

Food Protein-Induced Enterocolitis Syndrome



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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.

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List of Design Committee Members: Stephanie A. Leonard, MD, and Mirna Chehade, MD, MPH

Learning objectives:

1. To recognize key diagnostic features of food protein-induced enterocolitis syndrome (FPIES).
2. To understand treatment and management of FPIES.
3. To provide anticipatory guidance to families of infants with FPIES.

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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 syndrome; Food allergy; Failure to thrive; Vomiting

A 10-month-old full-term male presented with a history of intermittent vomiting, anemia, feeding difficulties, poor weight gain, and loss of developmental milestones. He had no other medical or surgical history, but had a family history of asthma, eczema, and diabetes.

Exclusively breast-fed from birth, the patient was well until age 2 weeks when he experienced projectile postprandial emesis, increased sleepiness, irritability, decreased feeding, and mucus in

his stools. Diagnosed with gastroesophageal reflux disease by pH probe and upper gastrointestinal series, he was treated with ranitidine and metoclopramide. No blood was detected in the stool; however, as a precaution, maternal avoidance of cow's milk was recommended without immediate improvement. The patient's symptoms improved gradually on the medications, and by age 5 to 6 months the patient's emesis resolved and the medications were discontinued.

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Solid foods were introduced at age 6 months. Initially, the patient tolerated oat and several fruits and vegetables. When he cycled back to sweet potato, squash, and avocado about 1 month after initial tolerance of the foods, he developed repetitive vomiting 3 to 4 hours after separate ingestions of each of the foods and appeared limp, pale, and lethargic as per the parents. The first reaction was treated in the emergency department with intravenous fluids and ondansetron; otherwise, he recovered from subsequent episodes at home. An outside allergist diagnosed him with food protein-induced enterocolitis syndrome (FPIES) to these foods.

By about age 7 months, all solids had been discontinued by the parents because of fear of reactions, and the patient was breast-feeding exclusively. At age 9 months, he was admitted to an outside hospital for poor weight gain, anemia, and loss of developmental milestones (not rolling over anymore, not pulling to stand). He appeared pale and tired, but otherwise his examination and vital signs were normal. His hemoglobin level was 10.7 g/dL and mean corpuscular volume 69 fL. He had a low iron level and normal total iron-binding capacity. No blood was found in his stool. He had normal serum amino acids, urine organic acids, brain magnetic resonance imaging, and food-specific IgE levels to common foods. The patient was discharged home when his weight stabilized after intravenous fluids and frequent breast-feeding. He was scheduled for allergy and gastroenterology follow-ups to continue the workup as an outpatient.

We evaluated the patient at age 10 months. His height and weight were in the 40% to 50% tiles but with little to no weight gain for the past 3 months and persistent developmental delay. No new foods had been added to his diet. Skin prick testing was negative to all foods screened. His anemia was thought likely due to exclusive breast-feeding, his poor weight gain due to low calorie diet secondary to little interest in eating, and his loss of developmental milestones due to poor nutrition.

Strict avoidance was recommended of sweet potato, squash, avocado, as well as other common FPIES triggers (*milk, soy, rice, oat, wheat, legumes, poultry*) until challenges could be performed. Corn was introduced at home because he had recently tolerated a semisolid medical food made with corn syrup solids and corn is not a common FPIES trigger. Iron and an amino acid–based formula supplementation were started, and feeding therapy was initiated. Inpatient food challenges were performed at age 13 months to a fruit, a grain, and 2 proteins taking into consideration his nutritional deficiencies. The patient showed tolerance to banana, wheat, and beef. One hour after ingestion of chicken, the patient developed emesis, lethargy, and pallor treated with intravenous ondansetron and fluids. Other fruits, vegetables, and grains were slowly added to his diet at home.

At age 16 months, the patient was tolerating many foods except for sweet potato, squash, avocado, and chicken. Cow's milk was still avoided. His anemia had resolved, his feeding improved with therapy, and he was gaining weight and meeting developmental milestones.

