Review

Neonatal Fpies: Current Insights and Knowledge Gaps

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Neonatal FPIES: Current Insights and Knowledge Gaps

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Abstract: Acute and chronic FPIES have been well characterized in children. Few data still exist on neonatal FPIES (N-FPIES) which may involve a distinct pathophysiology and is characterized by specific clinical features which make challenging the diagnosis. Although risk factors remain poorly understood, scientific evidence suggests that gut microbiota alterations may play an important role in the development of FPIES. In regard to N-FPIES clinical presentation, there is evidence of two distinct phenotypes, according to the presence or absence of bloody stools. Although N-FPIES shares symptom similarities with infant acute FPIES, it may not fully meet the diagnostic criteria at onset. The present review highlights our current understanding of N-FPIES, focusing on risk factors, including microbiota alterations, clinical characteristics and differential diagnosis with other neonatal medical and surgical conditions. In addition, current treatment strategies for both term and preterm infants are also described and commented. Refining diagnostic criteria for N-FPIES represents a clinical priority to help physicians in approaching this challenging condition. Last, but not least, larger clinical trials are needed to optimize treatment practices in term and preterm newborns with FPIES.

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1. Introduction

Initial descriptions of Food Protein-Induced Enterocolitis Syndrome (FPIES) depicted infants under nine months old with severe vomiting and diarrhea in response to cow's milk (CM) or soy-based formula.[1,2] Over the years, different definitions of FPIES were adopted with a broader range of foods implicated in triggering this allergic reaction.[2].A major advancement in knowledge came in 2017 with the establishment of international consensus guidelines for the diagnosis and management of FPIES and the introduction of specific diagnostic criteria. For acute FPIES, the major criterion is vomiting occurring 1–4 hours post-ingestion of a suspected food, without accompanying IgE-mediated allergic skin or respiratory symptoms. Nine minor criteria were also defined, including a second episode of repetitive vomiting upon re-exposure to the same food, vomiting 1–4 hours after ingestion of a different food, profound lethargy, marked pallor, admission to emergency department, intravenous fluid requirement, diarrhea within 24 hours (often occurring 5–10 hours post-ingestion), hypotension, and hypothermia. [3] Acute FPIES is diagnosed in patients who meet the major criterion along with at least three minor criteria. Chronic FPIES, instead, is defined by ongoing or intermittent vomiting, watery diarrhea, and growth failure associated with the repeated ingestion of a specific trigger food. Diagnosis is confirmed when symptom resolution follows the elimination of the trigger food from the diet, and acute FPIES symptoms reoccur upon re-exposure to the food, as outlined in

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the international consensus guidelines.[3]These guidelines not only established clear diagnostic criteria but also enabled standardized comparisons of FPIES cases worldwide, regardless of geographic differences in disease presentation and implicated foods. Indeed, our understanding of FPIES clinical characteristics has rapidly advanced and heterogeneity among FPIES patients has become apparent, with variability in trigger foods, age of onset, geographic prevalence, and presenting symptoms. Very recently, it has been proposed to classify FPIES into four distinct entities based on age of onset and presumed pathophysiology: acute FPIES in children, acute FPIES in adults, chronic FPIES, and early-onset neonatal FPIES[4]. While acute FPIES in children, acute FPIES in adults, and chronic FPIES may share a similar underlying pathophysiology, early-onset neonatal FPIESmay involve a distinct pathophysiology and is characterized by different clinical features which make even more challenging the diagnosis. The present review focuses on neonatal FPIES (N-FPIES), highlighting risk factors and clinical characteristics, differential diagnosis and treatment strategies, also addressing knowledge gaps and future needs.

2. Literature Search

The literature search was based on the MEDLINE database and Google Scholar engine.

