



Letters

Cow's milk–associated chronic food protein–induced enterocolitis syndrome exacerbated by extensively hydrolyzed formula



Food protein–induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE)–mediated food allergy predominantly seen in infancy or early childhood. Although its incidence has been steadily increasing over the past 2 decades, it is still often misdiagnosed because of lack of awareness.¹ It presents in 2 forms: acute and chronic.

Acute FPIES is the better classified of the 2 and involves repetitive vomiting, diarrhea, pallor, dehydration, and in severe cases, metabolic acidosis within 1 to 4 hours after ingestion of the culprit food.¹ Although it can develop at any age, it predominantly occurs in infancy before 12 months of age. The most common foods implicated are cow's milk and soy, but it also can occur with foods such as rice, oat, wheat, poultry, fish, egg, and peanut.² In contrast, chronic FPIES occurs before the age of 3 months and is caused by frequent ingestion of either cow's milk or soy formula. The clinical phenotype includes protracted diarrhea, vomiting, hypoalbuminemia, and poor weight gain.¹ Avoidance of the offending food remains the standard of care. This often leads to a transition from cow's milk–based or soy-based formula to hypoallergenic formulas, including extensively hydrolyzed casein–based formula (eHCF) or amino acid–based formula (AAF).

A 2-month-old female baby girl came to the emergency department with a 5-day history of bloody diarrhea with mucus and frequent emesis. The patient had initially been exclusively breastfed but began supplementation with a cow's milk–based formula because of poor weight gain on day 19 of life. At the time of presentation, she had declined from the 56th percentile for weight to the 1.5th percentile. She was initially believed to have cow's milk protein–induced allergic proctocolitis and was switched to an AAF. Her bloody diarrhea resolved, but her feeding goals were not reached because of frequent emesis for the following 3 days. Consequently, formula was changed to an eHCF via nasogastric tube.

She quickly deteriorated after starting eHCF over the next 4 days, with listlessness and signs of dehydration, including sunken fontanelles with multiple metabolic abnormalities. Her blood work was notable for hyponatremia to 128 mEq/L, metabolic acidosis with a

pH of 7.18, lactic acidosis at 2.6 mmol/L, and hypoalbuminemia to 2.1 g/dL (Table 1). Food-specific IgE and skin prick testing was not performed.

By endoscopy, gross visualization of the esophagus, stomach, and duodenum were normal. Duodenal biopsy revealed patchy active inflammatory changes with partial villous atrophy, and focal neutrophilic and eosinophilic cryptitis without granulomas. An overall increase of eosinophils was not noted. Colonoscopy showed patchy colitis with colonic biopsies consistent with acute and chronic inflammatory cells in the lamina propria, neutrophilic cryptitis, and multiple crypt abscesses. Infectious staining was negative for cytomegalovirus and adenovirus on all biopsy specimens.

Extensive infectious and immunodeficiency workups were nonrevealing. Based on clinical presentation, acute worsening with reintroduction to eHCF, and characteristic blood work with hypoalbuminemia, metabolic acidosis, and neutrophilia, chronic FPIES from cow's milk was suspected. Strict dairy avoidance was continued, and all soy products were discontinued because of high coreactivity of up to 40% in US studies. She clinically improved over a 1-week period with total parenteral nutrition and oral diet restriction. Laboratory results also returned to normal levels. AAF was introduced and was well tolerated, and she was weaned off total parenteral nutrition.

On outpatient follow-up, our patient continued to avoid cow's milk and soy without any accidental ingestions. At 5 months after discharge, she had improved to the 22nd percentile for weight while on an exclusive AAF diet, and her family reported no persistent diarrhea or vomiting. No additional tests or interventions were performed, and her diet was advanced with vegetables, fruits, and grains. If progress continues along her growth curve, oral food challenges will be considered in 1 to 2 years for cow's milk and soy.

Table 1

Laboratory Levels for Presented Case Compared With the Most Typical Laboratory Findings in Chronic Food Protein–Induced Enterocolitis Syndrome^a

	Patient	Typical findings indicative of chronic FPIES
Serum albumin ^b (g/dL)	2.1	Hypoalbuminemia (<3.5)
Leukocyte count(thousand/mm ³)	44.7	Leukocytosis (>19.5)
Neutrophil count (thousand/mm ³)	26.4	Neutrophilia (>5.10)
Eosinophil count (thousand/mm ³)	0	Eosinophilia (>1.0)
Platelet counts (thousand/mm ³)	575	Thrombophilia (>600)
Serum pH	7.18	Can have metabolic acidosis (<7.35)
Lactic acid (mmol/L)	2.6	Can be elevated (>2.5)
Weight gain per day ^b	9.9 g	Less than 10 g

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

^aPatient met 6 of 8 criteria.

