Dietary management of food protein induced enterocolitis (FPIES)

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Disclosure

- Provided and reviewed education material for:
  - Danone
  - Abbott
  - Reckitt Benckiser Group
  - DBV technologies

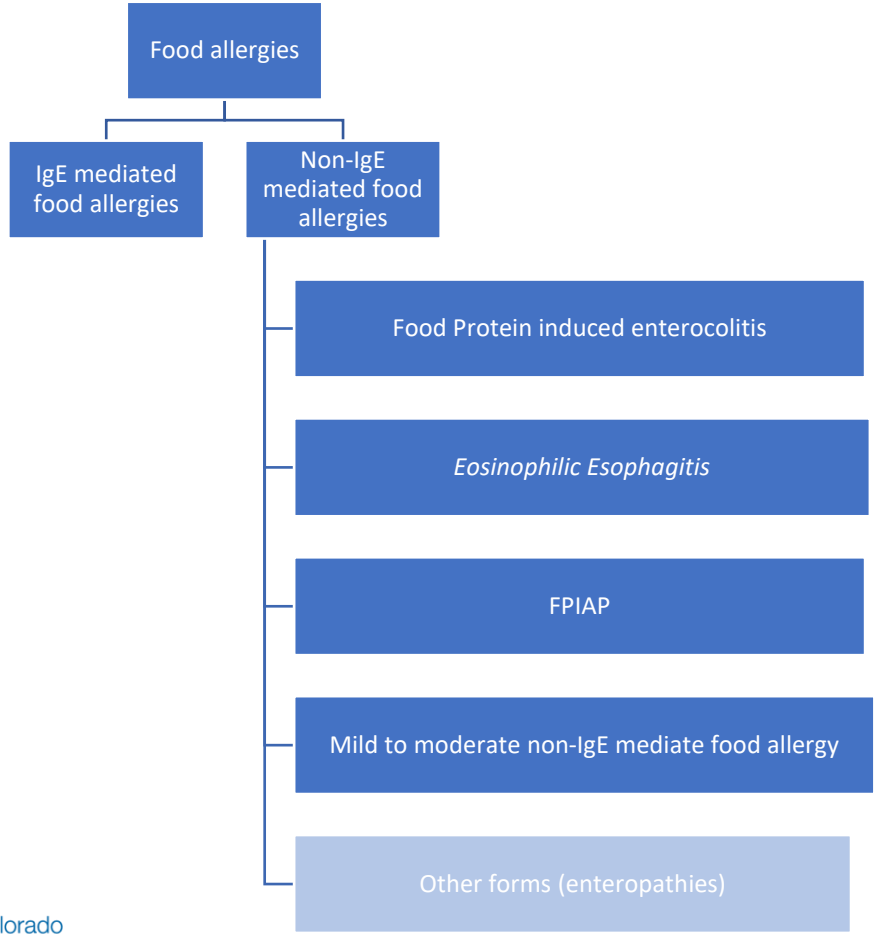
- Research support
  - Reckitt Benckiser Group

Objectives

10 most asked questions

1) Should I avoid the FPIES trigger food while breastfeeding?
2) Which are the most common foods associated with FPIES?
3) My child's FPIES is triggered by rice, should I avoid all grains?
4) Does all children with FPIES react to multiple foods?
5) Which formula is recommended for the management of FPIES?
6) In which order should foods be introduced in infants with FPIES?
7) Should I be concerned about nutritional deficiencies in children with FPIES?
8) When can I start using plant-based milks in children with FPIES?
9) Should I be concerned about feeding dysfunction in children with FPIES?
10) Can children with FPIES eat baked foods?

1. What is the difference between FPIES and EoE?



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Mechanisms of non-IgE mediated food allergies