The following MESH and Boolean terms were used in PubMed: (“Neonatal food protein induced enterocolitis” OR “Neonatal FPIES” OR “neonatal allergic colitis”)

All types of articles (case reports, clinical trials, reviews, and guidelines) were

considered. The search was limited to neonatal period (birth to first 28 days of life) and the English language and was performed from inception to September 2024. The Google database and Google Scholar engine were used to find potentially relevant references in the grey literature. Additional references were retrieved from the included papers.

3. Risk Factors for FPIES

A cohort study of 13,019 Israeli newborns showed a weak association between FPIES and cesarean delivery and Jewish religion , but no association with gestational age, maternal age, number of siblings, maternal dairy consumption, or the age of introduction of CM[5].The Healthy Start study supported no connection between maternal dietary intake during pregnancy and allergic diseases in offspring[6]. It has been also hypothesized that changes in the maternal microbiome might increase the infant’s risk for developing FPIES, but more data is required. A recent survey of parents or guardians of infants with and without FPIES under 12 months old revealed higher prenatal maternal antibiotic usage in the FPIES group. [7]Some reports have explored a possible association between Down syndrome and FPIES and suggested that surgical history, such as colostomy, and postoperative cow’s milk formula nutrition might increase the risk[8].In contrast, case series from the US, Italy, and Australia have not demonstrated prenatal or postnatal risk factors[2,9–16] Genetic predisposition seems to play a role, with more cases of FPIES being reported across generations, often involving an affected father and siblings, especially twins[10,13–15,17] However, genetic factors alone do not fully explain FPIES development, as shown by reports of monochorionic twins where only one is affected. [18] The role of male gender as a risk factor is unclear. Some studies indicate that FPIES is more common among boys,[12,19–22] while others do not. [23–26].

Breastfeeding seems to play a protective role against FPIES, since FPIES is rare among exclusively breastfed infants, who prove asymptomatic until direct feeding with the causal food[27].

A recent study comparing the white blood cell differentials from cord blood and peripheral blood samples between FPIES patients and matched controls showed a significantly higher percentage of eosinophils in cord blood in FPIES patients (P=0.0002)[28], with an additionally significantly elevated absolute eosinophil count in cord blood (P=0.0001). Furthermore, in vitro cultures of peripheral blood mononuclear cells exposed to cow's milk antigen showed a significantly greater presence of type 2 cytokines, such as IL-4, IL-5, and IL-13, in patients with early-onset neonatal FPIES (characterized by bloody stool) compared to patients with infant CM-FPIES (without

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bloody stool). [29] The mechanisms behind cord blood eosinophilia remain unclear, though these findings suggest that milk-antigen-specific Th2 cells generated in the fetus may trigger gastrointestinal (GI) inflammation upon exposure to milk antigens from the mother in the pathophysiology of early-onset neonatal FPIES. Although there is no clear causal relationship, a high frequency of intrauterine and delivery abnormalities was also observed. One limitation of this study is the small sample size, with only six FPIES cases (N=6). [28] Moreover, methaemoglobin levels have been shown to be higher in patients with neonatal-onset FPIES than in those with other gastrointestinal diseases[30].

4. Gut Microbiota in FPIES

Although risk factors remain poorly understood, scientific evidence suggests that gut microbiota alterations may play an important role in the development of FPIES.

Gut dysbiosis is increasingly associated to many different disorders including allergy[31,32] In utero and in early life the microbiota diversity and an healthy ecosystem foster the barrier integrity and modulate the immune system towards a protective and tolerogenic milieu. [33] Distinct diet, nutritional intervention and "biotics" supplementation have been attempted to shape the intestinal microbiome and metabolome to prevent the development of inflammatory, autoimmune and allergic diseases. [32,34]

In a prospective birth cohort study that enrolled 874 children followed up for 3 years, 8 FPIES cases (3 related to oat, 3 to rice and 2 to cow's milk) were identified, mostly occurring at 6 months of age. The 16S rRNA sequencing revealed significantly less fecal Bifidobacterium adolescentis, but more pathobionts, including Bacteroides spp. (especially Bacteroides fragilis), Holdemania spp., Lachnobacterium spp., and Acinetobacter lwoffii in children with FPIES.. [35]

