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Abstract

Food protein-induced enterocolitis syndrome is still a mysterious disease, pathogenically poorly characterized, although the first FPIES case has been described in 1967.

Mainly, food protein-induced enterocolitis syndrome diagnosis is based on clinical history. The oral food challenge remains the gold standard to confirm the diagnosis, especially in particular situations. Although there are no diagnostic laboratory or imaging tests which are specific for

diagnosis, they could however sometimes be helpful to rule out clinical conditions which are similar to food protein-induced enterocolitis syndrome reactions.

The purpose of this review is to define the clinical features of FPIES and to summarize the current available tools for the diagnosis of FPIES.

This review is intended to be a practical guide for the clinician facing a patient with food protein-induced enterocolitis syndrome avoiding delayed diagnosis with unnecessary laboratory tests and detrimental treatments.

Moreover it highlights the unmet needs in diagnosis that require urgent attention from the scientific community to improve the management of patients with FPIES.

1. Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non- IgE-mediated allergy that occurs with gastrointestinal symptoms¹. FPIES can present in its acute or chronic form, based on the frequency and the dose of the offending food allergen assumed¹. It is suggested that if the culprit food is ingested intermittently and at a lower dose, the acute FPIES occurs, otherwise if the offending food is ingested frequently and at higher dose, a chronic form of gastrointestinal food allergy may emerge¹. Some children with the latter form will present with acute FPIES reactions after a period of food avoidance¹. This phenomenon has been named chronic FPIES¹. Whether the chronic gut inflammation in this context is a separate entity from the predominantly non-IgE-mediated, broad umbrella ‘gastro-intestinal food allergy’ remains open for debate.

Further classifications have been used for FPIES, based on a number of concepts, as follows: 1) based on the severity of clinical manifestations into mild, moderate and severe for acute FPIES and in milder and severe forms for chronic FPIES²; 2) based on the age of the onset, in early, late and adult-onset³; 3) based on the type of the trigger foods, in non solid food (cow’s milk/soy) FPIES, solid food FPIES and multiple foods FPIES (i.e. when FPIES to multiple unrelated foods occurs)³ and finally, 4) based on the presence of specific IgE to the culprit food, in classic and atypical FPIES². The classification scheme of FPIES is shown in Figure 1.

1.1 Phenotypes of food protein-induced enterocolitis syndrome (FPIES)

1.1.1 Acute FPIES

Acute FPIES is characterized by repetitive and projectile vomiting usually within 1 to 4 hours from food ingestion¹. It may be associated with lethargy, hypotonia, pallor and hypothermia¹.

Watery diarrhea, when present, occurs usually after 6-8 hours from the symptom's onset¹. The acute episode resolves within 24 hours. The interval between the acute episodes is free from symptoms; therefore the infant suffering from acute FPIES is in his usual state of health¹.

Significant geographical differences have been noted regarding the FPIES clinical presentation. For instance, fever and bloody stools have been described in Japanese infants with acute FPIES; however, this is a rare occurrence in other areas or ethnic populations^{4,5}.

1.1.2 Chronic FPIES

Chronic FPIES is characterized by profuse diarrhea (with or without blood and/or mucus) associated with intermittent but progressively worsening vomiting leading, over time, to a failure to thrive. The symptoms may require days to weeks to fully resolve. After a period of elimination diet of the culprit food followed by its re-introduction, the acute FPIES symptoms typically occur¹ and confirm chronic FPIES diagnosis⁶.

Both acute and chronic forms may result in dehydration, metabolic acidosis, hypotension and hypovolemic shock¹.

Clinical symptoms of acute and chronic FPIES are illustrated in Table 1. The severity of clinical manifestation of both acute and chronic FPIES is shown in Figure 1.

1.1.3 Early on-set FPIES

It occurs in the neonatal and early infancy (usually within 3 months of age). It mostly presents in chronic form³.

1.1.4 Late on-set FPIES

Non-solid food [cow's milk (CM)/soy] FPIES typically appears in early infancy when formula is introduced. However, both for non-solid as well as solid foods, FPIES can present late infancy (4-7 months of age), at weaning timing (i.e. with the introduction of complementary foods or supplementary formula into the diet). It generally presents in acute form, after the first few feedings of the culprit food or after the re-introduction of the avoided food into the diet³.

1.1.5 Adult FPIES

It is a relatively rare entity, probably partly due to under-diagnosis and under-reporting. The first case report of acute FPIES in adult is described in 2012 by Fernandes BN et al.⁷. It presents in acute form with the same characteristics of infantile acute FPIES. Abdominal pain is the

predominant symptom in adult patients followed by vomiting and diarrhea⁸. Whether this reflects a difference in the clinical presentation between adults and children with FPIES, or the potential difficulty in capturing abdominal pain in young children requires further study. In adults, FPIES is more common in females than in males, contrarily to what happens in infancy⁹. Fish and shellfish are the most common trigger foods although other food allergens (wheat, egg and dairy) have also been described⁸⁻¹¹.

1.1.6 Non-solid food (CM/soy) FPIES

It can occur in acute or chronic form, in early or late onset³. CM is the most common food associated with FPIES in most series around the world¹²⁻¹⁶. Some exceptions to this are series from Australia¹⁷ and the Southwest US¹⁸ where rice is the major culprit food, and Spanish series where fish is the main culprit^{19,20}. Rarely acute and chronic FPIES forms have been described in exclusively breast-fed infants, caused by CM proteins²¹⁻²⁷.

FPIES to soy or combined with CM in formula fed infants is frequently described as a common trigger food in countries, such as the US and Korea, in which soy formula is commonly used, whereas in other countries, such as Italy, Spain, Israel, UK and Australia, it is rare^{12,14,16,28,29}. No cases of soy FPIES in exclusively breast-fed infants have been described so far.

Children with CM-FPIES are at risk of having FPIES to solid foods, in particular to grains (rice and oat)^{17,30}.

1.1.7 Solid food FPIES

This presents usually with the first few solid food introductions into the infant's diet as late-onset FPIES³.

Rice is the most commonly reported solid food in Australia¹⁷ and in Southwest US¹⁸ and whereas fish is more prevalent in Italy and Spain^{19,20,31-35}. This may partly reflect the diverse diet practices in different countries around the world. Virtually any solid food can trigger FPIES reactions, and relatively common ones include meat, fruits, vegetables, legumes and egg³⁶⁻³⁸.

Solid food FPIES occurs in about one third of children with CM and/or soy FPIES³ and up to 80% of children with solid FPIES tend to have multiple food triggers FPIES in some series^{18,38-41}.

