

# FPIES: An Overview for Health Professionals

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### What Is FPIES?

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE, presumably cell-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting often with diarrhea, leading to acute dehydration and lethargy. [1] In a chronic form, FPIES may cause anemia, hypoalbuminemia and failure to thrive.

### How Common Is FPIES?

In a birth cohort of 13,019 infants under 12 months old in Israel, 0.34% were diagnosed with cow's milk FPIES during the physician-supervised oral food challenge (OFC). [2] {Katz, 2011 #342} In comparison, 0.5% infants were diagnosed as having IgE-mediated cow's milk allergy. Although it is impossible to extend the results from Israel to other patient populations, this study suggests that FPIES may be a more common condition than previously assumed.

### Which Foods Cause FPIES?

The disease is most commonly triggered by cow's milk or soy with several studies showing that up to 50% react to both foods. Symptoms of FPIES usually begin in early infancy (1-3 months, but up to 1 year of age) within 1-4 weeks following introduction of cow's milk or soy protein. [3] Delayed introduction of cow's milk or soy in breastfed infants may result in later onset. FPIES to cow's milk and soy in exclusively breastfed infants is very rare, suggesting a protective role of breastfeeding. [4] {Nowak-Wegrzyn, 2003 #81} Only four cases of exclusively breastfed infants presenting with symptoms consistent with cow's milk FPIES have been reported to date. [5] {Monti, 2011 #343; Nomura, 2011 #344}

Rice, oats, barley, chicken, turkey, egg white, green pea, peanut, fish and mollusks were also reported as FPIES triggers. [6] {Nowak-Wegrzyn, 2009 #305} Mean age at onset of solid food FPIES is later than that of cow's milk and soy FPIES, typically presenting when these foods are first introduced between the ages of 4-7 months. [7] {Mehr, 2009 #171; Sampson, 2000 #44} The onset of FPIES after 1 year of age is rare, but onset FPIES to fish and shellfish has been reported in older children and adults. [8] [ref Sampson Anderson 2000] Rice is the most common solid food that induces FPIES. [7] {Mehr, 2009 #165} Those with a history of FPIES to one grain have a 50% risk of developing FPIES to other grains. However, wheat FPIES has not been reported in infants with oat or rice FPIES, presumably because significantly delayed introduction of wheat in these cases avoids the "window of physiologic susceptibility." [4] {Nowak-Wegrzyn, 2003 #81; Sicherer, 2005 #112} Among infants with solid food FPIES, 80% reacted to more than one food, 65% were previously diagnosed with cow's milk and/or soy FPIES, and 35% were breastfed. {Nowak-Wegrzyn, 2003 #81} Delayed diagnosis of solid food FPIES may be due to the assumption that grains, such as rice and oats, and vegetables have low allergenic potential and are not usually suspected as triggers of allergic reactions. 2

### What Are the Manifestations of FPIES?

FPIES was originally described as chronic emesis and severe bloody diarrhea in formula-fed infants. FPIES may be chronic, such as with cow's milk or soy formula, or acute, either after the food has been removed from the diet and then re-introduced, or if the food is ingested intermittently.

Overall, approximately 75% of infants with FPIES appear acutely ill and 15% develop hypotension and require hospitalization. {Nowak-Wegrzyn, 2009 #305} Infants with chronic symptoms usually improve within 3-10 days of switching to a casein hydrolysate-based formula with or without temporary intravenous fluids. About 10-20% of infants may require an elemental amino acid-based formula.

### **Laboratory Findings in FPIES**

Anemia, hypoalbuminemia, an elevated white blood cell count with a left shift, eosinophilia, and thrombocytosis were reported. Transient methemoglobinemia was reported in about one third of infants with severe reactions and academia. Methemoglobinemia may be caused by severe intestinal inflammation and reduced catalase activity resulting in increased nitrites.

### **Differential Diagnosis**

FPIES is considered the most severe of the non-IgE-mediated gastrointestinal food hypersensitivities. FPIES needs to be differentiated from food protein-induced proctocolitis, food protein-induced enteropathy and eosinophilic esophagitis/gastroenterocolitis. Acute emesis, diarrhea and dehydration may mimic a gastrointestinal anaphylaxis, viral illness, sepsis or food poisoning. In newborns, necrotizing enterocolitis (NEC) needs to be considered. Severe gastroesophageal reflux, intestinal obstruction and metabolic disorders should be ruled out as well.