IgE

APC

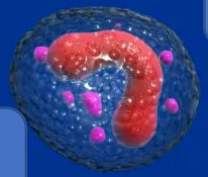
TH2

B Cell

Antigen

EoE

TH1



Monocytes
Neutrophils

FPIAP

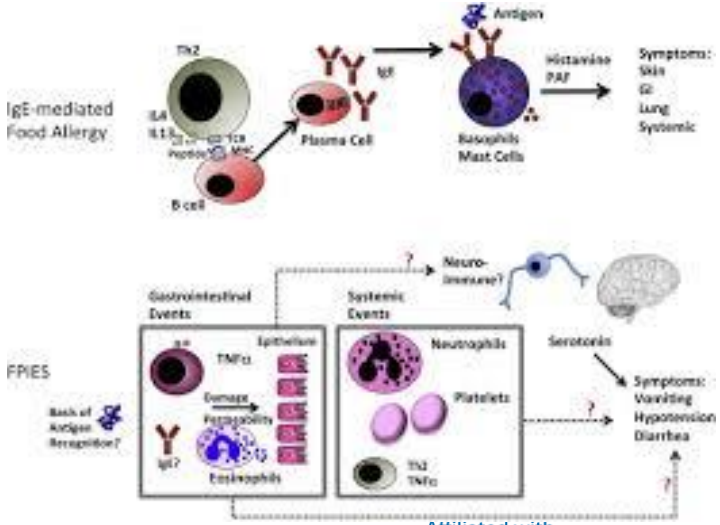
Eosinophil

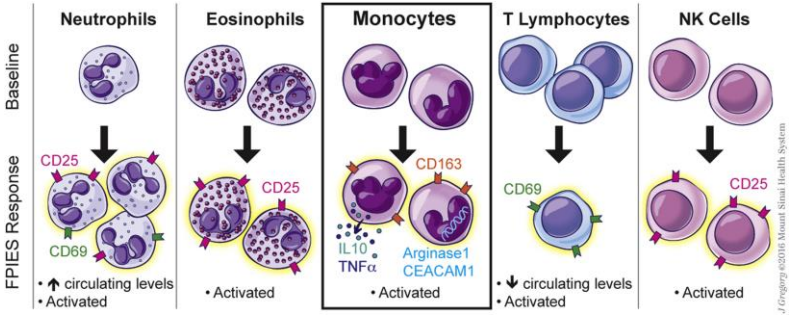
FPIES

Mild to moderate
Non-IgE ?

Pathopysiology

- Berin et al. Immunopathophysiology of food protein–induced enterocolitis syndrome, JACI 2015
- Goswami et al. Systemic innate immune activation in food protein–induced enterocolitis syndrome, JACI 2017





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Natural history and risk factors

- **Food protein-induced enterocolitis syndrome in the US population-based study**
- **Prevalence generally accepted to be around 0.35%**
- FPIES prognosis is generally favorable, with most children becoming tolerant to the trigger food by age 3 to 5 years,
- Risk factors have not been well studied

TABLE I. Estimated prevalence of FPIES in the US population

Reported physician-diagnosed current or past FPIES	Prevalence estimate (95% CI)
All ages (N = 374)	0.28 (0.24-0.33)
Children	
Age < 18 y (N = 261)	0.51 (0.42-0.62)
<1 y (N = 6)	0.11 (0.04-0.26)
1 y (N = 17)	0.59 (0.32-1.08)
2 y (N = 20)	0.76 (0.39-1.47)
3-5 y (N = 41)	0.52 (0.29-0.93)
6-10 y (N = 74)	0.56 (0.40-0.78)
11-13 y (N = 58)	0.61 (0.43-0.88)
14-17 y (N = 45)	0.37 (0.24-0.57)
Adults	
Age ≥ 18 y (N = 113)	0.22 (0.17-0.28)
18-29 (N = 38)	0.33 (0.22-0.49)
30-39 (N = 29)	0.26 (0.16-0.43)
40-49 (N = 15)	0.21 (0.11-0.43)
50-59 (N = 12)	0.11 (0.06-0.21)
60+ (N = 19)	0.18 (0.10-0.30)

Nowak-Wegrzyn et al. JACI 2019

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

Anna Nowak-Węgrzyn, MD, Mirna Chehade, MD, Marion E. Groetch, MS, RDN, Jonathan M. Spergel, MD, PhD, Robert A. Wood, MD, Katrina Allen, MD, PhD, Dan Atkins, MD, Sami Bahna, MD, PhD, Ashis V. Barad, MD, Cecilia Berin, PhD, Terri Brown Whitehorn, MD, A. Wesley Burks, MD, Jean-Christoph Caubet, MD, Antonella Cianferoni, MD, PhD, Marisa Conte, MLIS, Carla Davis, MD, Alessandro Fiocchi, MD, Kate Grimshaw, PhD, RD, RNutr, Ruchi Gupta, MD, Brittany Hofmeister, RD, J.B. Hwang, MD, Yitzhak Katz, MD, George N. Konstantinou, MD, PhD, MSc, Stephanie A. Leonard, MD, Jennifer Lightdale, MD, Sean McGhee, MD, Sami Mehr, MD, FRACP, Stefano Miceli Sopo, MD, : 10.1016/j.jaci.2016.12.966