1.1.8 Multiple foods FPIES

Up to 65-80% of children have FPIES to a single food, nonetheless, FPIES to multiple foods can occur³⁷⁻⁴¹. This involves presenting FPIES reactions to more than one unrelated food or food group³. In the US, about 10% of children react to 3 or more foods^{40,41}.

Risk factors to have multiple foods FPIES are reported to be early age of onset, FPIES to vegetable and/or fruit and more than two trigger foods already identified¹⁷.

1.1.9 Atypical FPIES

A subgroup of FPIES patients present positive skin prick test (SPT) and/or serum specific IgE (s-IgE) to the trigger food, defined as atypical FPIES². More details of this FPIES subtype are discussed in the allergy testing session.

2. Diagnosis

FPIES diagnosis is challenging for several aspects: the presenting symptoms are unspecific and are not the typical allergic ones (no skin and no respiratory involvement)³⁰, the time latency between the food ingestion and the onset of symptoms is delayed (1-4 hours)³⁰, the culprit foods are perceived to be hypoallergenic (rice, oats and chicken)^{37,40,41} awareness among clinicians is poor⁴²⁻⁴⁴, the diagnostic biomarkers are absent¹, allergy testing is usually negative³⁰ and specific diagnostic tests are still missing³⁰. For all these reasons FPIES is misdiagnosed^{33,45,46}; in fact, some studies reported a median delay of four to seven months¹⁶ from the first episode to the correct diagnosis with the occurrence of multiple reactions experienced by the same child^{30,37,47}. Mehr et al.¹⁷ found that only 25%, 44% and 30% of patients received the correct diagnosis after the first, the second and the third FPIES episode, respectively.

Therefore, the diagnosis of FPIES is based on the physician's ability to suspect the disease based on detailed clinical history³⁰.

2.1 Clinical History

The clinicians must carefully obtain information on all suspected culprit foods, the time latency between food intake and the onset of symptoms, clinical symptoms, general health between episodes and during elimination diet and the reproducibility of symptoms with the re-exposure to the trigger food³⁰.

2.1.1 Suspicion criteria for acute FPIES

Unfortunately, validated suspicion criteria for acute FPIES are still lacking. Recently, Sopo et al.⁴⁸ have proposed their criteria of suspicion (Table 2) on the basis of which the clinicians should refer a child to perform a diagnostic oral food challenge (OFC), if necessary.

2.2 Diagnostic criteria

Several unvalidated expert-based diagnostic criteria^{30,49-54}, have been proposed over time (Table 3), to assist clinicians in the diagnosis on the basis of clinical history. This allows to establish a clinical diagnosis in most cases without the need to perform an OFC, the gold standard for food

allergy diagnosis, which is time and resources intense and potentially risky⁵⁵. An excursus on diagnostic criteria of FPIES published over time in the literature is briefly reported. The first author who defined the diagnostic criteria of FPIES was Geraldine Powell in 1978⁵⁶. However, her criteria best defined the chronic form of FPIES, describing children of few months of life with the main feature of protracted diarrhea. Some years later, in 1986, Powell slightly modified the version of her criteria and incorporated features of acute FPIES⁴⁹. Sicherer et al.⁵¹ were the first to include repetitive vomiting, the main symptom of acute FPIES, in their criteria and, moreover, for the first time, the age limit of 9 months at initial presentation, is mentioned. In 2012, Leonard et al.⁵² proposed criteria similar to Sicherer⁵¹ regarding the age limit for the first episode of FPIES reaction. FPIES symptoms⁵² are not specified except for the involvement of the gastrointestinal system. The criteria specified by Leonard et al.⁵² required at least two episodes as well as those mentioned by Powell⁴⁹ and Sicherer⁵¹. Afterwards, in 2013, Sopo et al.⁵³ proposed their criteria for acute FPIES. The authors introduced, for the first time, the severity of FPIES episodes, in fact, repetitive vomiting must be accompanied by pallor, hyporeactivity and lethargy to avoid the diagnostic OFC. Furthermore, the duration of symptoms was described: “the symptoms last a few hours, usually fewer than 6 h”. The age limit of 9 months, for the first FPIES episode, was increased to 2 years of age, considering that the onset of FPIES could occur in older children and in adults^{7,57,58}. The importance of diarrhea is reduced, in fact, it is specified that “the diarrhea may be present much less frequently and later”. As well as the previous criteria^{49,51,52}, at least two episodes are necessary to diagnose FPIES. In 2015, Leonard et al.⁵⁴ published a modification of their diagnostic criteria for acute FPIES⁵², by removing the age limit for the FPIES reaction. For the first time, the diagnostic criteria are divided into major and minor ones. The presence of diarrhea without vomiting is considered possible, the time latency between the food ingestion and the occurrence of symptoms is extended to 6 hours, the need for at least 2 episodes to diagnose FPIES has remained unchanged. The episode severity is not included in the major criteria, but it is mentioned in the minor criteria, where the possibility to have hypotension, lethargy, pallor or hypotonia was taken into account. In 2017, Lee et al.⁵⁰ published diagnostic criteria in which the division between major and minor criteria is maintained, although only one major criterion is identified. The time latency between food ingestion and symptoms varied from 30 minutes up to 4 hours, the need to emergency room visit and/or intravenous fluid therapy is introduced as well as the need of a second episode with the same culprit food or an episode with a different food. The severity of the reaction and the occurrence of diarrhea within 24 hours are contemplated in the

minor criteria. According to the authors, the diagnosis of FPIES required the major criterion and at least 2 minor criteria. Finally, in 2017, Nowak et al.³⁰ published the international consensus guidelines that identified one major criterion and nine minor criteria. The diagnosis of acute FPIES is satisfied if the major criterion and at least 3 minor criteria are met. For chronic FPIES a well-defined set of criteria does not exist, but the most important criterion is “the resolution of symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced”. Furthermore, the guidelines assess that without a confirmatory OFC the diagnosis of chronic FPIES is not ensured³⁰. Diagnostic criteria for acute and chronic FPIES are summarized in Table 4. A practical algorithm to diagnose acute and chronic FPIES has been provided recently⁵⁹ (Figure 2).

