

EXPERT
REVIEWSFood protein-induced
enterocolitis syndrome, from
practice to theory*Expert Rev. Clin. Immunol.* 9(8), 707–715 (2013)**Stefano Miceli Sopo^{*1},
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Food protein-induced enterocolitis syndrome (FPIES) is an allergic disease, probably non-IgE-mediated, with expression predominantly in the GI tract. The most characteristic symptom is repeated, debilitating vomiting. It occurs 2–6 h after ingestion of culprit food and is usually accompanied by pallor and lethargy. There may be diarrhea, and in 10–20% of cases, severe hypotension. These symptoms resolve completely within a few hours. The food most frequently involved is cow's milk, followed by rice, but many other foods may be involved. The prognosis is generally good in a few years. In this review the authors try to cope, with the help of some case histories, with the practical clinical aspects of FPIES. The authors also try to provide a management approach based on current knowledge, and finally, to point out the aspects of FPIES that are still controversial.

KEYWORDS: cow's milk allergy • food allergy • food protein-induced enterocolitis syndrome • oral food challenge • vomiting**Sometimes you need to be
lucky – Bridget's story**

Since her birth Bridget had almost always been breast-fed; she drank cow's milk (CM) formula only during the first week after birth and at the 45th day of life, without showing any adverse reaction. When she was 4 months old, Bridget drank 120 ml of CM formula and then fell asleep for approximately 90 minutes. A few minutes after she woke up, she started to vomit repetitively and became hyporeactive, pale, hypotonic and so sleepy that her parents could not wake her up completely. Worried about her condition, Bridget's parents drove her to the nearest first aid station, where doctors monitored the baby's vital signs, including oximetry, blood pressure and heart rate, and found they were normal. A few hours later Bridget felt better and acted as though nothing unpleasant had happened. Doctors interpreted this episode as a vagal reaction associated with vomiting and suspected a probable diagnosis of gastroesophageal reflux disease (GERD), on the basis of the clinical history which reported sleep difficulties and opisthotonos. Therefore Bridget returned home with the suggestion of a gastroenterological consultation. At the end of the same day, she had a huge evacuation of liquid and acrid-smelling

feces. Following the doctor's suggestion Bridget went to the pediatric gastroenterologist. He told Bridget's mother that her child had no gastroenterological problem and that she did not need to change anything in the baby's diet. In spite of that, Bridget's mother decided that exclusive breast-feeding would have been the safest solution, so she did not feed the child with artificial milk anymore. One day she met a young resident and told her her daughter's story. She was fortunate in that this young doctor attended the pediatric allergic center, so she suspected an allergy and planned a specialist examination for the baby. During the visit, skin prick tests (SPT) were performed and tested negative for CM proteins. An oral food challenge (OFC) was scheduled and performed in a day-hospital (DH) regimen, one month after the critical episode. During that day, the baby drank 60 ml of CM in one dose, which was half of the quantity that caused the previous reaction. Two hours after the ingestion, Bridget started to vomit and became pale and hyporeactive, but blood pressure was normal. These symptoms continued for 4 h and blood pressure decreased, especially the diastolic parameter, to below the physiological range (81/35 mmHg). The child received intravenous (iv.) fluids, hydrocortisone and intramuscular

(im.) epinephrine. Six hours after CM ingestion Bridget was fine and returned home with the diagnosis of food protein-induced enterocolitis syndrome (FPIES) caused by CM, and the young resident's suspicion was confirmed. Bridget had to eliminate CM from her diet and, in case of lack of breast milk, she would have to replace it with a extensively casein-hydrolyzed formula. It was also suggested to perform two other OFCs in day-hospital regimens. The first one had to be performed soon with a mixture of cereals, legumes (including soy) and poultry, and the second at the age of 18 months with CM, to verify the possible achievement of tolerance.

