

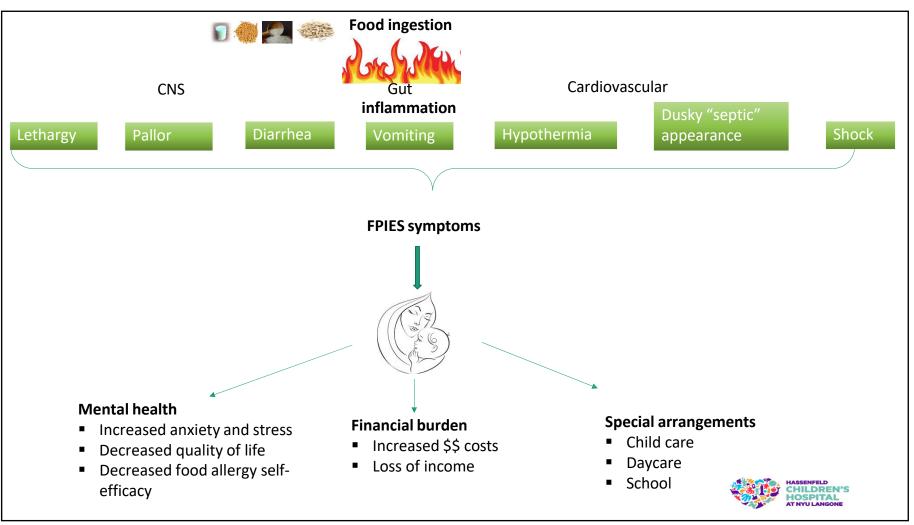
FPIES: non IgE-mediated food allergy

Delayed (1-4 hrs) projectile, repetitive emesis, lethargy, pallor, low muscle tone

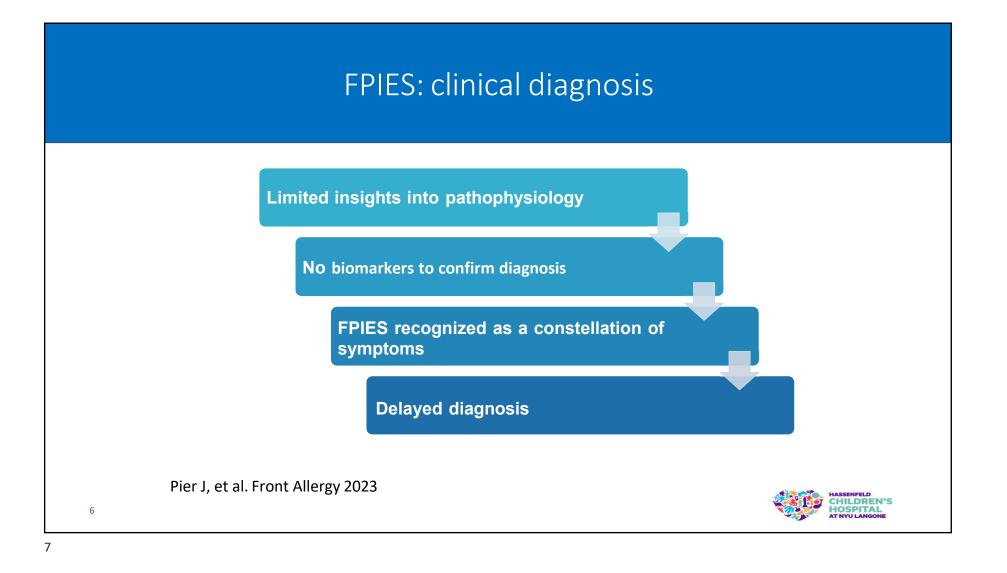
FPIES reactions can be severe:

- dehydration
- hypovolemic/distributive shock (15-20%)
- leukocytosis with left shift
- metabolic derrangements: acidosis, methemoglobinemia, low albumin/t. protein
- anemia
- elevated CRP
 - 4



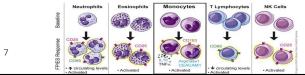


| FPIES is not rare | | | | |
|---------------------------|-------------------------------------|--------------------------------------|------------------------------------|---------------------------------------------------------------|
| | Katz et al 2011 | Mehr et al 2017 | Bellon-Alonso et al 2018 | Nowak-Wegrzy et al 2019 |
| Country | Israel | Australia | Spain | USA |
| Design | Unselected birth cohort | Population based (APSU) | Unselected birth cohort | Population-based |
| Diagnosis confirmation | OFC | Case-definition of acute FPIES | OFC | Self report |
| Foods | Cow's milk | Rice, CM, egg | CM, fish, egg yolk | n/a |
| Incidence | 0.34% in the first 12 months | 0.015% in the first 24 months | 0.7% in the first 12 months | 0.51% in less than 14 years; 0.22% in ≥18 years |