Acute FPIES

- Ingestion of a new food or following a period of avoidance (at least several days)
- Onset of repetitive, profuse vomiting: **1- 4 hours after ingestion**
- Lethargy, pallor, limpness (“septic appearance”)
- 20% **shock**
- 15% with methemoglobulinemia
- May experience diarrhea 5-10 hours later (may contain blood)
- If a CBC with differential was obtained before and after challenge, there is an increase in the neutrophil count (>1500 cells/mL), peaking 6 hours after food ingestion

Chronic FPIES

- Young infants fed milk or soy formulas
- Watery diarrhea
- Mucous, blood in stools
- Intermittent but progressive emesis (not necessarily associated with ingestion)
- Low albumin and total protein
- Elevated WBC with predominance of neutrophils
- **Growth faltering**
- Onset: within 1-4 weeks of formula introduction

Atypical FPIES

- Patients with a compelling history of FPIES also have evidence of IgE mediated sensitization
- May also have sensitization to other foods
- Estimated to occur is 5-25% of cases (more common for CM and Egg)
- Associated with a more prolonged disease course

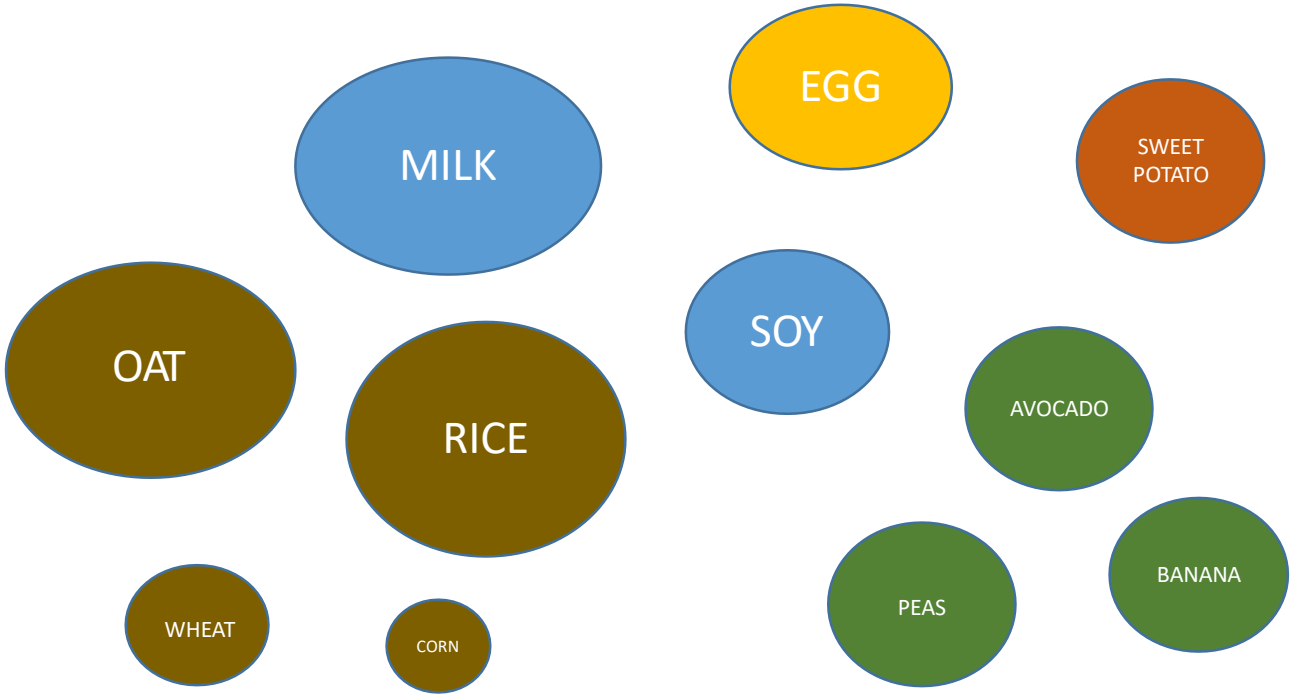
1. Should I avoid the FPIES trigger food while breastfeeding?