FPIES typically presents with delayed vomiting 1 to 4 hours after ingestion, pallor, lethargy, and sometimes diarrhea.¹ Chronic forms may exist with continuous exposure, leading to failure to thrive. This case illustrates that even an intermittent acute FPIES presentation can develop chronic sequelae. It is not uncommon for infants to have feeding difficulties or families to be reluctant to continue trying new foods after multiple reactions. Without expansion of the diet, nutritional deficiencies

can result in growth and development stunting. In this case, inpatient oral food challenges were offered to find some safe foods that the family could start with and to give the family confidence to try additional foods at home. Because FPIES reactions do not always appear with the first ingestion, giving anticipatory guidance and educating the family about management of acute reactions is important.

There is debate over whether common FPIES foods should be prophylactically avoided if an infant is not already tolerating them, at least until age 1 year when they are presumed to be outside the window of susceptibility. Some of the most common FPIES triggers in the literature include cow's milk and soy, grains (rice, oat), sweet potato, squash, poultry, fish, egg, legumes (including peanut), and banana.² Wheat FPIES has been related to other grain FPIES^{2,3}; however, it is not seen as often as oat and rice FPIES. This is thought to be because oat and rice are typically added to infants' diets first, and then when FPIES develops, wheat is often prophylactically avoided. The uncertainty regarding prophylactic avoidance likely comes from studies reporting that 6% to 34% have multiple FPIES triggers, with variation among populations. In US cohorts, for example, 37% to 44% of children with milk FPIES also had soy FPIES, and many had solid food FPIES as well.³ Also, in US cohorts, 40% to 50% with grain FPIES reacted to 2 or more grains.

Laboratory findings in FPIES often include increased absolute neutrophil count (typically peaking at 6 hours after symptoms begin) and thrombocytosis, although this was not picked up in this patient possibly because of delayed timing of when the tests were drawn after symptoms started. Diagnosis is clinical, with oral food challenges if needed. Testing to foods is often negative, which is expected for a non-IgE-mediated food allergy. However, less than 10% of patients may demonstrate positive skin prick test results, and up to 11% to 24% may have or may develop during a period of avoidance detectable specific IgE levels to trigger foods. Those with positive testing tend to have more protracted courses and the potential for IgE-mediated reactions must be considered. FPIES is underrecognized and therefore delays in diagnosis and misdiagnoses are common, and the diagnosis is often not made until after several reactions have occurred.

Treatment of acute FPIES reactions involves rehydration with oral or intravenous fluids. In some more severe cases, physicians may administer corticosteroids or ondansetron, although the efficacy of these medications is still being studied. Management involves food trigger avoidance. Only rare cases of acute FPIES have been reported after breast-feeding due to maternal ingestion of the trigger food; therefore, it is not recommended that mothers avoid trigger foods when nursing unless a reaction after breast-feeding has been documented. Most children who develop FPIES in infancy outgrow it by school age, but these data have also been shown to vary in different populations and with different food triggers.

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Food Protein-Induced Enterocolitis Syndrome

AAAAI 2016: 1002 Difficult Cases

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Case 1 History of Presenting Illness

- 10 mo. old FT male presents with history of:
 - Episodes of vomiting
 - Anemia
 - Feeding difficulties
 - Loss of developmental milestones
- Birth History: Birth weight 7lbs 13oz. Diagnosed mild jaundice, no treatment needed.
- Family History: Significant for asthma, eczema, diabetes.
- Social History: Lives with family. No daycare.

Case 1 History of Presenting Illness

- Exclusively breastfed from birth. Well until age 2 weeks when he developed projectile postprandial emesis x 3 and over the next 2-3 days had increased sleepiness, irritability, decreased feeding, and mucus in his stools.
- Diagnosed with GERD by pH probe and upper GI series, treated with ranitidine & metoclopramide, and mother restricted top 8 allergens + beef.
- By age 5-6 months, the postprandial emesis had resolved, his reflux medications were discontinued, and his mother liberalized her diet and continued to breastfeed.