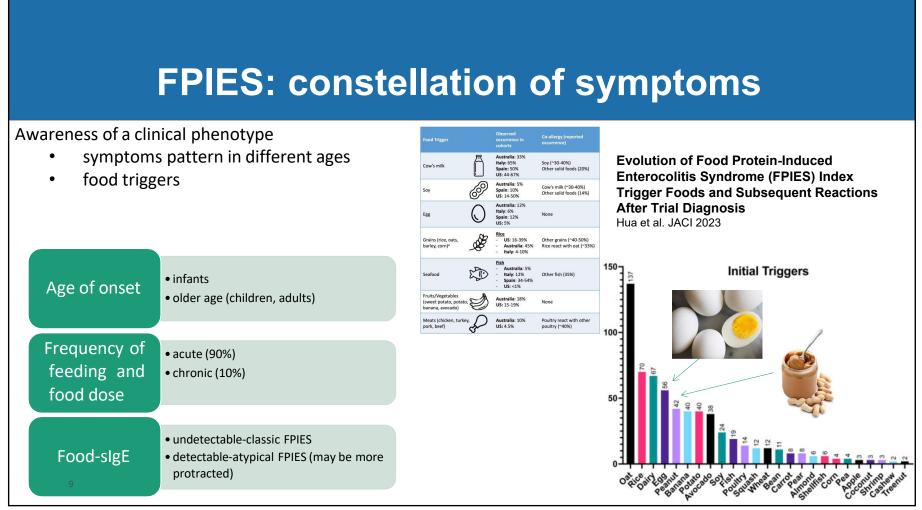


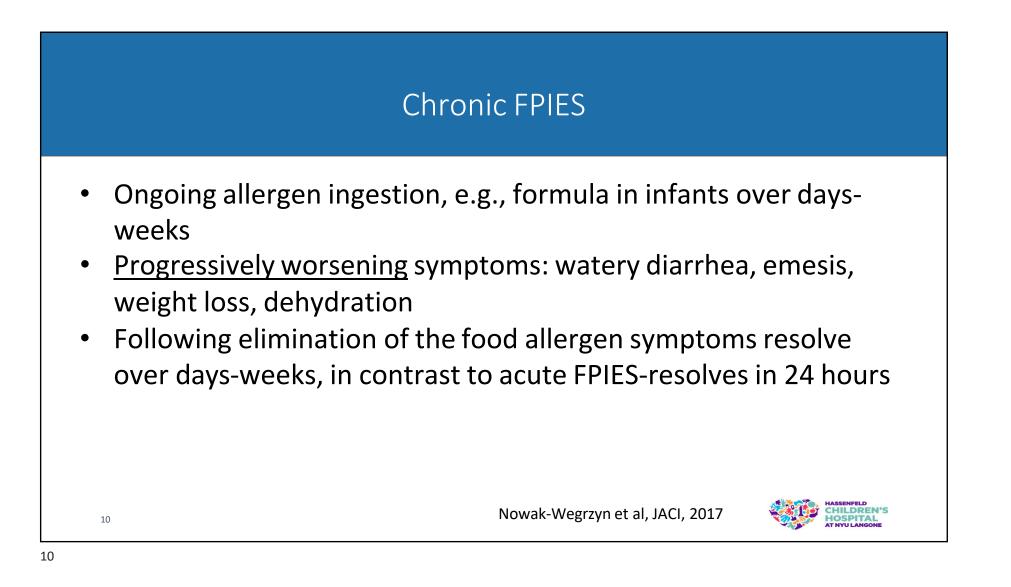
- No evidence of humoral immune responses (Caubet JC et al, JACI, 2017)
- CyTOF: Broad systemic innate activation with pan-lymphocyte activation 4 hrs after symptom onset Goswami et al, JACI 2017
- Proteomics: 3 of the top 4 biomarkers were in TH17 pathway: IL-17A, IL-17C, CCL20; their source were T cells Lozano-Ojalvo D, et al, JACI, 2021
- Innate cytokines produced by monocytes were also increased: IL-6, IL-10, oncostatin M (OSM), leukemia inhibitory factor (LIF) and TNFa, REG1a
- Metabolomics: elevated inosine Lozano-Ojalvo D, et al, JACI, 2022
- Inosine was significantly and positively correlated with REG1a (Rs=0.49, p=0.0004), a regulator of mucosal barrier function that we previously reported to be upregulated after OFC.