Presentation of FPIES during exclusive breast feeding

COUNTRY	STUDY CHARACTERISTICS	NUMBER	FINDINGS
Australia	population-based survey	240 infant and children	5% (n=11) acute FPIES while exclusively breastfed (milk, grains, chicken)
Japan	Clinical cohort	46 children	6.5% reacted during exclusive breastfeeding (rice and soy)
Israel	Birth cohort	64 children	9.3% presented with first FPIES reaction whilst breastfed
USA	Clinical cohort	16 children	50% presented with first FPIES reaction whilst breastfed
Italy	Clinical cohort	66 children	95% of children with FPIES were breastfed, but it is unclear if exclusively breastfed
Australia	Case	1 infant	Infant; exclusively breastfed developed acute FPIES from maternal ingestion of a large amount of soy. This group reported that 21 breastfed infants with acute FPIES presented during breastfeeding, but not clear if they were exclusively breastfed.
USA	Case study	1 infant	Infant exposure to rice and sweet potato while exclusively breastfeeding
Italy	Case studies	2 children	Chronic FPIES caused by maternal cow's milk ingestion
USA	Retrospective study	160 children and adults	3 children presented with chronic FPIES by while exclusively breastfed (milk)

Groetch et al. .Ann Allergy Asthma Immunol. 2021 Jul;127(1):28-35.

2. Which are the most common foods associated with FPIES?



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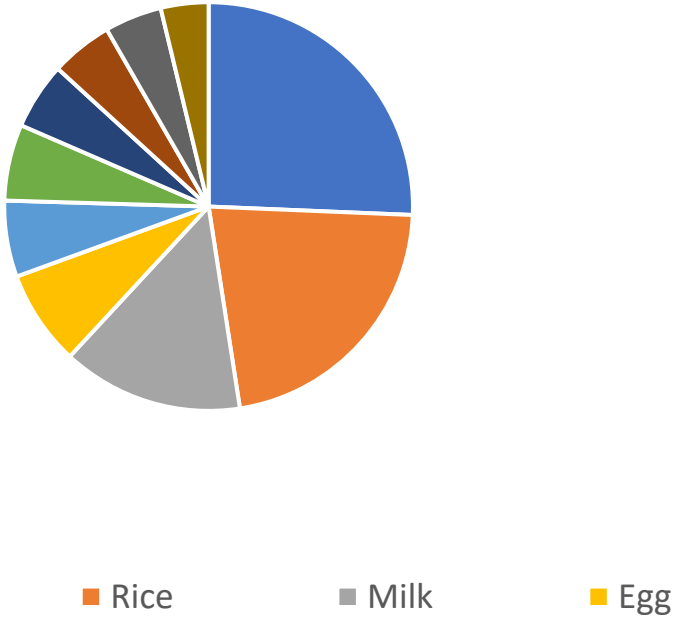
Venter C, Groetch M. Curr Opin Allergy Clin Immunol 2014; 14(3):255-62.

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



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Su et al. J Allergy Clin Immunol. 2020; 145; 5, 1430-1437.e11

4. My child's FPIES is triggered by rice, should I avoid all grains?

What % of children with rice FPIES also react to wheat?

- < 5%
- 5%
- 15%
- 50 %

Grains

Trigger food	No. (%) of patients (N = 74)
Grains	65 (88)
Rice	39 (53)
Oats	26 (35)
Wheat	4 (5)
Quinoa	3 (4)

Blackman AC, et al. Ann Allergy Asthma Immunol. 2019

- Wang *et al.* reported no patient (n=13) challenged to wheat due to oat or rice triggered FPIES had a positive challenge
- Blackman *et al.* also reported low cross reactivity with wheat (5%) in those with rice FPIES (n=39)
- Mehr *et al* with a cross reactivity of 5% for wheat and 1% for corn

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Groetch et al. .Ann Allergy Asthma Immunol. 2021 Jul;127(1):28-35.