Case 1 Food introduction

- At age 6-8 months, solids were trialed in 3 day cycles. Initially tolerated oatmeal, sweet potato, squash, avocado, apples, peas, zucchini, pears, broccoli.
- When cycled back to the following foods: **sweet potato, squash, avocado**, 3-4 hours after ingestion the patient developed repetitive vomiting and was limp, pale and lethargic. He experienced repeat episodes (x2 each) to both sweet potato and avocado.
- After the first sweet potato reaction, he was treated in the ED, receiving IV fluids and ondansetron. He recovered at home after the other reactions.
- The patient was diagnosed with food protein-induced enterocolitis syndrome (FPIES) by a local allergist.

Case 1 Hospitalization

- Admitted at age 9 months for:
 - Poor weight gain
 - Anemia
 - Loss of milestones
(not rolling over anymore, not pulling to stand)
- All solids had been stopped and the patient was only breastfeeding.
- Vitals: temp 98.6, HR 126, BP 97/50, RR 45, O2 sat 99%, pale and tired-appearing, otherwise exam normal

Case 1 Work-up

- Hgb 10.7/Hct 33, MCV 69, low iron, normal TIBC
- Serum IgE food panel testing all undetectable
- Stool occult blood negative
- Serum amino acids and urine organic acids – normal
- Brain MRI – normal

Case 1 Outpatient Allergy Evaluation

- At age 10 months, the patient was still breastfeeding only without solids or formula.
- Ht/Wt was 40-50%-tile but he had had little to no weight gain in past 3 months and had developmental delay.
- Skin prick test: negative to sweet potato, squash, avocado, chicken, turkey, pork, codfish, tuna, salmon, egg, wheat, oat, rice, white potatoes, broccoli, spinach, orange, banana, peach, pear, apple

Case 1 Assessment

- FPIES to sweet potato, squash, and avocado
- Anemia due to poor feeding and exclusively breastfeeding
- Poor weight gain due to low calorie diet secondary to little interest in eating
- Loss of developmental milestones due to poor weight gain

Case 1 Recommendations

- Patient to strictly avoid sweet potato, squash, avocado, as well as other common FPIES triggers until challenges
- May introduce corn at home (had recently tolerated semi-solid medical food made with corn syrup solids)
- Start iron supplementation
- Referred to occupational therapy for feeding therapy
- Inpatient food challenges done at age 13 months
 - Tolerated banana, wheat, beef
 - Developed emesis, lethargy, and pallor 1 hr after ingestion of chicken

Case 1 6-month Follow-up

- Weaned to amino acid based formula
- Tolerating: corn, wheat, apple, pork, beef, prune, broccoli, quinoa, coconut, eggs, blueberries, carrots, chickpeas, pears, peaches, grapes
- Anemia resolved, feeding improved, gaining weight and meeting developmental milestones

FPIES

- Clinical manifestations: delayed (1-4 hr) repetitive vomiting, diarrhea, dehydration, pallor and lethargy; chronic forms may exist with continuous exposure, leading to failure to thrive
- Laboratory findings: increased absolute neutrophil count (typically peaking at 6 hours), thrombocytosis; if severe or prolonged: metabolic acidosis, methemoglobinemia, anemia, hypoalbuminemia, and eosinophilia has been seen
- Diagnosis: is clinical, with oral food challenges if needed; is under-recognized and therefore delays in diagnosis and misdiagnoses are common; <10% have positive skin prick testing and 11-24% may have food-specific IgE levels [Leonard et al. Pediatr Clin North Am 2016]
- Treatment/Management: PO or IV fluids, steroids and ondansetron may be used when vomiting is severe or persistent; food avoidance; maternal avoidance of trigger is not advised while breastfeeding unless an acute reaction has been reported
- Prognosis: depends on population; most outgrow by school age

Common FPIES foods

- Milk, soy
 - Grains (rice, oat, wheat)
 - Sweet potato, squash
 - Chicken/turkey
 - Fish
 - Egg
 - Legumes (incl. peanut)
 - Banana
- In studies, 6-34% have multiple triggers.
 - In U.S. cohorts: 37-44% with milk FPIES also had soy FPIES, many had solid food FPIES as well.
 - In U.S. cohorts: 40-50% with grain FPIES reacted to ≥ 2 grains.

Leonard et al. Pediatr Clin North Am 2016