Food protein-induced enterocolitis syndrome: guidelines summary and practice recommendations

Sam Mehr[1,2], Dianne E Campbell[2,3]

Food protein-induced enterocolitis syndrome (FPIES) is a poorly understood food allergy that most commonly affects infants under the age of 2 years.[1] It is so named due to the targeting of the small and large bowel in this disorder, with relative absence of additional extragastrointestinal manifestations typical of IgE-mediated food allergy. Although FPIES is assumed to be rare, it is probably not. Only a few regions have collated data to determine the prevalence of FPIES.[2,3] Estimates vary widely, and are likely to under-represent its true prevalence, due to a combination of underdiagnosis, under-reporting and non-attendance for health care in milder cases.

There appears to be significant regional variation in relation to the most common food triggers and clinical phenotypes.[1,4] The condition presents most commonly as acute FPIES, in which the cardinal clinical feature is profuse, repetitive vomiting that typically occurs 1–4 hours after ingestion of the food trigger.[1,5] An acute on chronic form is also recognised, characterised by persistent emesis, watery diarrhoea and failure to thrive during regular exposure to the food trigger.[6,7] After a period of avoidance and reintroduction of the culprit food, the acute phenotype then occurs.[6,7] FPIES can mimic more common paediatric conditions such as gastroenteritis and sepsis and there is often a delay in diagnosis.[8,9] There is no current laboratory, radiological or IgE- or non-IgE-based allergy test that can confirm a diagnosis of FPIES. Oral food challenges (OFC) are used to confirm diagnosis and to check for tolerance over time.

Up until 2017 there were no agreed criteria to use for diagnosing FPIES. Only a few countries had produced FPIES-specific guidelines or health professional resources.[10,11] Hence, there has been a need for standardised and reliable criteria to make a diagnosis of FPIES. This need is met, in some ways, by the 2017 international consensus FPIES guidelines, which were designed to assist practitioners in the care of patients with FPIES based on the best available evidence and are summarised in this review[1] (Box 1).

This narrative review used a PubMed search of original and review articles from 1970 to 2017, as well as specialist society publications. The 2017 international consensus FPIES guidelines,[1] produced by the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma and Immunology, were formulated based on a literature search including PubMed, MEDLINE, Web of Science and EMBASE. Evidence was graded by subcommittees according to the grading criteria of the Joint Task Force on Practice Parameters[11] using Appraisal of Guidelines for Research and Evaluation (AGREE) II methodology.[12]

Epidemiology and prevalence

FPIES as a recognised entity was not specifically identified until the 1970s.[6] Since then, different definitions and the heterogeneous nature of clinical presentations have hampered accurate estimates of prevalence.[5,13–17] Only since 2015 has FPIES had an International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), code (K52.2).

A 2018 study examined non-IgE allergic gastroenteritis-related admissions to Australian and New Zealand hospitals and found an increase from 6.8 admissions per 100 000 per year in 1998–2000 to 26.5 per 100 000 by 2014. Since most of these cases occurred in infants under 12 months of age, the authors speculated that the bulk of the presentations were likely due to FPIES.[18] A population-based survey of paediatricians using the Australian Paediatric Surveillance Unit network has recently estimated the prevalence of acute FPIES in infants aged under 2 years at about 15 per 100 000 infants per year,[3] which likely underestimates the true prevalence.[3] To date, the only other estimate of FPIES was based on a prospective birth cohort in Israel that reported a higher rate of 3 per 1000 per year of cow's milk FPIES.[2] Reasons for the wide discrepancy between the estimated prevalence comprise the inclusion of milder phenotypes in the prospective birth cohort, under-reporting of mild reactions in the general community, and misdiagnosis due to lack of awareness of the disorder as an entity. It is also possible that real regional variations in prevalence do occur.