A case-control study compared the fecal microbiota profiles of 17 children with FPIES and 12 age-matched controls using tag sequencing of the 16S ribosomal RNA gene hypervariable V4-V5 regions. Compared to controls, children with FPIES (65% due to fish) showed a significantly higher proportion of Lachnospiraceae spp and a lower proportion of Ruminococcaceae spp, Lactobacillaceae spp, and Leuconostocaceae spp. [36]

Recently, the gut microbiota and the level of fatty acids of 12 infants with CM FPIES and of 14 matched healthy controls were investigated by 16S amplicon and shotgun sequencing and by gas chromatography. Actinomycetota, Bifidobacteriaceae and Bifidobacterium were significantly more abundant in the fecal samples of the control group infants, whilst Pseudomonadota (earlier known as Proteobacteria), Enterobacteriaceae, Klebsiella, and Escherichia were significantly higher in infants with FPIES. The concentration of fecal fatty acids, specifically acetic acid, isovaleric and isobutyric acids, were significantly higher in patients compared to controls, possibly related to impaired colonocyte absorption induced by Proteobacteria proliferation. [37]

Moreover, the authors found a positive association between bifidobacteria and the levels of interleukin (IL)-1 receptor antagonist protein (IL-1ra), the cytokine interferon gamma inducible protein-10 (IP-10) and the platelet-derived growth factor BB (PDGF-bb), that were significantly reduced in the FPIES group. [38] The increased detection of fecal acetic acid has been explained as a sign of a reduced absorption and an alteration of colonocyte metabolism. These observations suggests that dysbiosis resulting in imbalance of metabolites can stimulate enterochromaffin or enteroendocrine cells of the GI tract to produce serotonin, which provokes gut dysmotility locally and food aversion, nausea, and vomiting due to its central effects.

5. Clinical Features of N-FPIES

N-FPIES is a non-IgE-mediated food allergy primarily affecting newborns within the first weeks of life.[16]The most common triggers for N-FPIES are CM and soy protein.

N-FPIES is characterized by moderate to severe gastrointestinal symptoms such as recurrent vomiting, diarrhoea, abdominal distension, and, in some cases, visible bloody stool[16].These

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symptoms usually develop within the first two weeks after birth in term babies[16,39,40], whereas it may be slightly later in preterm newborns, [39]aligning it closely with early feeding exposure. There are two distinct clinical phenotypes of N-FPIES, according to the presence or absence of bloody stools[40]. This differentiation is significant because infants with bloody stool tend to have earlier onset and display unique proinflammatory responses, possibly representing a distinct entity within FPIES, the so called early-onset N-FPIES. [40]The incidence of bloody diarrhoea varies a lot when comparing data from different countries: in western studies only 4-10% of patients with FPIES exhibited blood stool, while Nomura and colleagues found 47% of Japanese patients exhibiting macroscopic hematochezia.[41]