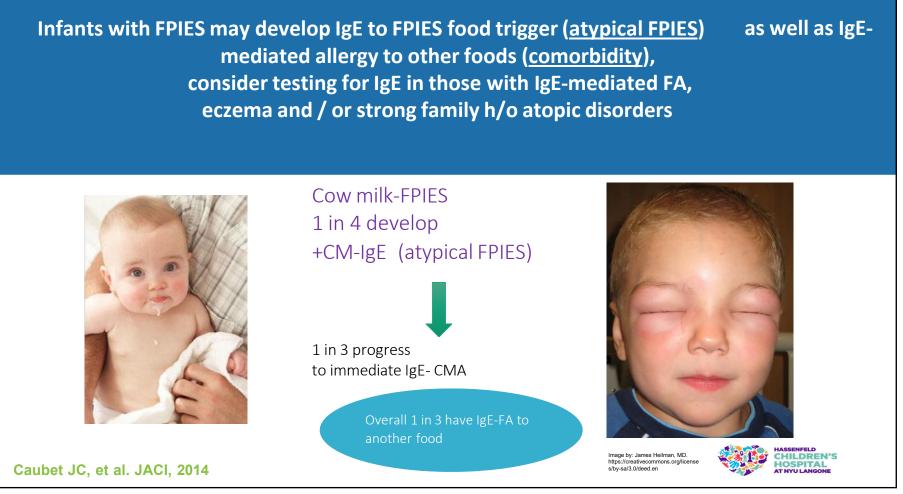


Nowak-Wegrzyn et al, JACI, 2017







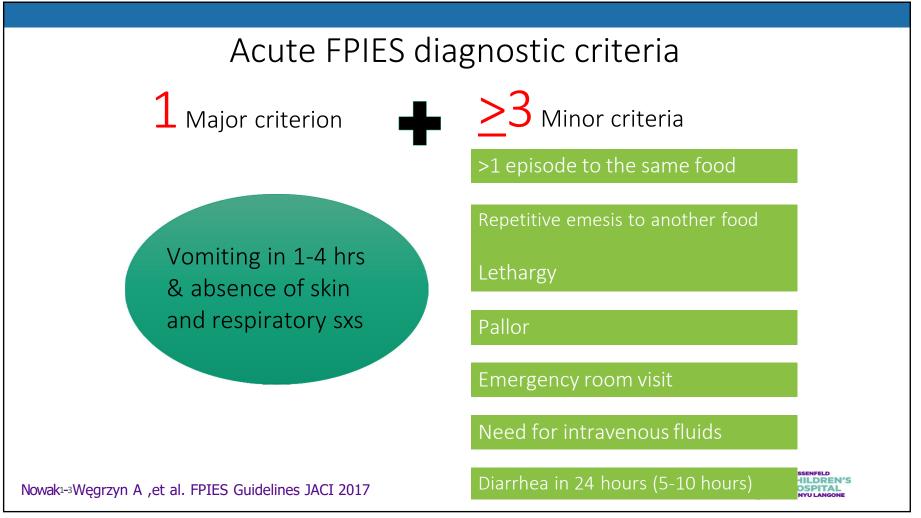


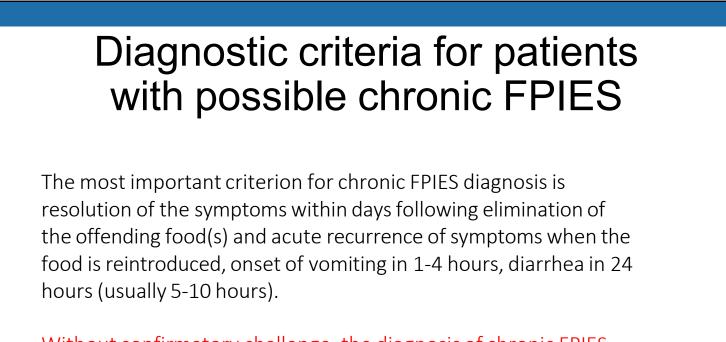
FPIES phenotypes: adult onset

- Seafood: crustaceans, fish, mollusks
- Dairy, wheat, egg
- SYMPTOMS: dramatic, severe abdominal pain, nausea, vomiting, LOC; onset up to 6 hrs
- Median age at onset 25 years (IQR 20.5-38)
- All tolerated the trigger foods before
- 22/25 (88%) female
- Median 8 reactions (IQR 5.5-10)
- Natural hx: unknown, may be persistent

Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. J Allergy Clin Immunol. 2012; Gleich GJ, Sebastian K, Firszt R, Wagner LA. J Allergy Clin Immunol Prac. 2015 Nov; Du Y, Nowak-Wegrzyn A, Vadas P. Annals of Allergy Asthma and Immunology 2018; Tan JA, Smith WB JACI in Practice 2014; Gonzales-Delgado P, et al JACI in Practice 2018







Without confirmatory challenge, <u>the diagnosis of chronic FPIES</u> <u>remains presumptive</u>.

Nowak-Węgrzyn A ,et al. FPIES Guidelines JACI 2017





FPIES OFC protocol

- No universaly accepted standardized OFC protocol
- Under physician supervision, inpatient or outpatient
- Potentially high risk procedure, requires immediate availability of fluid resuscitation
- 50% of positive challenges require treatment; consider peripheral iv acces
- Gradual (over 30 min, 3 equal doses) or a single dose administration of food protein 0.06*- 0.6 g / kg body weight, not to exceed total 3 g food protein
- If no reaction, discharge after 4-6 hours; post-reaction-6 hours and tolerating p.o. well

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Nowak-Węgrzyn A ,et al. FPIES Guidelines JACI 2017

| Interpretatio | n of FPIES OFC |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Major criterion | Minor Criteria: at least 2 present |
| Vomiting within 1- to 4-hours following consumption of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms | Lethargy Pallor Diarrhea 5-10 h after food ingestion Hypotension Hypothermia Increased neutrophil count ≥1500 above the baseline count |
| | HASSENFELD HASSENFELD HOSPITAL AT NYU LANGONE |

Interpretation of FPIES OFC: caveats

A challenge might be interpreted as positive even if only the major criterion was met, under special circumstances:

1. In adults, severe abdominal pain may appear later, up to 6 hours after food consumption and emesis may be absent

2. Early administration of ondansetron might prevent repetitive emesis, pallor and lethargy

3. Evaluation of absolute neutrophil count may not be possible in some settings

Additionally, in young patients with atypical FPIES, transient, mild skin rashes may be observed early after food ingestion and be followed by typical delayed, repetitive emesis.