Based on case cohorts, FPIES predominantly affects infants under 2 years of age, has no specific sex predilection and is more

Summary

- Food protein-induced enterocolitis syndrome (FPIES) is a poorly understood non-IgE gastrointestinal-mediated food allergy that predominantly affects infants and young children.
- Cells of the innate immune system appear to be activated during an FPIES reaction.
- Acute FPIES typically presents between one and 4 hours after ingestion of the trigger food, with the principal symptom being profuse vomiting, and is often accompanied by pallor and lethargy. Additional features can include hypotension, hypothermia, diarrhoea, neutrophilia and thrombocytosis.
- In Australia, the most commonly reported foods responsible for FPIES are (in descending order) rice, cow's milk, egg, oats and chicken.
- Most children with FPIES react to only one food trigger, and thus, avoidance of multiple foods is often not indicated.
- FPIES is often misdiagnosed as sepsis or gastroenteritis. However, a diagnosis of FPIES is favoured if there is rapid resolution of symptoms within hours of presentation, an absence of fever, and a lack of a significant rise in C-reactive protein at presentation.
- Diagnosis is often hampered by the lack of awareness of FPIES, absence of reliable biomarkers, the non-specific nature of the presenting symptoms, and the delay between allergen exposure and symptoms.
- Although some national peak allergy bodies have attempted to improve the diagnosis and management of FPIES, up until 2017 there were no internationally agreed guidelines for its diagnosis and management.

[1] Royal Children's Hospital, Melbourne, VIC. [2] Children's Hospital at Westmead, Sydney, NSW. [3] University of Sydney, Sydney, NSW. dianne.campbell1@health.nsw.gov.au • doi:10.5694/mja2.12071

Podcast with Dianne Campbell available at https://www.mja.com.au/podcasts

1 Major recommendations and summary statements from the 2017 international consensus guideline

Recommendation/statement	Level of evidence	Strength of recommedation*
Most infants have FPIES to a single food, and avoidance of other foods is generally not required	IIb/III	Strong
Ensure fluid resuscitation for acute FPIES presentations	IIa	Strong
Consider ondansetron for management of an acute FPIES reaction	IV	Weak
Diagnostic criteria for standardisation of FPIES diagnosis is proposed (Box 4)	III/IV	Weak
Diagnostic food challenges should be considered in patients who have had only a prior single FPIES reaction to confirm diagnosis	III/IV	Weak
Diagnostic food challenges for FPIES should be conducted where access to rapid fluid resuscitation is available	IIa	Strong
Avoidance of trigger food remains the mainstay of management	IIb/III	Strong
Avoidance of trigger food in the maternal diet while breastfeeding is not usually required	III-IV	Moderate
Age at which tolerance to FPIES occurs varies depending on the food trigger	IIa/IIb	Strong

FPIES = food protein-induced enterocolitis syndrome. * Strength of recommendation as per previously established grading system for clinical practice parameters used by the Joint Task Force on Practice Parameters.[12] ◆

common in infants with a personal and family history of allergic disease.[1,3] In Australian cohorts, almost 10% of index cases had a sibling with a history of FPIES.[3] Birth by caesarean section is the only known risk factor reported to date.[2] Acute FPIES in adults is also described and is predominantly reported to seafood.[19,20] Prevalence data for chronic FPIES are unknown and complicated by the syndrome's similar clinical appearance to food protein enteropathies.[21]

Pathophysiology

The underlying mechanism of action by which the trigger foods in FPIES cause symptoms and disease remains unclear. Markers of immune activation, including peripheral neutrophilia, increase in mucosal IgM- and IgA-positive plasma cells, eosinophils and T cells, have been variably and largely inconsistently described.[1,22] The current guideline proposes that FPIES should be classified as a non-IgE-mediated food allergy and that its postulated T cell mechanism of action requires further validation.[22] However, since the publication of the guideline, two further studies have suggested it is more likely that it is the activation of the innate arm of the immune system, not the adaptive arm, that characterises the mRNA signature of acute FPIES reactions.[23,24] Here, monocytes, neutrophils and natural killer cells are the key cells of interest.[23,24]