The primary symptoms of early-onset N-FPIES include recurrent or intermittent vomiting, bloody stool, abdominal distension, and diarrhea. In some cases, these symptoms are accompanied by shock-like episodes, fever, jaundice, and failure to thrive.[16,29,39,40]. Although early-onset N-FPIES shares symptom similarities with infant acute FPIES, it may not fully meet the diagnostic criteria for these forms at onset.Despite their initially severe presentation, infants with early-onset N-FPIES tend to develop tolerance sooner than those with infant acute FPIES.[29]. N-FPIES may even present with compromised general conditions due to dehydration with hypovolemic shock, hypoalbuminemia, metabolic acidosis, and hypothermia, representing a medical emergency in this vulnerable population.[42,43]. Such severe presentation may be misdiagnosed as IgE-mediated anaphylaxis[44]or sepsis. Distinguishing N-FPIES from other medical and surgical conditions is pivotal for a proper diagnosis and treatment. In preterm infants FPIES presents unique challenges that can complicate its diagnosis, particularly due to its overlap with necrotizing enterocolitis (NEC)[45]. Symptoms such as hematochezia, vomiting, diarrhea, dehydration and abdominal distension do not differ between these two pathologies, while systemic symptoms are more common in NEC than in FPIES, Diagnostic differentiation is critical but challenging in the early stages. Radiographic findings in NEC commonly include pneumatosis intestinalis, portal venous gas, and global intestinal motility loss. Abdominal ultrasound reveal stickened bowel walls, absent intestinal motility, and fluid collections across the abdomen.[46] In contrast, FPIES is characterized by more localized bowel involvement, with normal intestinal motility outside the affected area. While pneumatosis intestinalis and portal venous gas can also be seen in FPIES, these findings are typically less extensive and resolve more quickly compared to NEC.[46]Furthermore, patients with FPIES usually have less leukopenia and thrombocytopenia, more eosinophilia, and are less likely to have an elevated CRP.[47]Management strategies highlight the importance of accurate diagnosis. NEC requires immediate medical intervention, including bowel rest (fasting), broad-spectrum antibiotics, and, in severe cases, surgical resection of necrotic bowel tissue. Delayed or inappropriate treatment can lead to significant complications, including long-term gastrointestinal sequelae or death. In comparison, FPIES is managed by removing the offending dietary protein and substituting it with extensively hydrolyzed or amino acid-based formulas. Unlike NEC, unnecessary fasting and antibiotic use in N-FPIES can exacerbate symptoms or delay recovery[39,46]. Nonetheless, NEC in neonates may also present as a severe complication of N-FPIES due to an already fragile intestinal mucosa and a deterioration of gastrointestinal function. Evidence revealed that a notable percentage of infants initially diagnosed with NEC were later reclassified as FPIES, particularly among term infants. [39]This suggests that the prevalence of early-onset N-FPIES may be higher than previously estimated. Lastly, in 2019 Ichimura presented a case of fetal FPIES and suggested that not only the sensitization to an antigen may occur in utero but also that early N-FPIES may show some intrauterine symptoms. In his report the patient had in utero, significant intestinal distension on ultrasonography and MRI(at 32 weeks' gestation) and bloody stool after initial feeding.[48].

6. Diagnosis

In 2017 Nowak-Węgrzyn et al published the first set of diagnostic criteria of FPIES, identifying one major and nine minor criteria [3].

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However, N-FPIES may not fully meet the definition of FPIES as it may present with bloody stools which are not included in the International Guidelines diagnostic criteria. Laboratory findings that can be present in N-FPIES often include leukocytosis with a characteristic eosinophilic predominance, especially in preterms, along with thrombocytosis, which seems more frequent than thrombocytopenia observed in NEC.

The existing Guidelines do not consider the different FPIES phenotypes in the diagnostic criteria; it is likely that early-onset N-FPIES may represent a unique pheno-endotype which needs specific clinical and laboratory criteria.

Moreover, the oral food challenge test (OFC), given the moderate to severe nature of symptoms in neonatal population, is often avoided in the early stages to prevent exacerbation [40].

Recent investigation demonstrated the absence of vomiting at relapsing on the reintroduction of triggering food in FPIES in selected preterm babies, making the diagnosis questionable[18]. In these cases, performing OFC allowed to diagnose FPIES starting the required diet elimination . Thus, the need of performing OFC in neonatal FPIES remains an issue to be further investigated in larger studies.

Table 1. Differential Diagnosis of N-FPIES.