TABLE VIII Common food co-allergies in children with FPIES

FPIES to	**Clinical cross-reactivity/co-allergy**	**Observed Occurrence***
Cow's milk	Soy	<30-40%
	Any solid food	<16%
Soy	Cow's Milk	<30-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	about 50%
Poultry*	Other poultry	<40%

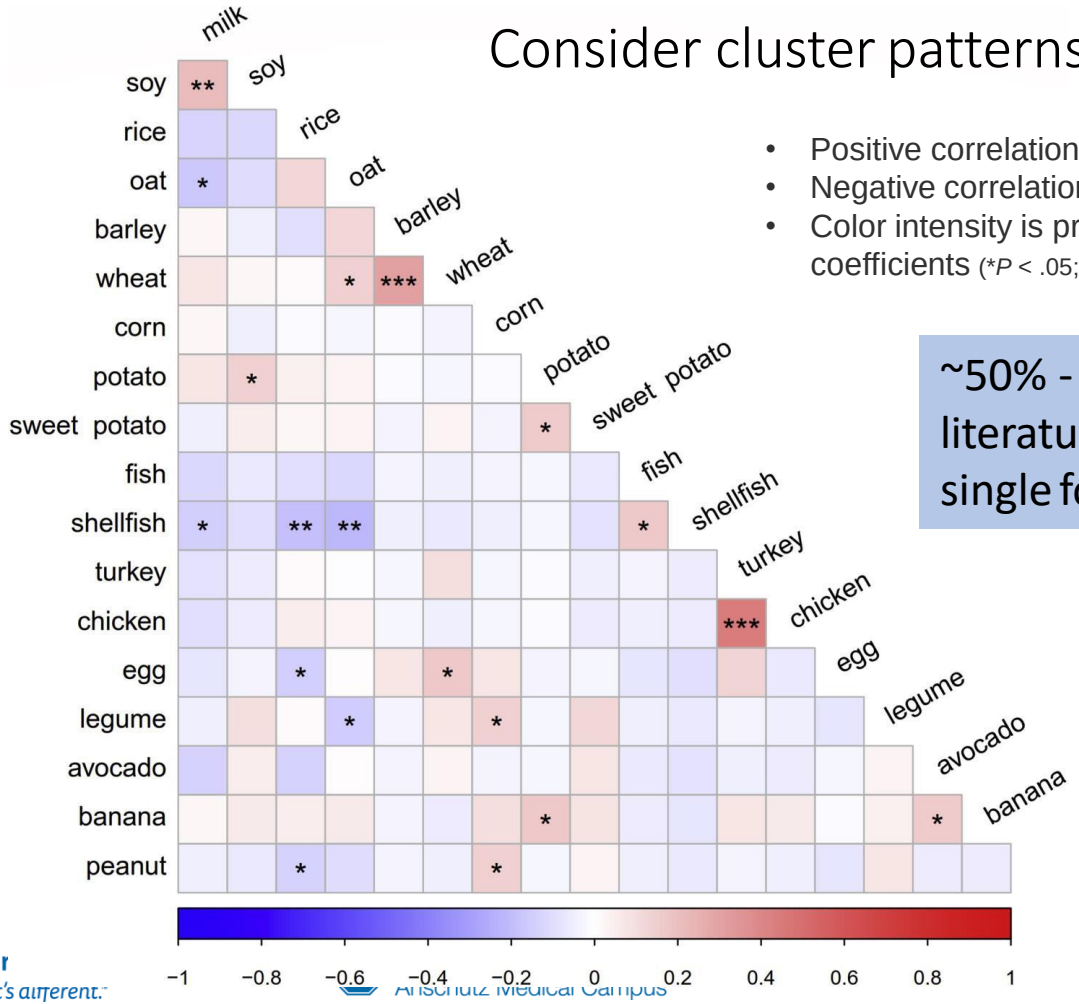
*Note: where a child already tolerates a food type in a particular group (e.g. beans), clinical react
unlikely. Caution is warranted in interpreting these data as they were derived from single centers
phenotype of FPIES and may overestimate the actual risk of co-allergy.

4. Does all children with FPIES react to multiple foods?

What percentage of children develop FPIES to a single food

a) <10%
b) 10 – 25%
c) 50%
d) 50 – 75%
e) >80%

Consider cluster patterns



- Positive correlations displayed in red
- Negative correlations displayed in blue
- Color intensity is proportional to the correlation coefficients (*$P < .05$; ** $P < .01$; *** $P < .001$)

~50% - 80% in the established literature showed FPIES to a single food

Su et al.
J Allergy Clin Immunol. 2020

Childr
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5. Which formula is recommended for the management of milk triggered FPIES?