Trigger foods

Although the common acute FPIES trigger foods include allergens typically associated with IgE-mediated food allergies (eg, cow's milk, egg), there are also foods, such as rice, oats and chicken, that are common triggers of acute FPIES, but which rarely cause IgE-mediated allergic reactions. There appears to be significant regional variation in common acute FPIES triggers, with rice being the most common trigger in Australia,[3] whereas cow's milk is the commonest trigger in the United States and Europe. Soy FPIES is uncommon outside of the US.[1,8,25] In Australia, the most commonly reported foods responsible for FPIES are (in descending order): rice, cow's milk, egg, oats and chicken.[3] Fruits and vegetables accounted for 10% and 8% of all food triggers, and tend to be associated with FPIES to more than one food group.[3]

In the US, 5–10% of children reacted to more than three foods, some to as many as six or more foods.[5,13] Similarly, in Australia, 68% of infants reacted to a single food trigger.[26] Most infants with cow's milk FPIES in Australia do not appear to have concurrent FPIES to other foods. Infants with rice FPIES may be at increased risk of reaction to oats,[3,9] but the risk is not absolute such that avoidance of both grains need not always be recommended. In one recent study of 26 children with rice FPIES who had exposure to both rice and oats, only 11 (42%) had FPIES to both grains.[3] Children with rice and/or oat FPIES can often tolerate other grains, such as wheat and corn. Those patients with FPIES to fish are generally advised to avoid all fish, as species specificity has not been well described. In certain patients for whom the likelihood of having FPIES to multiple foods appears high (ie, early age of onset, vegetable and/or fruit FPIES, more than two triggers already identified[3]), it is recommended to seek specialist allergist advice regarding further food groups to avoid.

Adults with FPIES appear to have seafood as their predominant acute food trigger, and often have had a prolonged period of tolerance to the trigger food beforehand. However, little information has been published on adult FPIES.[19,20]

Clinical presentation

Acute FPIES typically presents between one and 4 hours after the ingestion of the trigger food, with the principal symptom being profuse vomiting, and is often accompanied by pallor and lethargy.[3,5,14] The key features of FPIES are summarised in Box 2. Additional features can include hypotension, hypothermia, diarrhoea and metabolic acidosis.[8,14,27] Bloody diarrhoea is more commonly reported in Japanese cohorts[28,29] and in infants presenting under 2 months of age with cow's milk or soy FPIES.[1] This clinical presentation may mimic sepsis, gastroenteritis, intussusception, other rare surgical abdominal emergencies, and metabolic crisis. No deaths have been reported following an acute FPIES reaction, but admissions to the intensive care unit have occurred.[25,30]

Patients may not react on their first known exposure to the trigger food; hence, a history of several previous ingestions with tolerance does not rule out an FPIES diagnosis.[3,8] Nevertheless,

2 The key features of acute food protein-induced enterocolitis syndrome (FPIES)

Key clinical features of FPIES	• FPIES often presents in infancy or early childhood with the introduction of a new food (may react on first known exposure or after initial tolerance a few times*) • Reactions are stereotypical and, hence, consider if an infant or child presents more than once after the introduction of a new food • Profuse, repetitive vomiting, pallor and lethargy are the cardinal features of an acute FPIES reaction (occurring 1–4 hours after ingestion of a food trigger) • FPIES is afebrile in the majority of patients, and in some cases, infants may have hypothermia • There should be a rapid resolution of symptoms within 24 hours of onset†
Common laboratory findings after FPIES reaction	• ± Raised white blood cell count with neutrophilia • ± Raised platelet count • C-reactive protein usually normal or only mildly elevated • If diagnosis remains unclear, consider hospital-supervised food challenge

* Most FPIES reactions occur after the first known ingestion of a food, or after a short period of tolerance one to four times beforehand; it is less common to have FPIES to a food that has been tolerated numerous times previously. † In some cases, diarrhoea may occur within 24 hours of a reaction and, in most patients, is non-bloody. ◆

FPIES reactions after four or more tolerated exposures to a new food are uncommon.[3]

A spectrum of severity is observed in acute FPIES reactions. Some children present only with profuse vomiting, while others can have co-associated hypotension, hypothermia and metabolic acidosis. The international guideline presents a proposed classification scheme (based on expert opinion) for differentiating mild, moderate and severe acute FPIES presentations[1] (Box 3). Patients presenting with (at least one of) hypovolaemia, hypothermia, lethargy or altered levels of consciousness and those who require intravenous rehydration are considered severe.