### **Diagnosis**

The diagnosis of FPIES is based on clinical criteria and, if necessary, an oral food challenge; endoscopy and biopsy studies are not routinely performed. Infants often present with multiple reactions and extensive evaluations for other causes before the diagnosis of FPIES is considered, especially when FPIES is caused by solid foods. [ANW 2003, Mehr S] The lack of definitive diagnostic tests and the atypical symptoms contribute to a delay in diagnosis.

Although OFC is the gold standard for diagnosis of FPIES, infants do not require confirmatory challenges for initial diagnosis if they have classic symptoms that resolve after avoidance of the offending food. Physician-supervised OFCs are necessary, however, if the history is unclear or to determine whether FPIES has resolved.

The majority of patients have negative skin prick tests and undetectable food-specific IgE at diagnosis. Elevated food-specific IgE levels can develop in some 10-20% of patients after the diagnosis of FPIES, so-called atypical FPIES. Children with atypical FPIES tend to have a more protracted course.

In one study, atopy patch testing (APT) was helpful for FPIES diagnosis but these findings have not been confirmed by other studies; thus, further evaluation is required to determine the role of APT in the diagnosis of FPIES.

### **Oral Food Challenge**

OFC should be conducted in a medical setting where intravenous access can be secured and rapid fluid resuscitation can be given if necessary. During an OFC, food is served in 3 equal portions over 45-60 minutes, followed by a minimum 4-hour observation. In case of symptoms, the first-line therapy is rapid intravenous hydration given in 20 ml/kg boluses. Intravenous corticosteroids (e.g., a single dose of methylprednisolone) are used in severe reactions to reduce the presumed cell-mediated intestinal inflammation. {Sicherer, 2005 #112} Epinephrine should be available for potential hypotension and shock; however, epinephrine does not improve symptoms of emesis and lethargy.

### **Management**

Management consists of avoiding the offending food. For infants, exclusive breastfeeding can be protective. If the infant is formula-fed, casein hydrolyzed-based formula is recommended due to frequent concomitant cow's milk and soy FPIES. Amino acid formula is rarely needed (10-15%); in extreme cases, temporary intravenous fluids and bowel rest may be necessary. It is helpful to provide a patient with a letter that describes FPIES features and optimal emergency management with vigorous re-hydration to avoid delay in treatment in case of acute reactions. A sample letter is available for download on the IAFFPE website.

About one-third of infants with cow's milk or soy FPIES develop solid food FPIES, most commonly to rice and other grains. Therefore, introduction of yellow fruits and vegetables has been suggested at 6 months of age. {Nowak-Wegrzyn, 2003 #81; Sicherer, 2005 #112} Introduction of cow's milk and soy in these infants may be attempted after 1 year of age if there is no prior reactivity to these foods. Tolerance to one food from each high-risk group, for example soy for legumes, chicken for poultry, or oat for grains, increases the likelihood of tolerance to other foods in the same group. {Sicherer, 2005 #112}

Patients initially presenting with or later developing food-specific IgE antibodies are at risk for persistent FPIES; skin prick testing and/or measurement of serum food-specific IgE levels in the initial as well as follow-up evaluations is useful.

OFCs can be used to establish the diagnosis or to evaluate for the resolution of FPIES. One conservative approach recommends follow-up challenges every 18-24 months in patients without recent reactions. {Sicherer, 2005 #112} However, in a Korean study, 64% of infants with FPIES tolerated cow's milk at 10 months and 92% tolerated soy at 10 months, and the investigators recommended follow-up challenges after 12 months for cow's milk and between 6-8 months of age for soy. {Hwang, 2009 #164}

### **Natural History of FPIES**

Resolution of FPIES may be population dependent, particularly for cow's milk and soy. While in our experience, cow's milk FPIES resolves in 60% by age 3 years, the Israeli birth cohort showed 90% resolution by 3 years. {Katz, 2011 #342; Sicherer, 1998 #106} In solid food FPIES, the majority of children become tolerant by age 3-4 years.

### **Conclusions**

Early recognition of symptoms of FPIES and avoidance of the offending foods are imperative. Close follow-up is required to determine when foods may be added back into the diet. Children with multiple food FPIES are at risk for nutritional deficiencies and feeding problems and may benefit from dietitian supervision and early feeding therapy.