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Recognizing Neonatal FPIES: Key Clues for Early Diagnosis and Treatment

You're listening to *Clinician's Roundtable* on ReachMD, and this is an *AudioAbstract.* I'm Ryan Quigley, and today, we're exploring neonatal food protein-induced enterocolitis syndrome—commonly known as N-FPIES—with a focus on its presentation, unique underlying pathology, and diagnostic challenges.

FPIES has long been recognized as a cause of severe vomiting and diarrhea in infants, often triggered by cow's milk or soy protein. While the condition is well documented in older infants, its early-onset form—N-FPIES—remains an emerging area of interest in pediatric allergy research.

Recent findings suggest that N-FPIES may be more common than previously believed, with some cases initially mistaken for necrotizing enterocolitis, or NEC, particularly in preterm infants.

N-FPIES often shows within the first two weeks of life in full-term newborns and slightly later in preterm babies. Early symptoms include feeding intolerance, recurrent vomiting, abdominal distension, and in some cases, visible bloody stools.

NEC and N-FPIES share some of these hallmark symptoms, such as vomiting and bloody stools. However, their management differs dramatically, so this overlap presents a major diagnostic challenge. NEC requires fasting, antibiotics, and surgery in severe cases, whereas N-FPIES can be resolved with dietary intervention alone, which involves substituting the dietary protein with extensively hydrolyzed or amino acid-based formulas.

Now, a key distinguishing feature between these two lies in the bloodwork. In N-FPIES, lab results often reveal leukocytosis with a predominance of eosinophils, along with thrombocytosis and elevated methemoglobin levels, while C-reactive protein is less commonly elevated. In contrast, NEC more frequently presents with thrombocytopenia.

Radiographic findings can also help clinicians distinguish between the two conditions. NEC typically involves widespread intestinal involvement with pneumatosis intestinalis, portal venous gas, and diffuse loss of intestinal mobility, whereas N-FPIES tends to show more localized bowel changes that resolve quickly after dietary modification.

Emerging research points to immune responses driving N-FPIES. Elevated levels of IL-4, IL-5, IL-10, and IL-13 are particularly prominent in newborns with FPIES, particularly those presenting with bloody stools. One study even found significantly higher eosinophil counts in umbilical cord blood of newborns later diagnosed with FPIES, suggesting the Th2 response begins prenatally.

The gut microbiome is also under investigation. Infants with FPIES often have lower microbial diversity, fewer beneficial short-chain fatty acid–producing bacteria, and higher levels of species such as *Pseudomonadota, Enterobacteriaceae*, *Klebsiella,* and *Escherichia*. This type of imbalance may weaken gut barrier function, promote intestinal inflammation, and disrupt serotonin signaling, all of which are believed to underlie the symptoms of FPIES.

Diagnosing N-FPIES relies heavily on clinical awareness as there are no definitive laboratory markers or imaging tests for diagnosis. The condition is typically confirmed by observing symptom improvement once the trigger food is removed from the diet.

Stabilizing patients with FPIES by stopping enteral feeds and starting intravenous fluids to correct dehydration and electrolyte imbalances is the priority. For formula-fed infants, the first step is to transition to an extensively hydrolyzed formula. If symptoms don't improve or there's poor growth, then an amino acid-based formula may be introduced, since these formulas are generally well tolerated, particularly in preterm infants.

For breastfed babies, eliminating cow's milk and soy proteins from the mother's diet is the first step. But in cases where this fails, temporary interruption of breastfeeding and switching to an extensively hydrolyzed or amino-acid based formula may be necessary.

Unlike with NEC, fasting and antibiotics are not required for N-FPIES and may even hinder recovery by disrupting the gut microbiota even further. Misdiagnosis of N-FPIES as NEC can lead to unnecessary invasive interventions and delay appropriate treatment.

We still don't know exactly how common neonatal FPIES really is, partly because so many cases are either missed or misdiagnosed. Right now, there's no standardized oral food challenge protocol designed specifically for newborns, which makes it harder for clinicians to confirm the diagnosis in a safe and consistent way. The preferred dietary treatment, especially for preterm infants, is also unknown, since we don't yet have strong evidence from randomized trials to guide which formula should be used first.

Looking ahead, refining the diagnostic criteria and treatment approaches will be key to providing the best possible care and outcomes for infants with N-FPIES.

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Reference

D'Auria E, Ferrigno C, Pellicani S, et al. Neonatal Food Protein-Induced Enterocolitis: Current Insights and Knowledge Gaps. *J Clin Med*. 2025;14(7):2461. Published 2025 Apr 3. doi:10.3390/jcm14072461