Chronic FPIES presents in young infants with features almost identical to that of a food protein enteropathy and is characterised by chronic or intermittent vomiting, watery diarrhoea and failure to thrive.[6,7,30] Cow's milk and soy have been commonly reported to cause chronic FPIES. This may represent a publication bias, but requires further exploration with prospective well characterised cohorts. It is likely that historical publications may have combined or misidentified these two conditions. The distinguishing feature of these two entities is the "switching" from chronic symptoms to the acute FPIES phenotype upon re-exposure to the trigger food allergen after a period of avoidance. Thus, it is a diagnosis that can conclusively be made only in retrospect.

Tolerance

Most children outgrow their FPIES. It was previously recommended not to rechallenge to the trigger food until the child was 3 years of age, with most patients outgrowing FPIES by this time. However, it has been increasingly recognised that many children outgrow FPIES earlier than previously appreciated. Time to tolerance is variable, but it appears to be most closely related to the type of trigger food[25,31] and does not appear to be prolonged if a child has a history of multiple FPIES triggers.[31] Recent local reports suggest that many patients with FPIES to grains and cow's milk are tolerant by 18 months of age, whereas FPIES to egg and seafood may persist beyond this time.[31] OFC is recommended within 12 months after the most recent reaction.

Diagnosis

Diagnosis of acute and chronic FPIES is difficult and relies on knowledge of the condition and its common triggers, careful history of prior similar episodes and exclusion of likely differential diagnoses. There are no current tests, other than an OFC, that can confirm an FPIES diagnosis. Investigations are usually performed in the acute setting in consideration of possible differential diagnoses,[1] but are not helpful in making a specific diagnosis of FPIES. Diagnostic delay is common and, often, infants have multiple reactions before a diagnosis of FPIES is considered.[1,8]

When the history is in doubt or when tolerance is anticipated after a prolonged period of avoidance, an OFC is the gold standard for diagnosis. When diagnosis is considered likely on the basis of the history, particularly in patients who have had two or more FPIES reactions, it is unnecessary to confirm acute FPIES with an OFC.

Due to the heterogeneity of previous diagnostic criteria and lack of available biomarkers, the consensus guideline has proposed more rigorous criteria for acute FPIES[1] (Box 4). The proposed criteria are designed to be applied to making a diagnosis based on

3 Proposed critera for differentiation of mild to moderate versus severe food protein-induced enterocolitis syndrome[1]

Required clinical features	Mild to moderate	Severe
Repetitive vomiting with/without diarrhoea	+	+
Pallor	+	+
Activity level	Decreased activity level	Altered behaviour ranging from decreased activity to lethargy
Dehydration	–	+
Outcome	Self-resolving, the child is able to tolerate oral rehydration	Requires intravenous rehydration
Optional clinical features	Mild watery diarrhoea (onset usually within 24 hours, can be occasionally bloody)	Hypotension, abdominal distention, hypothermia, diarrhoea (onset usually within 24 hours, can be bloody), hospitalisation

4 Proposed diagnostic criteria* for patients presenting with acute food protein-induced enterocolitis syndrome (FPIES) in the community setting

Major criterion	• Vomiting (1–4 hours after ingestion of the suspect food) and absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria (≥ 3)	• A second (or more) episode of repetitive vomiting after eating the same suspect food • Repetitive vomiting episode 1–4 hours after eating a different food • Extreme lethargy with any suspected reaction • Marked pallor with any suspected reaction • Need for emergency department visit with any suspected reaction • Need for intravenous fluid support with any suspected reaction • Diarrhoea in 24 hours (usually 5–10 hours) • Hypotension • Hypothermia