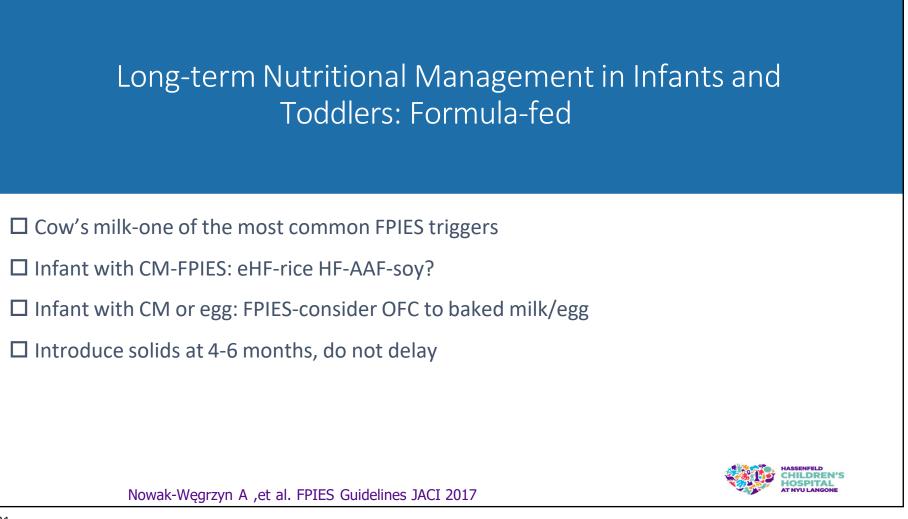
Management of FPIES emergencies

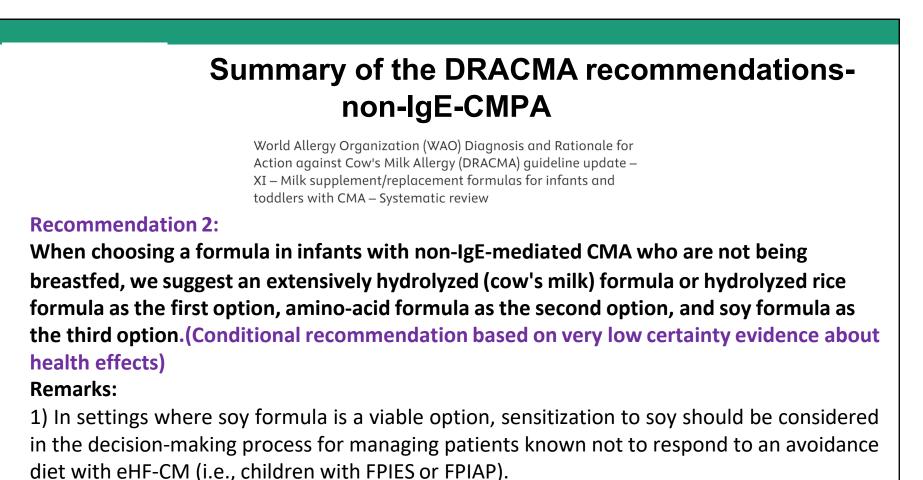
<u>SUMMARY STATEMENT 17</u>: Treat acute-FPIES as a medical emergency, and be prepared to provide aggressive fluid resuscitation as approximately 15% of patients may develop hypovolemic shock. [Strength of Recommendation: Strong; Evidence Strength: IIa; Grade: B]

- Acute: manage FPIES emergencies (rehydration, ondansetron, methylprednisolone), no role for EAI (unless atypical and concern for ana), oral antihistamines
- Spectrum of severity: not every reaction needs ED evaluation and management

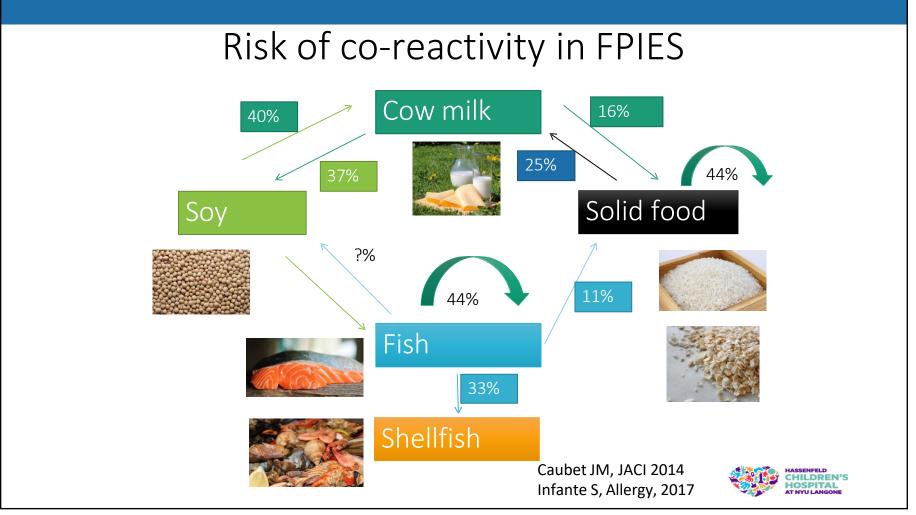
Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. Miceli Sopo S, Bersani G, Monaco S, Cerchiara G, Lee E, Campbell D, Mehr S. Allergy. 2017 Apr;72(4):545-551. doi: 10.1111/all.13033. Epub 2016 Sep 6. PMID: 27548842

| Long-term Nutritional Management in Infants and Toddlers: Breast-fed |
|-------------------------------------------------------------------------------------------------|
| □ FPIES to food proteins in maternal milk is rare; infants usually react to direct feeding of a |
| food |
| Restricting maternal diet for the baby's FPIES triggers is usually not indicated |
| □ Modification of maternal diet may be necessary for growth concerns / FTT, chronic or acute |
| symptoms |
| Introduce solids at 4-6 months, do not delay |
| Nowak-Węgrzyn A ,et al. FPIES Guidelines JACI 2017 |