^bIndependent predictors of chronic FPIES.³

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The diagnosis of chronic FPIES remains challenging and poorly defined because of the nonspecific nature of symptoms. Based on International consensus guidelines by the American Academy of Allergy, Asthma & Immunology, the most important criterion for diagnosis is resolution of symptoms after removal of the offending food from the diet, along with recurrence of acute symptoms on reintroduction.¹ At this time, no specific biomarkers exist for chronic FPIES, but several characteristic laboratory findings have been described. Leukocytosis with a neutrophil predominance, eosinophilia, and thrombophilia are often observed.⁴ Based on observations by Hwang et al,⁵ weight gain of less than 10 g/day and hypoalbuminemia are independent predictors of chronic FPIES.⁵ In severe cases, metabolic acidosis and methemoglobinemia have been described, but the sensitivity and specificity of these derangements are low.³ Our patient met 6 of 8 common laboratory findings seen with chronic FPIES (Table 1). Although an oral food challenge remains the gold standard for FPIES diagnosis, it was not performed because of the characteristic improvement with the elimination of cow's milk and soy products, which aligns with the most current guidelines.¹

Allergy testing, including serum specific IgE, skin prick, and patch testing, has not been shown to be reliable in diagnosing FPIES.¹ Endoscopic biopsies are also nonspecific and can range from normal to involving friable colonic mucosa with crypt abscesses, villous atrophy of the small intestine, and cellular infiltration throughout the gastrointestinal tract with plasma cells, eosinophils, and mast cells.^{2,6}

Elimination of the offending food is the cornerstone in the long-term management of chronic FPIES, which includes transitioning from cow's milk-based formula to hypoallergenic formulas. Improvement is typically observed within 3 to 10 days.^{1,7,8} Extensively hydrolyzed casein-based formula is often used as the first-line agent because of its availability and high tolerance amongst patients. To the best of our knowledge, our patient is the first reported case of chronic FPIES to eHCF. This is in contrast to acute FPIES, in which 10% to 40% remain symptomatic on eHCF.^{2,9,10}

In summary, our case demonstrates the importance of high clinical suspicion for chronic FPIES in young infants with intermittent vomiting, diarrhea, and FTT. Although switching from cow's milk-

based or soy-based formula is paramount in management, some may remain symptomatic on eHCF. If deterioration or lack of improvement is noted on eHCF, AAF should be considered immediately as an alternative therapy.

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Does the asthma visual analog scale relate to the Asthma Control Questionnaire?



Control-based asthma management, comprising a continuous cycle of assessment, adjustment, and review of treatment response, is recommended by the Global Initiative for Asthma (GINA) guidelines.¹ Objective measurement and documentation of asthma control in UK clinical practice are often poor. In the National Review of Asthma Deaths (United Kingdom), of the 69% of patients who had an asthma review before their death, only 27% had any formal assessment of asthma control.² Therefore, having a simple but effective tool to detect changing severity of asthma is important.

The Asthma Control Questionnaire 6 (ACQ-6) is a widely used and well-validated nonbinary metric that strongly predicts future exacerbations.³ It demarcates controlled, partially controlled, and uncontrolled based on cut point scores of less than 0.75, 0.75 to less than 1.5, and 1.5 or greater, respectively.⁴ The asthma visual analog scale (VAS) is a 10-cm continuum that indicates the overall symptom

burden⁵ and can be patient or physician administered. It has been demonstrated, in a large Japanese population, to discriminate among GINA-defined categories of controlled, partially controlled, and uncontrolled as less than 1.5 cm, 1.5 cm to less than 7.19 cm, and 7.19 cm or greater, respectively.⁵ The VAS is also effective in adolescents at detecting changes in asthma symptoms, reflecting more detailed multi-item asthma diaries.⁶ We have evaluated for the first time, to our knowledge, whether VAS correlates to ACQ-6 and if the predefined GINA cut points relate to ACQ-6-defined levels of control.

We retrospectively analyzed 84 patients who volunteered for asthma screening in clinical trials at the Scottish Centre for Respiratory Research. All patients gave written informed consent for their anonymized screening data to be used. Patients had to have a physician-based asthma diagnosis for at least 3 months before attending screening and be free of an asthma exacerbation that required steroids for 3 months before screening. Patients underwent basic spirometry (Micromedical, Chatham, United Kingdom), exhaled nitric oxide (FeNO) measurement (NIOX MINO, Circassia Ltd, United Kingdom), and recording of medical history and concomitant medications and completed the ACQ-6 (Qoltech Ltd) and VAS questionnaires. As per Ohta et al,⁵ for the VAS, patients were

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