* The diagnosis of acute FPIES reactions required the major criterion and three or more of the minor criteria. If only a single FPIES reaction has occurred, it is strongly recommended to perform a diagnostic food challenge. Source: Nowak-Węgrzyn et al.[1] Reproduced with permission. ◆

5 Proposed diagnostic criteria for the interpretation of food protein-induced enterocolitis syndrome (FPIES) oral food challenges* conducted in a medical setting

Major criterion	• Vomiting (1–4 hours after ingestion of the suspect food) and absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria (≥ 2)	• Lethargy • Pallor • Diarrhoea 5–10 hours after food ingestion • Hypotension • Hypothermia • Increased neutrophil count of ≥ 1500 neutrophils above the baseline count

* The challenge is considered diagnostic of FPIES if the major criterion and two or more minor criteria are met. Source: Nowak-Węgrzyn et al.[1] Reproduced with permission. ◆

a historical recount of an acute reaction, or during a reaction unfolding in an emergency department or doctor's office (triggered by a prior food ingestion), and not for use in the setting of a deliberate OFC. One major and three minor criteria are required to make a diagnosis. Emphasis is given to profuse vomiting as a cardinal feature, and recurrent episodes on re-exposure to the same trigger food, or a reaction to another newly introduced food.

Although not part of the diagnostic criteria, it is well recognised that most infants with acute FPIES completely recover within a matter of hours (although diarrhoea may occur over the next 24 hours), compared with infants with sepsis, gastroenteritis or surgical abdomen.[32] Thus, a rapid clinical response should alert the clinician to the possibility of FPIES as a differential.

Ancillary testing

Although there are no laboratory investigations required for making a diagnosis of acute FPIES, peripheral neutrophilia and/or thrombocytosis and stool leucocytes or eosinophils may be present after an acute reaction.[6,8] The presence of these laboratory features is unnecessary but optional in the diagnosis of acute FPIES. Consideration may be given to preforming limited allergy skin testing or serum-specific IgE. Sensitisation (ie, detection of IgE by skin prick or serum-specific IgE testing) to the food trigger may be associated with delayed acquisition of tolerance, particularly in patients with cow's milk FPIES.[5,31]

Making a diagnosis of food protein-induced enterocolitis syndrome in a food challenge setting

Separate criteria are proposed for making a diagnosis of acute FPIES in the OFC setting (Box 5). The rationale for having different criteria for OFC is to improve reliability of research and outcome reporting and to allow more rapid treatment when the likely diagnosis is known. With these specific criteria, it is acknowledged that the use of ondansetron may improve symptoms such as vomiting, pallor and lethargy, and that not all facilities may be able to perform a neutrophil count in a timely manner. It is suggested that the presence of minor criteria is not critical in the OFC setting for making a diagnosis. However, for purposes of research, the criteria should be strictly adhered to. The current guideline did not propose a set of criteria for the diagnosis of chronic FPIES.[1]

There are a variety of published protocols used for acute FPIES food challenges. In general, when chronic FPIES has been suspected, and rechallenge required, the same format of challenge is recommended. Unless there is suspicion of an IgE-mediated food allergy, challenges are generally conducted with either a single serve of food or divided into three equal portions given every 30–45 minutes.[5,15,33,34] All protocols require an observation period of at least 4 hours after ingestion. Given that about 50% of published food challenges report the use of intravenous fluids upon reaction, OFC for FPIES should be conducted in a hospital setting.[34]

Performing allergy skin prick or serum-specific IgE tests before an FPIES challenge is recommended for certain foods, especially for cow's milk and egg, because transformation from a non-mediated-IgE FPIES reaction to an IgE-mediated allergy has been reported.[5,35] That is, infants with a definite past history of FPIES who have avoided the trigger food may develop IgE antibodies to the same trigger food and now react in an IgE-mediated fashion. If production of food allergen-specific IgE is identified (and it is considered safe to proceed), a graded IgE-mediated OFC should be used.[34] IgE transformation appears most common in the setting of cow's milk FPIES,[5,31] and to date, it has not been reported to have occurred with allergens such as rice, chicken, fruits or vegetables.