The diagnostic criteria proposed by the International Consensus on FPIES are widely accepted and currently used by physicians, although they are not validated, basing on personal experience and on retrospective studies³⁰. The inconsistency between the different diagnostic criteria has already been mentioned by Sopo et al.⁶⁰ when different diagnostic criteria are applied to individual patients. Recently, the performance of different diagnostic criteria sets (DCSs)^{30,50-53} has been compared¹⁹ in a cohort of 51 children with high clinical suspicion of acute FPIES from Southern Europe. The sensitivity of the various DCSs was as follow: 1) Lee⁵⁰: 92.2% (47/51); 2) Nowak-Wegrzyn³⁰ 2017: 76.5% (39/51); 3) Powel modified by Sicherer⁵¹: 64.7% (33/51); 4) Sopo⁵³: 43.1% (22/51); 5) Leonard⁵²: 17.6% (9/51). These results showed that, to date, DCSs have limitations in identifying all patients with a high clinical suspicion of acute FPIES. In particular, 25% of children in this series did not meet the 2017 Consensus DCSs, the main reference for FPIES care, despite meeting other criteria sets published in the literature. The authors suggested that probably their cohort included children with milder FPIES phenotypes that might not be captured by the latest Consensus proposal³⁰. Similarly, Sopo et al.⁴⁸ proposed to include particular presentations where acute FPIES diagnosis is highly likely and the 2017 Consensus criteria might not be fully met. This includes ‘mild FPIES’, i.e. a child with at least 3 consecutive episodes consisting of only one vomit, without any other manifestations, and ‘multiple FPIES’, i.e. where a single typical episode would be sufficient to diagnose FPIES in a child who has already received a diagnosis of FPIES for another food. Although classically some DCS require “the absence of IgE-mediated signs or symptoms” to establish the diagnosis of acute FPIES, Sopo et al.⁴⁸ proposed a particular mixed phenotype named ‘FPIES with IgE-mediated symptoms’, in which patients present with typical FPIES features in addition to IgE mediated respiratory or cutaneous

symptoms. Whether the gastrointestinal manifestations (vomiting, abdominal pain, diarrhoea) and potential cardiovascular involvement seen in such cases reflects an IgE-mediated mechanism or the less understood FPIES pathophysiology, particularly in children reacting within 2 hours from food ingestion, requires further study. Finally, to further strengthen the concept of ‘reproducibility’, Sopo et al.⁴⁸ suggest incorporating to the 2017 Consensus criteria that the separate episodes of vomiting must occur in consecutive exposures to a given food. Moreover, it is difficult to assess the lethargy as “extreme”, as required by the 2017 Consensus DCS³⁰, basing one's judgment on subjective interpretation. Therefore, the validation of the diagnostic criteria for FPIES through prospective studies, that establish stronger criteria, is of paramount importance.

2.3 The Oral Food Challenge

The OFC is considered as the “gold standard” test for FPIES diagnosis. In most cases, the history and use of available DCS allows the clinician to establish a clinical diagnosis with high degree of certainty. However, in some cases, an OFC should be considered to clarify the diagnosis, for instance when the clinical history unclear or atypical, the child has experienced a single non severe episode, the culprit food is not easily identifiable or when the symptoms persist despite the removal of the trigger food from the diet³⁰. Most children with acute FPIES develop tolerance to the culprit food over time. As there is no diagnostic or prognostic biomarker for tolerance development, re-introducing the food, usually as a formal OFC, is the only way to check the acquisition of tolerance. This is generally recommended at least after a period of 12-18 months on avoidance since the most recent reaction³⁰. Evidence to guide the optimal timing to re-introduce the food in FPIES is very limited. Significant differences in resolution rates over time have been found in the few studies^{12,14,15,40,50} exploring this issue for different foods in different countries. Therefore, where available, clinical decisions on reintroduction should be made based on local data for the particular food involved. Generally, tolerance development in acute FPIES to CM occurs at a younger age although differences have been found in different series: for example, in Israel¹², 90% of children with FPIES to cow’s milk had reached tolerance by the age of 3 years, which is very similar to the resolution rate in an Australian⁵⁰ study (88% by the age of 3 years). In a cohort study from South Korea¹⁵, patients with CM-induced FPIES reached the tolerance earlier, 27.3% by 6 months of age, and 100% by 2 years. In contrast, in a study from the US⁴⁰, the median age of CM at resolution was higher (53% by 5 years of age) whereas in Italy¹⁴ the resolution rate of CM was 63% by 24 months of age. Fish and egg FPIES have been considered as persistent in

US⁴⁰ and Australian⁵⁰ series. However, in Spain, where fish is the leading cause of FPIES^{28,61} most children with fish FPIES develop tolerance over time, although later (75% by 5 years of age) than those with FPIES to CM (50% by 29 months of age)²⁰.

The reason for the significant differences in FPIES resolution rates in diverse countries remains uncertain. Plausible explanations may be the differences in diet habit, feeding practices, and genetics as well as the different time of the tolerance assessment by the OFC. Moreover, it could be explained by the differences in study design that conducts to population selection bias (i.e. general or referral population). For instance, studies based on general population could capture milder/less complex FPIES phenotypes, whereas studies on patients referred to tertiary allergy centers could include more severe/persistent or complex cases.

OFC might be helpful to verify the tolerance to foods belonging to the same group of the culprit's food, as co-allergy/cross-reactivity has been described³⁰ (see Table 6). Tolerance to one food from the same group (i.e. chicken and turkey from poultry's group or soy, bean, pea, chick-pea from the legumes group or rice, oat and wheat from the grains group) favors the tolerance to the other ones⁶².

FPIES to multiple foods is frequently found in some series, generally from complex reference centers in the US^{38,40}. This has led to particular weaning recommendations for children with FPIES, including categorizing foods into low, moderate and high risk of FPIES⁶³. FPIES to multiple foods seems much less common in other regions, where most children present with single food FPIES^{14 28,64}. Also, virtually any food can cause FPIES. Thus, the applicability of such weaning recommendations in many clinical settings remains unclear.

Sopo et al.⁶⁵ recently proposed a physician-supervised introduction of a mixture of risky foods (legumes, cereals, poultry) not yet introduced into the diet of children younger than 1 year, in countries where FPIES to multiple foods has a low prevalence^{12,14,37}, an approach that is yet to be validated.

Barni et al.⁶⁶ examined in Italian children with FPIES to both liquid and solid foods the tolerance of a range of foods on first exposure through an OFC. Only 3.3% of OFCs were positive and all positive OFCs occurred in patients with already known FPIES to multiple foods (16% of the infants). Moreover, 13.2% of patients with negative OFCs in hospital setting presented acute-FPIES symptoms with the same food at home. This phenomenon of reacting with acute FPIES on the subsequent exposure after a negative follow-up OFC has been recently observed in a recent study⁶⁷. For these reasons, given the low prevalence of reactivity to other foods in children with

single food FPIES and the possibility of reactions at home after negative OFCs in hospital, Barni et al.⁶⁶ suggested to reintroduce new foods at home with a graded approach, at least in those countries where the prevalence of multiple FPIES is low. Strong evidence on the optimal approach to weaning in children with FPIES in different countries and settings is lacking. Thus, it remains at the physician's discretion based on the available evidence, in conjunction with the family preference⁶⁸.