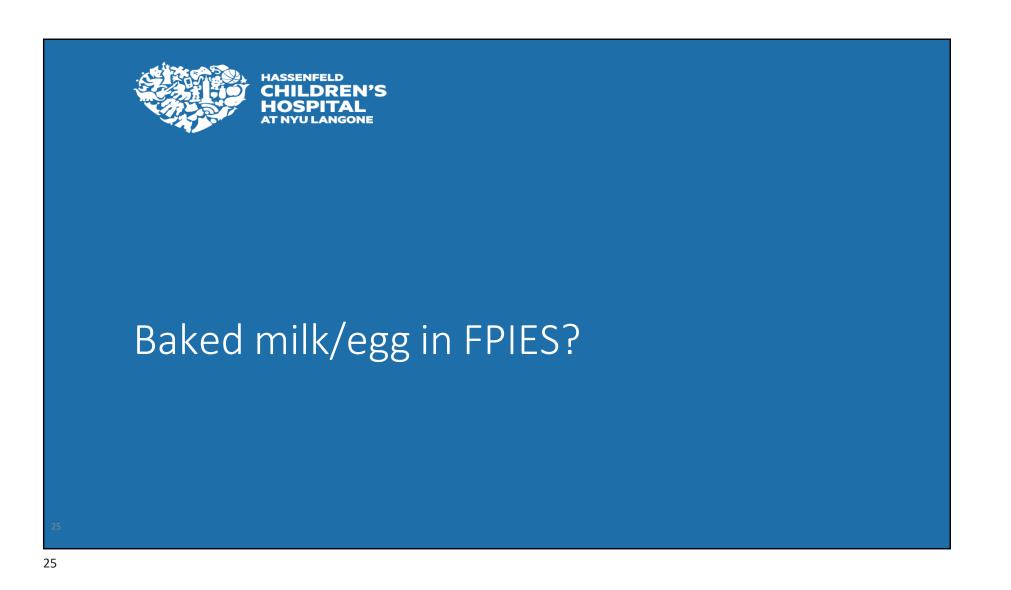


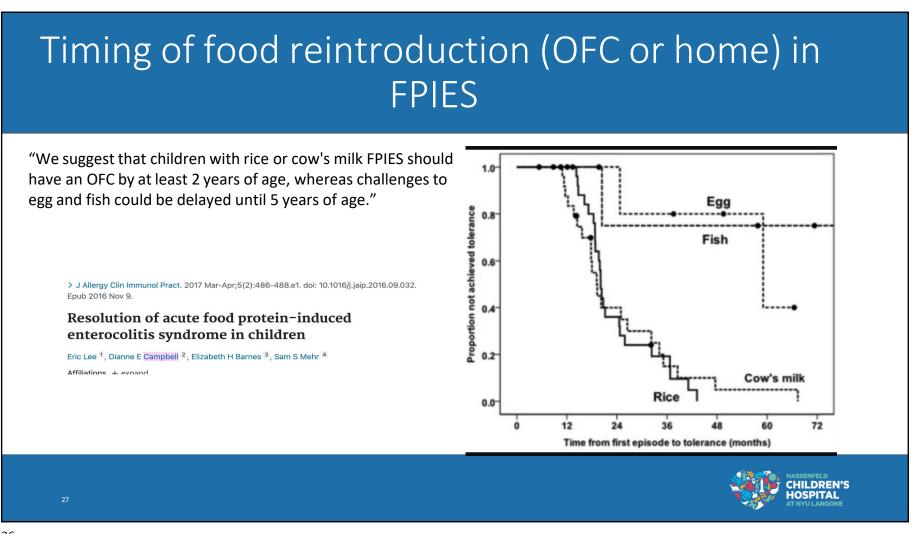






| serving. Serve tw <u>E</u> Con <u>Infant serving size</u> | od over 5-10 days. Start with 1/4 tsp vice per day (separated by 6 hours). <u>xample</u> : DAY ONE: ¹ / ₄ tsp at 9am at DAY TWO: 1 tsp at 9am and 2 ntinue increasing until reaching an 1-3 Tablespoons meat, 2 ounces fr (1-3) may be needed per day depen | Stop feeding if any symptoms. and ½ tsp at 5pm tsp at 5pm infant serving size uit or vegetable, ¼ - ½ cup grains | |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--|
| Food Group | Lower Risk | Higher Risk (unless already tolerated) | |
| Milk and alternatives | Breast milk Hypoallergenic formula Fortified coconut, flax, hemp milk (for cooking only) | Milk, Soy, Pea, Oat, and Rice beverages | |
| Meat, Seafood, Poultry | Lamb, Beef, Pork | Chicken Fish (adults), Shellfish (adults) | |
| Grains | Quinoa, Millet, Amaranth | Rice, Oats | |
| Vegetables | Broccoli, Cauliflower, Parsnip, Turnip, Pumpkin | Pea, Sweet Potato | |
| Fruit | Blueberries, Plum, Peach, Strawberries, Watermelon | Avocado, Banana | |