Acute treatment

The first-line treatment for acute FPIES reactions is fluid replacement, either by the oral route in patients with a mild to moderate presentation or via the intravenous route (20 mL/kg intravenous bolus of normal saline) in severe FPIES.[1] Several reports now suggest that the use of ondansetron (either intramuscular, intravenous or oral wafer) may be effective in shortening the duration of emesis.[36] Although use of corticosteroids has been variably reported, there is insufficient evidence to recommend their routine use in the management of acute or chronic FPIES.[1] There is no role for intramuscular adrenaline in the management of an FPIES reaction.[1]

Management

If a diagnosis of FPIES is suspected, a referral to an allergy specialist for confirmation, dietary advice, provision of action plans and follow-up is suggested. Outside acute FPIES presentations,

avoidance of identified trigger foods is the mainstay of management for both acute and chronic FPIES. Although symptoms on exposure to food allergens present in breast milk have occasionally been reported,[3,37] in the absence of a history suggestive of reactions via breast milk (eg, in exclusively breastfed infants presenting with chronic vomiting, diarrhoea or irritability), maternal avoidance of the trigger food while continuing to breastfeed the infant is not recommended. Once elimination of the trigger food has occurred, infants with chronic FPIES should make a complete recovery, and prolonged persistence of symptoms or ongoing failure to thrive should prompt a search for an alternative diagnosis.

Guidance on whether to avoid other foods in the context of an identified FPIES trigger is difficult due to the potential bias in reporting of multiple versus single FPIES from tertiary cohorts. There appears to be a regional variability in the proportion of patients who experience single versus multiple FPIES.[3] Tolerance to one food from the food group is considered a favourable prognostic indicator for tolerance to other foods from the same group.[1]

The current guideline notes that infants with cow's milk or soy FPIES appear to be at higher risk of FPIES to other foods,[1] but this was not noted in a recently published Australian cohort study.[3] Soy FPIES appears to be rare outside the US.[1] When cow's milk and soy milk FPIES coexist, first-line options include an extensively hydrolysed infant formula or hydrolysed rice-based formulas (if no concurrent rice FPIES) when breastfeeding is not possible.[38] The safety of hydrolysed rice-based formulas has not been studied in infants with rice FPIES and, hence, their use in this setting cannot be recommended at this time.

It is suggested that caregivers introduce a new food as a single ingredient and, with high risk trigger foods not yet introduced, waiting at least a few days before introducing another food, as trigger foods may be tolerated on the first few exposures. Dietary guidelines for the introduction of complementary foods in children with FPIES are available through the website of the Australasian Society of Clinical Immunology and Allergy (ASCIA).[10]

Infants and children with FPIES are at risk of significant dietary restrictions and nutritional deficiencies due to parental anxiety about trying new foods, and particularly so for those infants with multiple FPIES triggers. Support and nutritional guidance by a dietician for parents of infants with FPIES is recommended.

Parents of infants with a diagnosis of FPIES should be provided with a written FPIES management plan, so that prompt appropriate treatment can be administered upon presentation to health care providers. In Australia, standardised FPIES action plans are available to download via the ASCIA website.[10]

Conclusion

Recent international consensus guidelines provide a more rigorous approach to diagnosis, introducing a system of major and minor criteria to facilitate early and accurate diagnosis and to guide diagnostic food challenge. They highlight the need for rapid fluid resuscitation in emergency presentations and the increasing evidence for the use of ondansetron in acute management. Diagnostic challenges should be performed in settings with suitable resuscitation facilities. Action plans and dietary information consistent with this guideline are available via ASCIA.[10]

It is likely that improved understanding of the immunological basis of FPIES will, in the future, facilitate the development of a sensitive and specific biomarker. Until that time, use of standardised diagnostic criteria, improved recognition, timely fluid resuscitation, avoidance of trigger foods, and education form current best practice.

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