2.3.1 The Oral Food Challenge Protocol

Evidence on reactivity thresholds for FPIES is very limited. The timing between ingestion and reaction is variable ranging from 0.5 to 6 hours³⁰, and poorly studied. Finally, FPIES reactions can vary from mild and self-limited to life-threatening reactions requiring intensive care³⁰. Therefore, the optimal approach to OFC in FPIES remains unclear.

The 2017 Consensus³⁰ suggest an OFC protocol involving administering the challenge food at a dose of 0.06 to 0.6 grams per kilogram of body weight (not exceeding a total of 3 g of protein or 10 g of total food) in 3 equal doses over 30 minutes followed by a 4 to 6 -hour observation.

When a very low dose of food protein (e.g., 0.06 g per kilogram of body weight) is administered and no reaction occurs after 2-3 hours of observation, it is recommended to give a full serving of an age-appropriate dose, followed by an additional 4 hours of observation³⁰.

A very low dose of food protein (as initial dose) and an increasing of interval between doses are recommended for those patients with a clinical history of severe FPIES reaction (e.g. treated with intravenous fluids or required hospitalization)³⁰.

A variety of other protocols for OFC have been published, differing in amount and number of doses and timing between the administered dose^{12,14,20,61,69-74}. Since the different OFC protocols have not been studied or compared systematically, it is at the supervising physician's judgment to adopt the protocol that best suits the patient's characteristics³⁰. The timing and severity of previous reactions, as well as the amount of food ingested, should be considered when tailoring OFCs to individual patients.

Before performing an OFC, it is recommended to perform a SPT or s-IgE tests to challenge food, especially after a period of elimination diet, since up to 30% of patients can develop specific IgE to the FPIES culprit food^{75,76}, although its clinical meaning remains unclear.

If the presence of IgE to the challenge food is detected, some authors suggest to follow the usual graded OFC protocol for IgE mediated food allergy with a longer post-challenge observation period for the possible occurrence of delayed FPIES reactions⁷⁴.

The OFC should be performed in a hospital setting and the immediate placement of peripheral venous access is recommended, since intravenous fluids are the cornerstone of acute management, and up to 50% of children with positive FPIES food challenges receive this treatment^{62,74}.

2.3.2 Interpretation of Oral Food Challenge

The diagnostic criteria for the interpretation of OFC proposed by the 2017 Consensus are shown in Table 5. The OFC is considered positive and therefore diagnostic of FPIES if the major criterion along with at least 2 minor criteria are met³⁰.

Obtaining a complete blood count (CBC) before performing the challenge and 4-6 hours after the food ingestion might be helpful to evaluate the potential increase of neutrophils greater than 1500 cells/mL. This feature, when present, represents one of the minor criteria to interpret the OFC as positive³⁰ and may help assess the OFC outcome.

Two particular scenarios should be taken into account when evaluating the OFC outcome, as suggested by the consensus guidelines³⁰. The prompt use of ondansetron could prevent the occurrence of some minor criteria symptoms such as repetitive vomiting, pallor or lethargy. Thus, an OFC may be considered positive when the major criterion alone (vomiting) is met if ondansetron has been administered early. Second, not all the hospital settings are able to collect the blood sample to determine neutrophil counts before and during the OFC. This may limit their ability to apply the existing criteria and decisions on the OFC outcome would be guided by the clinical manifestations only. In research settings the more stringent criteria should be met to consider an OFC positive.

A recent study⁶⁷ highlighted that children presenting with mild symptoms at OFC may not fulfill the criteria for a positive OFC, leading to being labeled as inconclusive. Subsequent mild reactions on further exposures in these children were also noted⁶⁷. Recently, Sopo et al.⁴⁸ suggested to consider a 'mild FPIES' phenotype as positive when interpreting the OFC outcome, especially if the patient experienced numerous episodes in the past.

2.4 Laboratory testing

To date, no laboratory nor image tests are pathognomonic of FPIES³⁰.

2.4.1 Blood testing

FPIES reactions are characterized by neutrophilia, and by a time-dependent, significant increase in C-reactive protein (CRP).

In an acute FPIES reaction, neutrophils start to increase approximately 2 hours after the onset of gastrointestinal symptoms with a peak at 6 hours⁷⁷ and a normalization in about 18-24 hours^{40,56}. Nowak et al.³⁸ reported an average increase of 4500 neutrophils/mm³, with a range from 700 to 15000/mm³, after a positive challenge.

For the first time, Pecora et al.⁷⁷ found that CRP does not increase until 6 hours after an FPIES reaction, with a peak at 12 hours.

In a Japanese study⁷⁸, the elevated CRP level, during a positive OFC, has been correlated with later tolerance acquisition to the culprit food (21 months versus 12 months) in a statistically significant manner. Moreover, the CRP levels significantly correlate with the degree of reaction severity⁷⁷ and has been evaluated as a possible marker for disease activity⁷⁹.

In one study, peripheral thrombocytosis has also been observed in 63% of patients with a platelet count of $>500 \times 10^9$ platelets/L³⁷.

Eosinophilia has also been noted in Japanese children⁷⁸ with acute FPIES during an OFC. The eosinophilia level has a positive correlation with the presence of vomiting and bloody stools whereas it is negatively correlated with the age of tolerance acquisition. Furthermore, in the same study, children with early-onset FPIES (<10 days of age) had a higher peripheral eosinophilia than children with late-onset FPIES (>10 days of age) (median peripheral eosinophilia: 9.8% versus 5.4%).

In patients with acute and chronic FPIES metabolic acidosis and methemoglobinemia have been shown at presentation^{80,81}.

Hypoalbuminemia, anemia, eosinophilia and leukocytosis have been observed in patients with chronic FPIES^{3,82}.

2.4.2 Allergy testing

SPT and s-IgE to the trigger food are usually negative in patients with FPIES. Thus, food-specific IgE testing is not routinely recommended at their initial evaluation³⁰.

Nevertheless, food s-IgE testing could be helpful in specific situations. First, a subpopulation of patients with FPIES have detectable IgE to the trigger foods at initial diagnosis. This condition, called “atypical FPIES”, which occurs with a rate of 2-20%^{14,40,83} seems to be associated with a delayed age of tolerance acquisition^{40,50}, in particular with cow’s milk as noted by Caubet et al.⁴⁰

The association between s-IgE to FPIES food and the persistence of FPIES requires further investigation⁸⁴.