There is uncertainty about the use of rice hydrolysates in children with rice triggered FPIES

Presentation or condition				ACI British ideline	DRACMA international guidelines
Food protein-indu enterocolitis syndrome (FPIES)				**AAF**	**EHF**

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Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99.; Boyce, et al. Nutr Res. 2011;31:61-75; Nowak-Wegrzyn, et al. J Allergy Clin Immunol. 2017.; Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9; Luyt, et al. Clin Exp Allergy. 2014;44.

6. In which order should foods be introduced in infants with FPIES?

- Introduce solid foods by 6 months of age.
- Start with one or two fruits and/or vegetables, red meats and grains including ancient/pseudo grains, fortified corn products and even wheat can be considered.
- Foods should be offered in age-appropriate forms and textures.

Introduction of peanuts should be delayed in children with FPIES to at least around 9 months

1. Yes
2. No

Lower risk	Moderate risk	Higher risk
Vegetables		
Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
Fruits		
Blueberries, strawberries, plum, watermelon, peach	Apple, pear, orange	Banana, avocado
High iron foods		
Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Fortified, infant rice and oat cereals
Other		
Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

Nowak-Węgrzyn, et al. Journal of Allergy and Clinical Immunology 2017

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Peanut FPIES

- Chart review from January 2015-June 2022.
- Twenty-eight patients with PN-FPIES were identified (61% male)
- Median age of first peanut ingestion was 6 months, first PN-FPIES reaction was 6.5 months, and PN-FPIES diagnosis was 7 months.
- An earlier ingestion of peanut was tolerated in 61%, with 6/17 tolerating >3 prior ingestions.
- Skin testing was performed in 27; 81% were negative (median 0 mm).
- Serum IgE testing was performed for 17, with 47% negative (median 0.11 kU/L).
- This is the largest case series of PN-FPIES yet, highlighting peanut as an emerging major FPIES trigger.
- Onset typically occurs in infancy, even after prior peanut tolerance. Like other triggers, reactivity may persist for years.

Rotella et al. JACI Volume 151, supplement.

Infant Feeding[85]
Approximate amounts to meet nutritional needs

Food Group	Daily Servings for 6-12 months of age
Milk & dairy	Continued breastfeeding or formula with an additional ¼-1/2 cup dairy foods such as plain yogurt
Grains	½ - 1 ounce ½ ounce daily should be fortified with iron and zinc for breastfed infants.
Meats & proteins*	¾-3 ounces with a variety of meat (4 and 2/3 -16 ounce/ week), poultry (½ -1 ounce/week), eggs (>1/week), fish (3 times/week), nuts and seeds (>=1/2 ounce/week)
Fruits and vegetables	1/8-1/2 cup each

Groetch et al. .Ann Allergy Asthma Immunol. 2021 Jul;127(1):28-35.

Read Product Labels

for FPIES

Do not avoid PAL unless in the rare circumstance your child has reacted to trace/invisible amounts in the past.

Your baby may need Supplementation

Generally safe ingredients: refined oils like soy and corn oil, soy lecithin, corn syrup, corn syrup solids, distilled vinegar, ammonium or sodium bicarbonate, baking soda, enzymes, spices, salts, sugars, preservatives, artificial flavorings or colorings, gums like guar gum, xanthan gum, cellulose gel or gum, carrageenan, silicon dioxide, calcium carbonate or other vitamins or minerals

7. Should I concerned about nutritional deficiencies in children with FPIES?

- Nutritional deficiencies in food allergy have been well described in IgE and non IgE-mediated food allergy.
  - ➢ Calories, protein, fat, vitamins (particularly B vitamins and vitamin D) and minerals (particularly calcium, zinc and iron)