Condition	Key Features
Necrotizing Enterocolitis (NEC)	Onset in the neonatal period, especially in preterm infants; unstable temperature or fever; lethargy, vomiting, abdominal distension or bloating, bloody stools; pneumatosis intestinalis on imaging; absence of peripheral eosinophilia
Sepsis	Positive cultures, severe clinical presentation,unstable temperature or fever, poor appetite, respiratory distress or diarrhea or reduced bowel movements, jaundice;evidence of systemic inflammation, hypoglyceamia; improvement with antibiotics; not food-specific.
IgE-Mediated Allergy/Anaphylaxis	Immediate onset after food exposure; associated respiratory and/or cutaneous manifestations and/or vomiting; hypotension and eventually shock if anaphylaxis; positive food specific IgE or skin prick tests.
Surgical conditions	Delayed meconium passage (Hirschsprung), abdominal distension ; bilious or fecaloid vomiting; signs of intestinal obstruction; possible bloody diarrhea
Congenital Metabolic Disorders	Vomiting, progressive neurologic deterioration, hypotonia, lethargy, liver dysfunction, hypoglycemia, acidosis, poor growth
Immunodeficiencies	Recurrent or severe or opportunistic infections; failure to thrive; possible cutaneous manifestations

7. Treatment of N-FPIES

In N-FPIES which presents with repetitive vomiting, enteral feeding should be stopped and intravenous hydratation should be started to prevent dehydration and electrolytes imbalance. For patients with severe symptoms consistent with shock (i.e. presenting lethargy, hypotension), intravenous fluid boluses followed by maintenance fluids should be administered and vital signs should be monitored closely. Rapid clinical deterioration should be considered more suspicious of NEC instead of FPIES and antibiotic treatment should be prompty started. In N-FPIES the interruption of enteral feeding usually leads to rapid improvement of general clinical conditions along with vomiting cessation. Elimination of the dietary protein trigger and supporting the infant's nutritional needs and recovery are further key steps of N-FPIES management. For breastfed infants, maternal dietary modification is recommended, with the elimination of the suspected protein, such as CM or soy, from the mother's diet. [40]. Prompt identification and removal of the trigger often lead to rapid gastrointestinal symptom resolution. In cases of severe presentation, such as dehydration or metabolic acidosis from recurrent vomiting and diarrhea, supportive care is necessary, including fluid and electrolyte infusion to stabilize the patient. For neonates who are not breast-fed, the primary intervention consists of transitioning the infant to an extensively hydrolyzed protein formula or an amino acid-based formula, the latter preferred in preterm infants as the first-line intervention due to their increased vulnerability and immature digestive and immune systems.[40].In absence of NEC, fasting and antibiotic therapy are not required for N-FPIES, as these can exacerbate the condition by

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modifying the gut microbiota and delaying recovery.[47] Nutritional monitoring and gradual reintroduction of foods under medical supervision may also be essential part of the long-term management to avoid unnecessary treatments and growth complications, ensuring a favorable outcome.[40]

Table 2. Dietary management of neonatal FPIES.

Formula Selection	**Extensively Hydrolyzed Formula (eHF)**	**First-line choice for most cases.**
	Amino Acid-Based Formula (AAF)	**Used if no improvement is observed with eHF or poor growth within 2 weeks. Consider as first choice in preterm infants**
Breastfeeding	Continue Breastfeeding if Tolerated	If symptoms persist, maternal elimination diet should be considered.
	Eliminate Trigger Food (dairy and soy) for 2-4 weeks.	Monitor infant's symptoms to assess improvement.
	Temporary Switch to Hypoallergenic Formula (eHF)	Consider this option only for severe cases who do not respond to maternal diet exclusion.
Nutritional Counseling	Individualized Dietary Plan	Ensure optimal growth and nutrition, avoiding unnecessary dietary restrictions.
	Monitor Growth and Development	Regular follow-up to assess weight gain.

8. Conclusion

There is currently little knowledge of the risk factors for N-FPIES, and further studies are needed to fully understand the mechanisms causing early life FPIES.

The most recent guidelines do not make any specific prenatal or post-natal recommendations for N-FPIES; identifying predisposing factors for FPIES is a priority for advancing patient care and preventive strategies.

Furthermore, refining diagnostic criteria for N-FPIES represents a clinical priority to help physicians in approaching this challenging condition. Last, but not least, larger clinical trials are needed to optimize treatment practices in term and preterm newborns with FPIES.

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