Secondly, patients with undetectable IgE to the offending food at the initial diagnosis can develop sensitization to the same allergen during the follow-up occurring up to 30%^{75,85}. This phenomenon is assumed to be caused by the presence, in the intestinal mucosa, of local IgE to culprit food that does not reach the serum but participates in allergic reactions⁸⁴. Therefore, although the pathophysiological role of IgE has not been completely understood, obtaining food-IgE testing in patients is useful before performing OFC³⁰.

Finally, patients with FPIES may have other allergic co-morbidities, mainly IgE-mediated food allergy and eczema, occurring in approximately 20-40% of the patients^{40,83}. Therefore, an appropriate clinical history taking, testing and management as required should be included at follow-up visits.

Atopy patch testing (APT) is designed to identify allergens that cause cell-mediated hypersensitivity. Its utility in FPIES has not been proven and it is not recommended. The only two small studies conducted in this area have provided conflicting results^{70,86}. Fogg et al.⁷⁰ identified a sensitivity of 100%, specificity of 71%, a positive predictive value of 75% and a negative predictive value of 100% whereas Jarvinen et al.⁸⁶ found a sensitivity of 12% a specificity of 85.7%, a positive predictive value of 40% and a negative predicted value of 55%. The differences in the findings between the mentioned studies could be attributed to the median time latency between APT performing and the most recent reaction: it was shorter in Fogg et al.⁷⁰ than in Jarvine et al.⁸⁶ study [12 months (range 4 –29 months) vs 24.5 months (range, 14.5–79 months)]. For this reason, children in Fogg study could represent a group with a more “active” disease as well as more reactive T cells responsible of the APT positivity.

2.4.3 Imaging

Radiologic studies, such as abdominal X-ray and barium studies of the small bowel, have shown non-specific findings in chronic FPIES infants. For these reasons such testing is not considered routinely to diagnose chronic FPIES³⁰.

Endoscopic evaluation with biopsy was performed in earlier studies on chronic FPIES showing jejuna villous atrophy, edema, inflammatory cells infiltration, ulcer and friable mucosa through the colon^{87,88}.

2.4.4 Other testing

Occult blood, leukocytes and eosinophils as well as increased carbohydrates are often positive in stool patients with acute FPIES, when diarrhea is present^{56,89}. The same findings can be seen in patients with chronic FPIES^{80,81}.

An increase in fecal calprotectin has been detected in other conditions involving gut inflammation, such as inflammatory bowel diseases⁹⁰. Some studies^{91,92} have suggested an increase in this parameter in non-IgE mediated food allergy, including FPIES⁹³. The lack of validated normal ranges in children affected by FPIES limits its utility for now in this condition⁹³.

To demonstrate local gut inflammation, Hwang et al.⁹⁴ performed an invasive approach in patients who underwent OFC. The gastric aspirates demonstrated >10 leukocytes per high powered field (hpf) in patients with positive OFC versus <10 leukocytes/hpf in patients with negative OFC.

Laboratory characteristics of acute and chronic FPIES are shown in Table 7. Little is known about the pathophysiology of FPIES. As a result, no specific systemic or local biomarkers are available to support the diagnosis. For this reason, this should be a key focus for future research.

2.5 Differential diagnosis

As previously reported, diagnostic tests specific for FPIES do not exist³⁰ and misdiagnosis/delayed diagnosis is very common. Some routine tests may help the clinician to rule out other pathological conditions that have clinical characteristics similar to FPIES³⁰.

In an Australian study, only 10% of patients, referred to the emergency department, were discharged with the correct diagnosis³⁷. In the same study, 34%, 28%, and 22% of patients received, respectively, abdominal imaging studies, sepsis workups and surgical consultations as additional evaluations.

Acute viral gastroenteritis and sepsis are the most common diseases misdiagnosed with FPIES reactions⁴⁷.

Similarly to FPIES, acute gastroenteritis presents with vomiting but has other different features like fever, profuse diarrhea and less serious and rapid onsets than FPIES. Moreover, in the stool patients affected by gastroenteritis, bacteria and viruses can be detected. In addition, FPIES episodes lasts hours, whereas gastroenteritis lasts generally a few days⁴⁷.

FPIES can share symptoms with sepsis, including weakness, vomiting, hypotension, tachycardia, as well as leukocytosis, thrombocytosis, neutrophilia, metabolic acidosis and methemoglobinemia⁴⁷. The differences between FPIES and sepsis is the lack of fever, except in Japanese children⁴, and the inflammatory markers that are normal or only slightly elevated⁴⁷.

The presence of vomiting, floppiness, pallor without fever and normal CPR should alert the clinician to reach a diagnosis of acute FPIES⁹⁵ more easily whereas an alternative diagnosis must be required in those patients with a highly elevated CRP.

Many other diseases can be confused with FPIES. Differential diagnoses and their similarities and distinguishing characteristics from FPIES are summarized in Table 8.

Conclusions

FPIES is mostly a clinical diagnosis based on the clinical history. OFC can help determine the diagnosis in unclear cases and it is key to assess the resolution of FPIES over time.

Laboratory and radiologic tests are not specific but can help support the diagnosis and rule out alternative diseases that may present with similar symptoms.

Many advances have been made in the past 20 years on the knowledge of FPIES but much more remains to be understood regarding its pathophysiology and diverse presentation across the globe to help improve our approach to diagnosis and management. Particularly, a specific biomarker that can help clinicians to diagnose FPIES at first presentation to avoid misdiagnosis and repeated reactions are lacking and urgently needed. Prognostic biomarkers to identify safe foods for weaning as well as tolerance development over time are also a priority.

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Table 1. Clinical characteristics of acute and chronic food protein induced enterocolitis (adapted with the authorization from Ref¹)

Acute FPIES	Chronic FPIES
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- Repetitive projectile vomiting 1-4 h after food ingestion
- Diarrhea within 24 h
- Lethargy
- Pallor
- Hypotonia
- Dehydration
- Hypovolemia $\pm$ shock
- Hypothermia
- Symptoms resolve within 24 hours

- Frequent watery diarrhea
- Intermittent but progressive emesis
- Lethargy
- Pallor
- Hypotonia
- Dehydration
- Hypovolemia $\pm$ shock
- Hypothermia
- Fever (rare, only in Asian infant)
- Abdominal distension
- Failure to thrive/poor growth
- Symptoms resolution over days to weeks

Table 2. Suspicion criteria for acute food protein induced enterocolitis (reprinted with the authorization from Ref⁴⁸)

Suspicion criteria for acute FPIES	
	• A single episode of projectile and repeated vomiting, occurring 2–4 h after food intake, accompanied by at least moderate pallor and lethargy. There should not be ingestion of the same food without adverse reactions after the episode of vomiting.
	• At least two consecutive episodes of one (not repetitive) vomit, without pallor and lethargy, within 2–4 h from ingestion of the same food. There should not be ingestion of the same food without adverse reactions after the episode of vomiting.