Sova et al. 2013
Meyer et al. 2015
Maslin et al. 2016

8. When can I start using plantbased milks in children with FPIES?

Brand	Calories (per cup)	Fat (g)	Protein (g)	Carbohydrates (g)	Dietary Fiber (g)	Added sugar (g)	Calcium (mg)	Vitamin D (mcg)
Horizon Organic Whole Milk	160	8	8	13	0	12	310	4.5
Pacific Foods Organic Oat Original	130	2	4	25	2	17	121	2
Edensoy Organic Soymilk	120	6	12	4	0	0	40	0
Silk Original Almond milk	60	2.5	1	8	0	7	450	2.5
Rude Health Organic Hazelnut Drink	163	3	<1	33	<1	-	-	-
Elmhurst Cashew Milk	130	10	4	8	0	1	15	0
Mariani Vanilla Walnutmilk	60	3.5	1	5	1	4	450	5
Ripple Original Pea Milk	90	4.5	8	6	<1	-	465	6
Silk Original Coconutmilk	70	4.5	0	6	0	5	460	6
Hope & Sesame Original Unsweetened Sesamemilk	90	5	8	2	<1	0	130	6
Manitoba Harvest Hemp Yeah! Original Hemp Milk	50	5	2	1	1	0	300	6
Rice Dream Original Organic Rice Drink	120	2.5	1	23	0	-	30	6
Rude Health Organic Tiger Nut Drink	132	5	1	23	0	-	-	6
Ecomil Quinoa Drink	68	3	1	8	-	-	-	6

Factors to consider that may indicate a toddler is ready to transition to a plant based beverage are the child:

1. Is at least one year of age and eats a varied solid food
2. Gets at least 2/3 of their energy from the diet and consumes no more than 16 ounces/500 mls of milk substitute per day
3. Eats age-appropriate textures and enough protein, fat and micronutrients
4. Has no feeding difficulties, micronutrient deficiencies or religious/cultural dietary requirements
5. All of the above

9. Should I be concerned about feeding dysfunction in children with FPIES?

Variable	Overall			FPIES			IgE			
	N	Median/ Percent	IQR	n	Median/ Percent	IQR	n	Median/ Percent	IQR	p-value
Feeding scale average	323	2.9	2.1	133	3.7	1.6	190	2.4	1.6	<0.0001
Individual Items										
1. How did you find mealtimes with your child?	323	4.0	5.0	133	6.0	3.0	190	4.0	5.0	<0.0001
2. How worried were you about your child's eating?	323	5.0	5.0	133	7.0	2.0	190	4.0	5.0	<0.0001
3. How much appetite (hunger) did your child have?	323	2.0	3.0	133	3.0	4.0	190	2.0	3.0	0.002
4. When did your child start refusing to eat during mealtimes?	254	4.0	4.0	114	4.0	3.0	140	4.0	5.0	0.0095
5. How long did mealtimes take for your child?	323	3.0	2.0	133	3.0	2.0	190	3.0	1.0	0.0364
6. How did your child behave during mealtimes?	322	2.0	4.0	133	4.0	4.0	189	2.0	3.0	<0.0001
7. Did your child gag or spit or vomit with certain types of food?	323	3.0	4.0	133	5.0	3.0	190	2.0	3.0	<0.0001
8. Did your child hold food in his/her mouth without swallowing it?	322	2.0	3.0	132	3.0	4.0	190	1.0	1.0	<0.0001
9. Did you follow your child around or use distractions so they would eat?	322	2.0	3.0	133	4.0	4.0	189	1.0	2.0	<0.0001
10. Did you have to force your child to eat or drink?	322	2.0	3.0	133	3.0	3.0	189	1.0	2.0	<0.0001
11. How were your child's chewing (or sucking) abilities?	322	1.0	2.0	132	2.0	3.0	190	1.0	1.0	<0.0001
12. How did you find your child's growth?	322	2.0	3.0	132	3.0	4.0	190	1.0	3.0	<0.0001
13. How did your child's feeding influence your relationship with him/her?	323	2.0	2.0	133	2.0	3.0	190	1.0	1.0	0.0004
14. How did your child's feeding influence your family relationships?	323	2.0	4.0	133	4.0	3.0	190	1.0	3.0	<0.0001

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Flom et al. *https://doi.org/10.1016/j.jaip.2023.05.035*

10. Can children with FPIES eat baked foods?

TABLE I. Characteristics and allergic reactions of children with food protein–induced enterocolitis syndrome to milk, who participated in oral food challenge (OFC) of baked milk