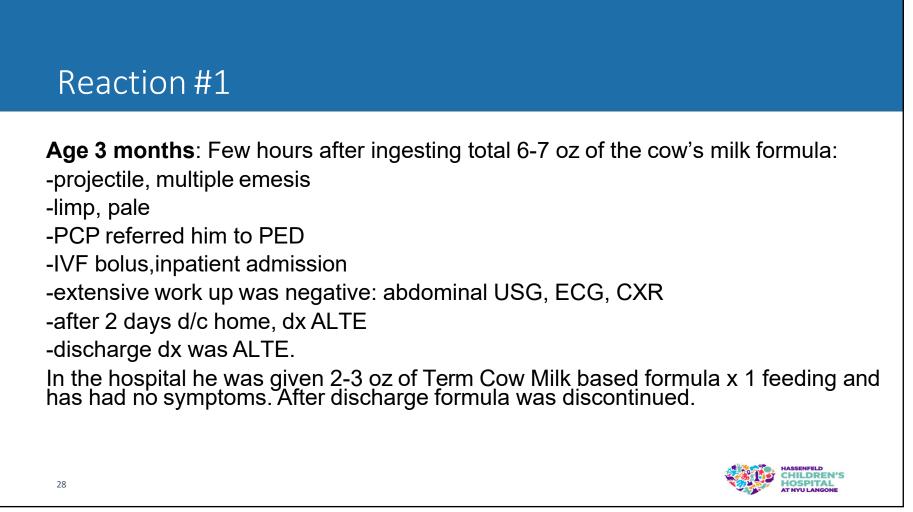






Case-13 month old male avoiding cow's milk / all dairy products due to acute infantile FPIES

Theo was fed breast milk and supplemented with Milk based term formula (CMF) x 2-4 weeks. He had no symptoms and was growing well. After that time, CMF was discontinued and he was exclusively breast-fed an unrestricted maternal diet.

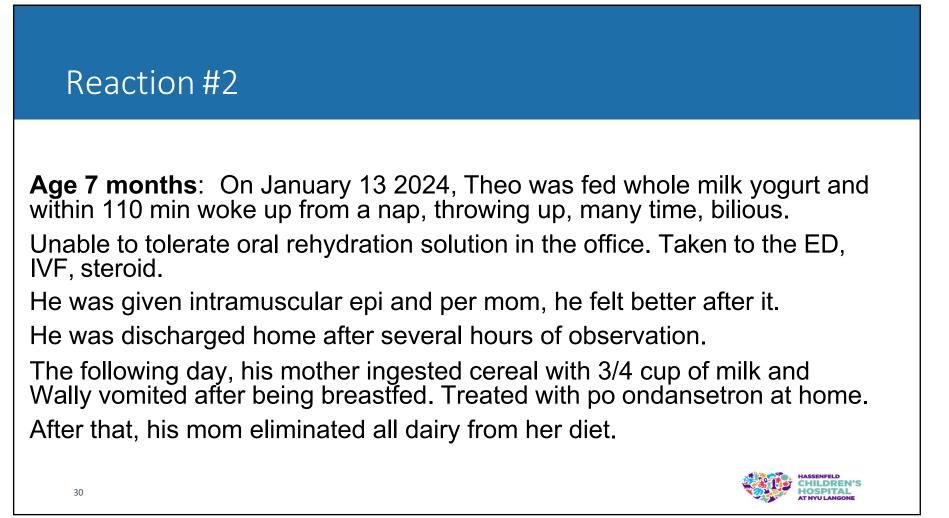


Laboratory test results at 3 month hospitalization

| 08/25/23 23:08 | Latest Reference Range & Units |
|---------------------------------------|--------------------------------|
| PH, VBG7.3 - 7.4 pH | 7.29 (L) |
| LACTATE, VBG0 - 1.9 mmol/L | 3.5 (H) |
| BASE DEFICIT, VBG0 - 2.5 mmol/L | 4 (H) |
| HEMOGLOBIN, VBG12 - 16 g/dL | 11.4 (L) |
| METHEMOGLOBIN, VBG0 - 0.5 % | 0.0 |
| CARBOXYHEMOGLOBIN, VBG0 - 2.9 % | 1.3 |
| SODIUM, VBG135 - 145 mmol/L | 134 (L) |
| POTASSIUM, VBG3.5 - 5 mmol/L | 5.1 (H) |
| CHLORIDE, VBG96 - 109 mmol/L | 102 |
| GLUCOSE, VBG74 - 106 mg/dL | 109 (H) |
| IONIZED CALCIUM, VBG1.11 - 1.3 mmol/L | 1.40 (H) |
| TEMPERATURE, VBGC | 37.0 |

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Theo: allergy evaluation

Age 7 months (4 days after his reaction): h/o mild AD, no topical CS, no rash on exam Diet:

- breast-feeding, supplemented with whey-based eHF with lactose
- no solids; Previously tolerated (starting from age 5-6 mo, tolerated banana, apple, sweet potato, avocado, spelt cereal, peanut x 1

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Testing and diagnosis

SPT (mm):

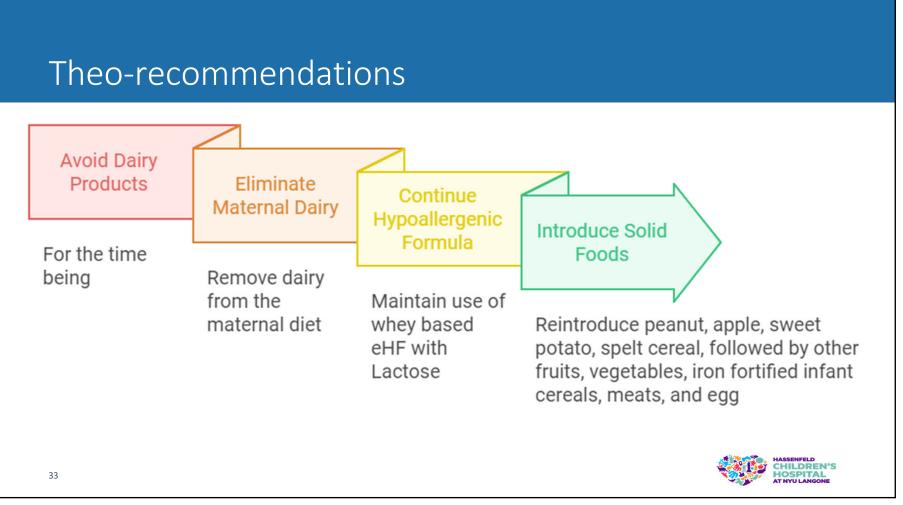
saline 0/0, histamine 5.5/20, cow's milk 4/22.5

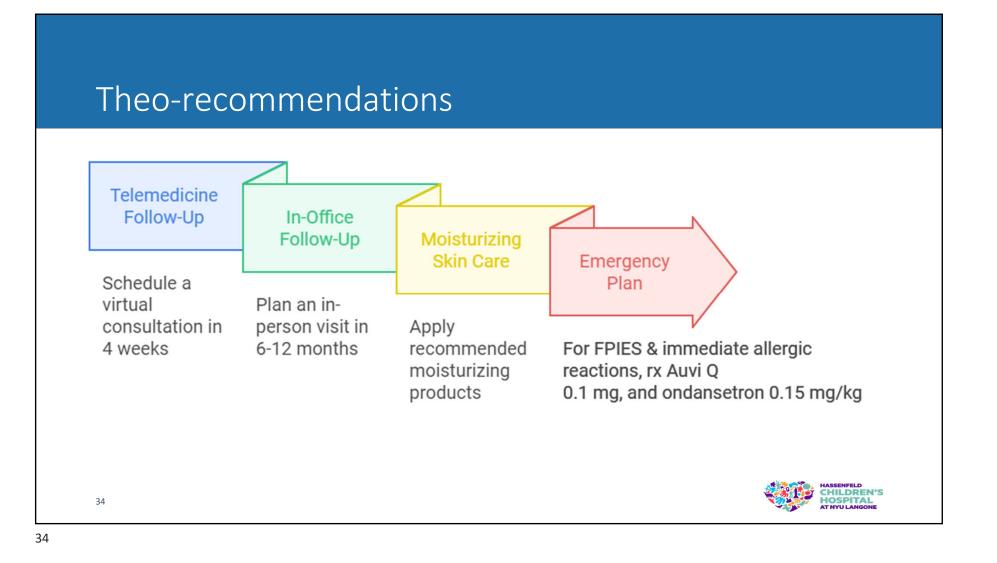
Diagnosis:

- 1. Infantile acute FPIES to cow's milk/dairy products-atypical, IgE+
- 2. Mild atopic dermatitis/eczema