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Table 3. Diagnostic criteria for food protein induced enterocolitis from the literature overtime (adapted with the authorization from Ref⁶⁰)

Authors	Powell, 1986 [49]	Sicherer, 1998 [51]	Leonard, 2012 [52]	Miceli Sopo, 2013 [53]	Leonard, 2015 [54]	Lee, 2017 [50]	Nowak-Węgrzyn, 2017 [30]
Clinical features	-Disappearance of the symptoms of vomiting and diarrhea, and of diagnostic findings in the stool (blood and leukocytes), after all antigens are removed from diet. -No other cause for the colitis is demonstrable. -Symptoms do not recur and weight gain is normal for one month on a low-antigen formula, such as breast milk or casein hydrolysate formula, as the only dietary source. -Challenge with milk or soy formula, or other offending food antigens, reproduces symptoms.	-Less than 9 months of age at initial presentation [reaction]. -Repeated exposure to the incriminated food elicited diarrhea and/or repetitive vomiting within 24 h without any other cause for the symptoms. -There were no symptoms other than gastrointestinal symptoms elicited by the incriminated food. -Removal of the offending protein from the diet resulted in resolution of the symptoms, and/or a standardized food challenge elicited diarrhea and/or vomiting within 24 h after administration of the food.	- Less than 9 months of age at initial diagnosis. -Repeated exposure to causative food elicits gastrointestinal symptoms without alternative cause. -Absence of symptoms that may suggest an IgE-mediated reaction. -Removal of causative food results in resolution of symptoms. -Re-exposure or oral food challenge elicits typical symptoms within 4 h.	-Less than 2 years of age at first presentation [frequent feature but not mandatory]. -Exposure to the incriminated food elicits repetitive and important vomiting, pallor, hyporeactivity and lethargy within 2---4 h. -Diarrhea may be present, much less frequently and later. The symptoms last a few hours, usually fewer than 6 h. -Absence of symptoms that may suggest an IgE-mediated reaction. -Avoidance of the offending protein from the diet results in resolution of symptoms. -Re-exposure or oral food challenge elicits typical symptoms within 2---4 h. Two typical episodes are needed to deliver the	- Major criteria -Repetitive vomiting or diarrhea within 6 h of food ingestion. -Absence of cutaneous and respiratory symptoms suggestive of an IgE-mediated allergy. -Removal of causative food results in resolution of symptoms. -Re-exposure or a food challenge elicits the typical symptoms. - Minor criteria - Hypotension. -Lethargy, pallor, or hypotonia. -Negative skin-prick test and undetectable specific IgE level. -Absence of fever or hypothermia [36°C]	- Major criterion: - repetitive vomiting (0.5-4 hours) after eating a suspect food(s) - Minor criteria: -A second (or more) episode of repetitive vomiting (0.5-4 hours) after eating the same suspect food -Repetitive vomiting episode (0.5-4 hours) after eating a different food - Associated floppiness, pallor, and/or diarrhea (within 24 hours) during at least one episode - Need for an emergency room visit and/or intravenous fluid therapy during at least one reaction	- Major criterion -Vomiting in the 1---4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms. - Minor criteria - A second [or more] episode of repetitive vomiting after eating the same suspect food. - Repetitive vomiting episode 1---4 h after eating a different food. -Extreme lethargy with any suspected reaction. - - Marked pallor with any suspected reaction. - Need for emergency room visit with any suspected reaction. -Need for intravenous fluid support with any suspected reaction.

				definitive diagnosis.			-Diarrhea in 24 h [usually 5---10 h]. -Hypotension. -Hypothermia.
Diagnosis of FPIES is satisfied if in the presenting episode(s)	All the above items are met	All the above items are met	All the above items are met	All the above items are met	All the above items are met	Major criterion and at least 2 minor criteria are met	Major criterion and at least 3 minor criteria are met

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Table 4. Diagnostic criteria for a patient presenting with possible food protein induced enterocolitis (adapted with the authorization from Ref³⁰)

Acute FPIES	
Major criterion: Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms	Minor criteria: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency department visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5-10 h) 8. Hypotension 9. Hypothermia
The diagnosis of FPIES requires that a patient meets the major criterion and ≥ 3 minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group. Furthermore, although not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.	
Chronic FPIES	
The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhea in 24 h (usually 5-10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.	

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Table 5. Diagnostic criteria for the interpretation of oral food challenge in patients with a history possible or confirmed food protein induced enterocolitis (adapted with the authorization from Ref³⁰)

Major criterion	Minor criteria
Vomiting in the 1- to 4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms	1. Lethargy 2. Pallor 3. Diarrhea 5-10 h after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of >1500 neutrophils above the baseline count

The OFC will be considered diagnostic of FPIES (ie, positive) if the major criterion is met with >2 minor criteria. However, we would suggest 2 important caveats to these criteria: (1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor, and lethargy can be averted, and (2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician might decide that a challenge be considered diagnostic in some instances, even if only the major criterion was met. However, in challenges performed for research purposes, providers should adhere to stringent criteria for challenge positivity.

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Table 6. Co-allergy/cross-reactivity between common foods in children with food protein induced enterocolitis (adapted with the authorization from Ref³⁰)

FPIES to	Co-allergy/cross reactivity	Observed occurrence [°]
Cow's milk	Soya	<30-40%
	Any solid foods	<16%
Soya	Cow's milk	<30-40%
	Any solid foods	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soya	<25%
Legumes [°]	Soya	<80%
Grains [°]	Other grains	About 50%
Poultry [°]	Other poultry	<40%

[°]where a child already tolerates a food type in a particular group (eg, beans), clinical reactions to other members of the same group (eg, other legumes) are unlikely. Caution is warranted in interpreting these data because they were derived from single centers and from patient populations skewed toward the more severe phenotype of FPIES and might overestimate the actual risk of co-allergy.