Sex	Atopic background (atopic dermatitis, IgE-mediated food allergy, recurrent wheezing)	Age at last allergic reaction, mo	Reaction characteristics	Time from milk exposure to reaction, h	Treatment of last allergic reaction	Hospital admission	Age at baked milk OFC, mo	Time from last reaction to baked milk OFC, mo	Results of baked milk OFC
M	—	1	Restlessness, vomiting, diarrhea	1-3	−	−	12	11	Pass
F	—	19	Vomiting, lethargy	3-6	−	−	22	3	Pass
F	—	6	Vomiting, pallor	1-3	−	−	8	2	Fail
F	—	8	Vomiting, pallor	1-3	−	−	14	6	Pass*
M	—	3	Vomiting, lethargy	1-3	+	+	8	5	Fail
F	Atopic dermatitis	10	Vomiting, lethargy	1-3	+	+	12	2	Pass
F	—	6	Vomiting, lethargy	1-3	−	−	11	5	Pass
F	—	9	Vomiting, pallor	1	−	−	12	3	Pass
M	—	3	Vomiting, pallor, ER visit	1-3	+	+	10	7	Pass
M	—	2	Vomiting, pallor, ER visit	1-3	+	+	10	8	Fail
M	—	13	Vomiting, lethargy	1-3	+	−	14	1	Pass
F	—	12	Vomiting, pallor, ER visit	1-3	+	−	18	6	Pass

ER, emergency room.
*The participant failed the first baked milk OFC but passed a second one after 6 months.

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Faitelson Yet al. . *J Allergy Clin Immunol Pract.* (2023) 11:329–31. doi: 10.1016/j.jaip.2022.10.013

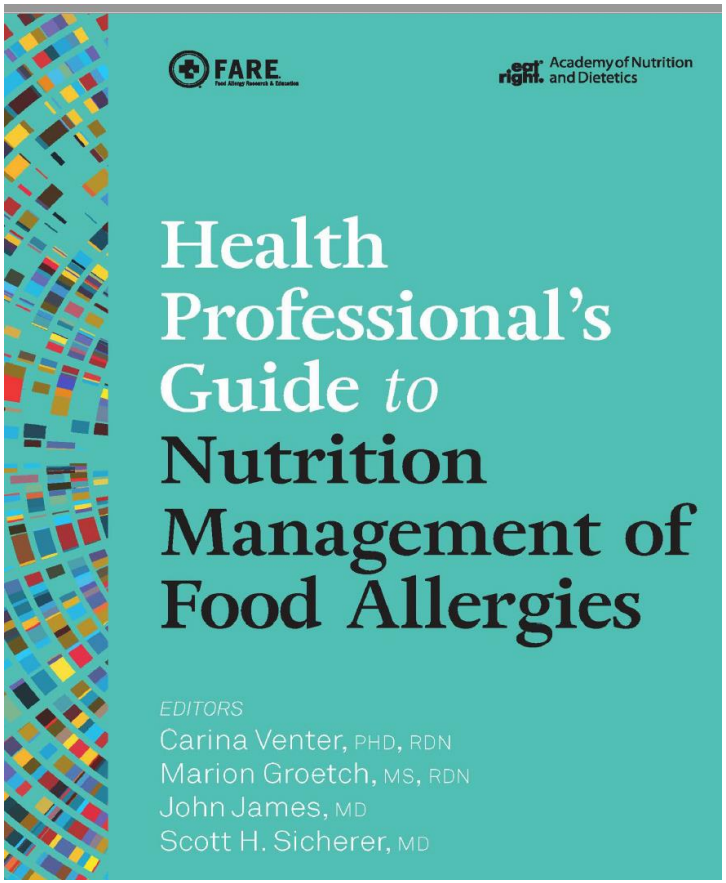
In summary

- There are many nuisances in the dietary management of FPIES
- An individualized approached is required
- Timely introduction of food is required
- Nutritional status should be monitored
- Feeding dysfunction should be assessed and managed
- Some children with FPIES can tolerate baked foods…safety issues unclear

Practical pointers for physicians

1) Measure height, weight, and plot on growth chart at every appointment to assess growth over time.
2) Timely referral to registered dietitian nutritionist for assessment of nutrient intake
3) Timely referral for feeding therapy if concerns for feeding difficulties/refusal/aversions
4) Consider iron studies (including serum ferritin), 25 [OH] vitamin D, zinc, in sera in children with multi-food avoidance and/or picky eating/ food phobia.

Thank You



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