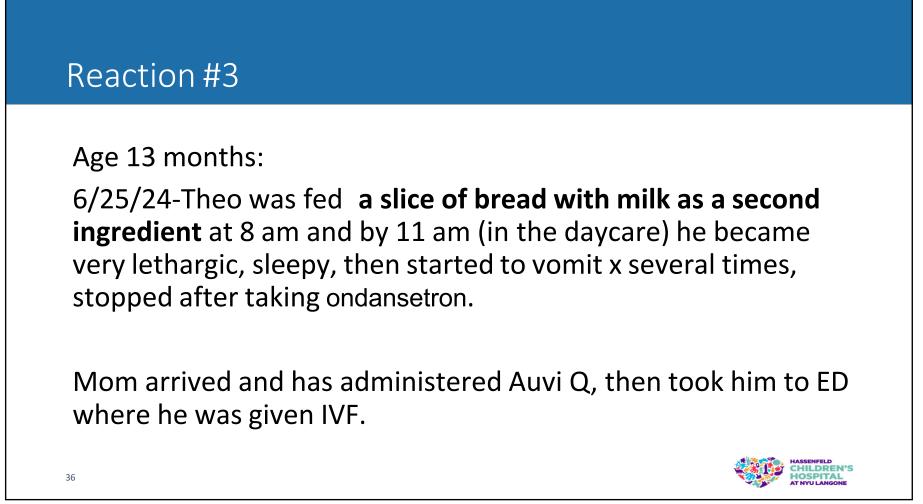


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| FPIES (Food Protein-Indu | <u> </u> | | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| AVOID these foods strictly: | bate of birth. | prognt. it | song (oncie one) | TARE FUUD ALLERGY & ANAP | HYLAXIS EMERGENCY CARE PL |
| History of Severe FPIES react 911 if the individual has ANY symp | | | hway and call | Name: | D.O.B.: PLACE PICTURE |
| IgE-mediated food allergy (i.e. Emergency Plan if an individual ha ondansetron and anaphylaxis mediated and anaphylaxis | s symptoms of hives, itching | | | Allergy to: | eaction) [] No |
| SIZERE PPIES SYMPTOMS What to look for: delayed onset (1-4 hours) severe abdominal pain and nausea following food inges petitive vomiting very pale or looks blue/grey faintness lethargy or unresponsivene or unable to tolerate liquids MILD FPIES SYMPTOMS What to look for: > delayed onset (1-4 hours) > delayed onset (1-4 hours) | or ition 2. Give dose of onda 3. Notify parents /em 4. Monitor symptoms 6. If sleepy or unres choking on vomit. | earest Emergency Room, if qu meetron (20/mg*) as prescribe ergency contact a ponsive, place individual on the no vomiting for 20-30 minutes, ps as tolerated. | icker d below ir side to prevent | Extremely reactive to the following foods: THEEEPORE: 1 If checked, give epinephrine immediately for AY symptoms if the a 1 If checked, give epinephrine immediately if the allergen was definit FOR ANY OF THE FOLLOWING: SEVERE SYMPTOMS UNG LUNG Short of breath, whereing, severe cough public, weak, regetive cough public, weak regetive cough public, wea | - |
| abdominal pain, nausea followi food ingestion | 3. Monitor symptoms | etron (Zofran [®]) as prescribed b | | | SYSTEM AREA, GIVE EPINEPHRINE. |
| vomiting | If sleepy, place individual on their side to prevent choking on vomit. If there has been no vomiting for 20-30 minutes, attempt to give clear liquids/ice-chips/breast milk as tolerated. <u>Call 911</u> if symptoms become savere, or individual appears <u>dehydratad</u> from repetitive vomiting (e.g., dry lips and tongue, not making saliva, tears, not urinating) | | SKIN GUT OTHER COMBINATION Marp hves over Repetitive Feeling for different body, widespread vomiting, severe something bad is redness diarthea about b hoppen, aminity, contraine | FOR MILD SYMPTOMS FROM A SINGLE SYSTEM AREA, FOLLOW THE DIRECTIONS BELOW: 1. Anthistamines may be given, if ordered by a healthcare provider. 2. Stay with the person; alert emergency contacts. 3. Watch closely for changes. If symptoms worsen, | |
| | MEDICATIONS | : | | 1. INJECT EPINEPHRINE IMMEDIATELY. | give epinephrine. |
| Ordansetron hydrochloride (Zot Orally disintegrating tablet: 4 mg_ May repeat the dose once if the i Acetaminophen (Tylenoff) Table | 8 mg placed on top of adividual vomits within 10 minut | tongue Liquid dose | al dose 16 mg | Call 911. Fait them the child is having anaphytaxis and may need apinophrine when they arrive. Consider aying additional madications following epinephrine: Analytic thronchodilator) if wheeding Inshaler (thronchodilator) if wheeding Lay the person flat, raise less and keep warm. If breathing is | MEDICATIONS/DOSES Epinephrine Brand. Epinephrine Dose. [] 0.15 mg IM [] 0.3 mg IM |
| PROVIDER Name | Signature | Phone number | Date | difficult or they are vomiting, let them sit up or lie on their side. If symptoms do not improve, or symptoms return, more doses of | Antihistamine Brand or Generic: |
| SCHOOL NURSE Name | Signature | Phone number | Date | epinephrine can be given about 5 minutes or more after the last dose. • Alert emergency contacts. | Other (e.g., inhaler-bronchodilator if wheezing): |
| | | | | Transport them to ER even if symptoms resolve. Person should remain in ER for at least 4 hours because symptoms may return. | |



Reaction #3: lab test results

| | 06/25/24 |
|--------------------------------|----------|
| WHITE BLOOD CELL COUNT | 20.2 (H) |
| RED BLOOD CELL COUNT | 4.31 |
| HEMOGLOBIN | 11.5 |
| HEMATOCRIT | 35.4 |
| PLATELET COUNT | 334 |
| NEUTROPHILS % | 59 |
| LYMPHOCYTES % | 23 (L) |
| MONOCYTES % | 15 (H) |
| EOSINOPHILS % | 0 |
| BASOPHILS % | 0 |
| NUCLEATED RBC, ABSOLUTE | 0.00 (L) |
| DIFFERENTIAL TYPE | MANUAL |
| LYMPHOCYTE ABSOLUTE CALCULATED | 5.3 |
| ATYPICAL LYMPHOCYTES % | 3 (H) |
| NEUTROPHIL ABSOLUTE CALCULATED | 11.9 (H) |
| ALLERGEN MILK COW IGE | 5.31 (H) |
| IMMUNOGLOBULIN E | 129 (H) |
| Tryptase (AA1) | 14.6 (H) |

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