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Table 7. Laboratory characteristics of acute and chronic food protein induced enterocolitis (adapted with the authorization from Ref¹)

Acute FPIES	Chronic FPIES
• Leukocytosis with neutrophilia • Thrombocytosis • Metabolic acidosis • Electrolyte derangements • Methemoglobinemia • Stools leukocytes, eosinophils • Stool reducing substances • Stool occult or frank blood	• Leukocytosis with neutrophilia • Thrombocytosis • Metabolic acidosis • Electrolyte derangements • Methemoglobinemia • Hypoalbuminemia and hypoproteinemia • Stools leukocytes, eosinophils • Stool reducing substances • Stool occult or frank blood

Table 8. Differential diagnosis (adapted with the authorization from Ref^{1,96})

Diagnosis	Similar features with FPIES	Differentiating features from FPIES
Infections Sepsis Gastroenteritis	Sudden lethargy, vomiting, hypotension, hypothermia, peripheral blood neutrophilia Vomiting, watery diarrhea	Fever present, treatment with fluid resuscitation alone does not improve Fever present, slower course over days, no specific food trigger, family members maybe affected
Anatomical gastrointestinal obstruction Malrotation/volvulus Intussusception Hirschsprung's disease Pyloric stenosis Necrotizing enterocolitis Very early onset inflammatory bowel disease	Vomiting in an infant, bloody stool (bowel ischemia), dehydration and shock, failure to thrive, distended loops of bowel on X-ray Vomiting, bloody diarrhea, intermittent, lethargy, and pallor Vomiting, failure to thrive in infant/young child Recurrent projectile vomiting leading to dehydration Lethargy, vomiting, bloody diarrhea, neutrophilia Failure to thrive, diarrhea, blood or mucus in stool, vomiting	Bilious vomiting, abdominal distension, sepsis from necrotic bowel, fluid resuscitation alone does not improve Severe intermittent, crampy abdominal pain, not associated with food, abdominal mass on exam, detectable on ultrasound Abdominal distention, constipation, delayed passage of meconium, bilious emesis No diarrhea, diagnosis with ultrasound Higher risk in premature and/or low-birth weight infants and formula-fed infants. Requires parental nutrition, intravenous antibiotics, pneumatosis intestinalis on X-ray Symptoms are not often linked to specific food; family history may be positive for IBD; confirmation by biopsy findings
Gastrointestinal disorders Celiac disease Gastroesophageal reflux Lactose intolerance Cyclic vomiting	Failure to thrive, chronic diarrhea, vomiting, anemia Intermittent vomiting Diarrhea with ingestion of specific food (lactose) Repetitive recurrent vomiting, lethargy	Celiac serology positive and confirmed with biopsy, malabsorption No diarrhea, no dehydration, vomiting usually minimal Symptoms only with cow's milk/lactose, bloating, flatulence, low prevalence under 5–6 years of age Not associated with food, stereotypical vomiting typically early in the day, associated with prodrome (can be associated with headache, photophobia)
Allergic disorders Eosinophilic esophagitis Food protein-induced allergic proctocolitis Food protein-induced enteropathy Anaphylaxis	Triggered by specific food, vomiting, failure to thrive Stool with blood or mucous, associated with cow's milk formula intake Failure to thrive, intermittent vomiting or diarrhea with ingestion of specific food (i.e., cow's milk, egg, etc.)	Dysphagia/food impaction sensation, chronic No failure to thrive, no vomiting, resolution sooner (approx 1 year of age), patients not sick appearing Small bowel injury and malabsorption. No lethargy, pallor, or dehydration; no methemoglobinemia or acidemia. Confirm diagnosis with endoscopy and biopsy

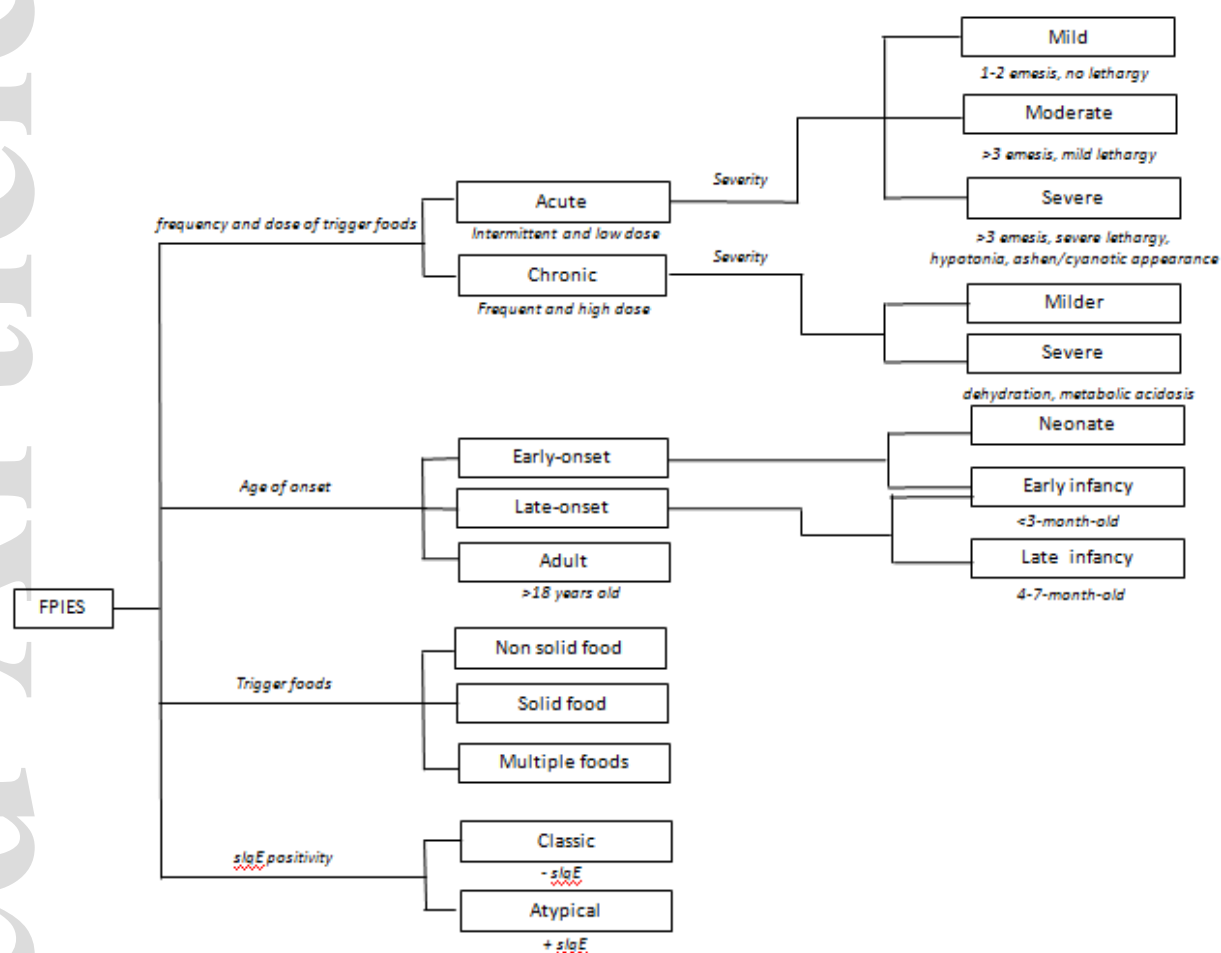
	Vomiting, diarrhea with ingestion of specific food, reproducible	Immediate symptoms with ingestion of food (minutes to 1 h), positive SPT and sIgE, other systemic symptoms (i.e., urticaria, angioedema, etc)
Inborn errors of metabolism (galactosemia, fructose intolerance, methylmalonic acidemia, ornithine transcarbamylase deficiency)	Intermittent vomiting/lethargy	Inability to process sugars, amino acids, and organic acids; many patients may self-avoid food that cannot be metabolized (avoidance of fruit in fructose intolerance and dairy in galactosemia)
Inadequate energy production (mitochondrial, fatty acid oxidation disorders, glycogen storage disorder)	Intermittent vomiting/lethargy	Failure to thrive, heart and muscle involvement, splenomegaly, hypoglycemia
Disorders of complex molecules Lysosomal storage disorders	Poor growth, feeding swallowing difficulties	Hepatosplenomegaly, developmental delay, short stature, chronic pain
Congenital disorder of glycosylation Congenital methemoglobinemia (type I)	Vomiting, diarrhea) Methemoglobinemia	Low tone, seizures, dysmorphic features Mostly asymptomatic, no vomiting or diarrhea, general fatigue, dyspnea
Primary immunodeficiency	Chronic diarrhea (due to frequent or persistent GI infections, eg, enterovirus)	Not specific to food, abnormality in lymphocyte counts, immunoglobulins, etc.
Immune enteropathy	Chronic diarrhea	Diarrhea frequently with blood or mucous, severe diarrhea with no food association, rare in infants and toddlers
Mast cell activation syndrome	Chronic/intermittent watery diarrhea	Symptoms food nonspecific, other organ systems, eg, skin, respiratory, cardiovascular; elevated serum tryptase and/or urinary histamine metabolites or PGD2 or 11-b-PGF2-alpha during at least 2 acute episodes

