPIES

Severe

- ▶ Offending food ingested on a regular basis (e.g. infant formula)
- ▶ Intermittent but progressive vomiting and diarrhea (occasionally with blood)
- ▶ May present with dehydration, metabolic acidosis

Milder

- ▶ Lower doses of trigger food (e.g. solid foods or food allergens in breast milk)
- ▶ Intermittent vomiting, and /or diarrhea, usually with poor weight gain/failure to thrive
- ▶ WITHOUT dehydration, metabolic acidosis.

Most important criterion:

- ▶ Resolution of symptoms within days after elimination of trigger
- ▶ Recurrence of symptoms when food reintroduced (vomiting 1-4 h, diarrhea in 24 h)
- ▶ **Without confirmatory challenge: diagnosis of chronic FPIES remains presumptive**

DDx Chronic FPIES

Condition	Features that may distinguish from FPIES
Inborn Errors of Metabolism	Developmental delay, neurologic sx's, organomegaly
GERD	Emesis more chronic, not usually severe, only upper GI symptoms present
Eosinophilic gastroenteropathies	Not associated with specific food intake, symptoms more chronic, vomiting less severe
Celiac disease	No temporal relationship to food, celiac serology
Immune enteropathies (IBD, autoimmune)	Rare in infancy, not food-specific
Food protein-induced enteropathy	Not associated with specific food intake, symptoms more chronic, vomiting less severe

Clinical Pearls: Case 2

There is no clear definition of chronic FPIES. There is recognition of a chronic process but if FPIES is the right term, and what the criteria should be are debatable

- ▶ “milk protein allergy” was certainly not an accurate diagnosis

Larger role for coordination of services—where is the line between GI and Allergy?

- ▶ Differential diagnosis key, but should chronic FPIES be diagnosis of exclusion?
- ▶ With any enteropathy type symptoms GI should be involve and endoscopy considered
- ▶ Beware overly deductive reasoning that improvement with AAF = immune mediated rxn

What is the failure rate with eHFc formula in any form of FPIES?

In a chronic case, consultation with a dietician is essential to make sure dietary needs are met, and that there is a plan to continue to introduce foods

As this case demonstrates, awareness for chronic FPIES may be low among non-allergists

Summary of Key Considerations

Keep FPIES, both types, in the differential

In acute cases, beware mixed presentation

Controversial role for sensitization in acute FPIES, more to come on this

What is the safety of any eHFc vs AAF in either type of FPIES

What is the role of cross-reactive foods and “safe” foods

How do we prioritize early allergenic solid food introduction in this patient population

Ondansetron has an important emerging role

We are lagging in studies explaining the pathophysiology

With possible chronic cases, multi-disciplinary team is key, including dietician

Guidelines are a start, but most recommendations have C level evidence

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