FPIES, Food protein-induced enterocolitis syndrome; GI, gastrointestinal; IBD, inflammatory bowel disease; IV, intravenous; PGD2, prostaglandin D2; SPT, skin prick test.

Figure 1. The classification scheme of FPIES (adapted with the authorization from Ref²)

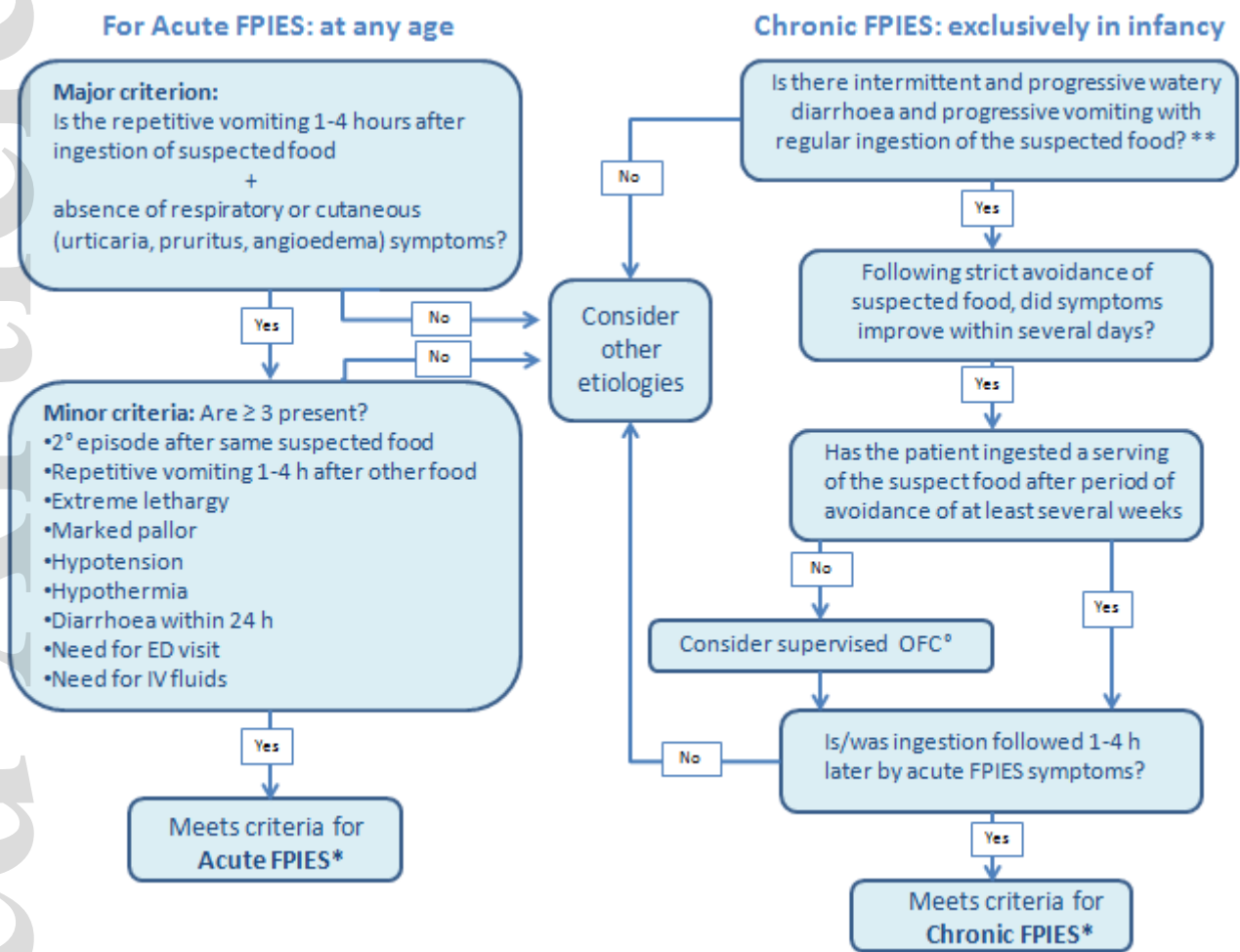
Figure 2. Diagnostic algorithm for acute and chronic FPIES (reprinted with the authorization from Ref⁵⁹)

Figure 1.



Legend: FPIES: food protein induced enterocolitis syndrome; sIgE: specific IgE

Figure 2.



*Based on Ref³⁰

**Chronic FPIES Is described almost exclusively with cow milk or soy in young infants

^owithout a confirmatory OFC or other ingestion with emesis onset in 1-4 hours, diagnosis of chronic FPIES is presumptive