Sometimes you need to be lucky – Ernst's story

Since his birth, Ernst was exclusively breast-fed; he started weaning when he was five months old. At 7 months he had already eaten cooked codfish twice, without showing any clinical problem. One day, 2 h after the ingestion of 50 g of steamed sole, Ernst started to vomit repetitively, he became hypotonic, hyporeactive and shortly after he started to suffer from diarrhea. Five hours later the baby recovered completely. After some time, Ernst's aunt, who was a doctor, suggested his parents give him fish again and consequently Ernst ate a homogenized sole baby food. After 4 h symptoms arose again and they were even more serious compared to those previously reported. When the baby was ten months old his parents decided to try again, giving Ernst a sea bream homogenized baby food, and unfortunately the baby fell sick showing all the symptoms mentioned before except diarrhea. As the third attempt failed as well, Ernst's parents brought their child to an allergist. SPTs performed with the culprit food (sole and sea bream) were negative and FPIES was diagnosed without needing to perform any OFC. The allergist recommended that Ernst keep eating everything he ate before (he had already eaten milk, legumes, cereals and poultry, without any problems) except fish, molluscs and crustaceans. Nevertheless, the allergist pointed out that the chances were that the baby was not allergic to every sea creature. Therefore, it could be possible to perform other OFCs with molluscs and crustaceans, but also with codfish, swordfish and tuna, since there was a discrete possibility of passing him without any adverse reaction.

From practice to theory

Bridget was lucky, since the story of her first clinical reaction was heard by a young resident pediatrician who knew FPIES and was able to plan a correct work-up to understand the baby's problem. Thanks to that, the second reaction was induced in a safest place which was well equipped and ready to face any harmful situation. Ernst instead wasn't as lucky as Bridget, because nobody considered either the hypothesis of FPIES or even a generic food allergy (FA). The child had three episodes at home without any appropriate assistance, in danger of a more severe outcome. These two stories are suitable for learning a lot about FPIES, as they exemplify some well-known and even uncommon aspects of this syndrome:

- FPIES pathogenesis is probably non-IgE-mediated, so culprit-food-specific IgE research is almost always negative;
- The period of life during which FPIES appears most frequently is the first 9 months after birth;
- The most frequent culprit food (except in Australia) is CM;
- The most frequent solid food that induces FPIES in Italy is fish, while worldwide it is rice;
- FPIES symptoms are vomiting, hyporeactivity, hypotonia and sometimes diarrhea;
- The evolution of FPIES is benign in a few hours;
- Diagnostic criteria consist of the occurrence of at least two typical episodes;
- There is often a diagnostic delay – as many as six episodes could take place before the situation is clarified;
- Acute therapeutical measures are iv. fluids and cortisone;
- Dietetic measures consist of eliminating the culprit food from the patient's diet;
- As far as prognosis is concerned, there is a good chance of achieving tolerance at 18 months if the responsible food is CM; however, there aren't enough data for other foods.

Table 1. Acute and chronic FPIES clinical manifestations.

Acute FPIES	Chronic FPIES
Important and repetitive vomiting (constant)	Regurgitation, small amounts of vomit
Lethargy (frequent)	Lethargy
Hyporeactivity (frequent)	Failure to thrive
Pallor (frequent)	Dehydration
Diarrhea (inconstant and tardive)	Diarrhea, sometimes bloody
Dehydration (rare)	Abdominal distention
Hypothermia (rare)	
Hypotension (rare)	

FPIES definition and diagnostic criteria

FPIES is an important cell-mediated food hypersensitivity, probably non-IgE-mediated and most commonly caused by CM and soy [1]. There could be other culprit solid foods, such as fish, rice, egg, legumes, poultry, but they are less frequent. Acute FPIES (the most frequent form) is characterized by repetitive and severe vomiting, pallor, hyporeactivity and is less frequently accompanied by diarrhea that can lead toward dehydration and shock in a 10–20% of patients. FPIES clinical findings are listed in TABLE 1. FPIES can also manifestate itself in a chronic form. This was most frequent in the past years, when it was used to be called 'CM protein intolerance' and it was often diagnosed by gastroenterologists. Nowadays the chronic form is very rare; our clinical records of 55 children report that only three patients are affected by the chronic form.

In FPIES some typical laboratory findings such as neutrophilia and thrombocytosis can be found, especially in the acute form, but their documented presence is not indispensable for the diagnosis. This last one is based on five clinical criteria, which must be fully satisfied to make the diagnosis. They were already listed by Powell in 1986 [2] and recently Leonard *et al.* [1] reviewed them and submitted a new version. These criteria are very important and it is necessary to understand their relevance. Now we would like to briefly make some comments concerning the original criteria of Powell [2] and the changes proposed by Leonard *et al.* [1]; TABLE 2 summarizes the above criteria and our proposal.

First criterion: 'Age younger than 9 months at initial presentation'

FPIES appears for the first time before the ninth month of life if the patient consumes the culprit food before that age. This statement is certainly true for CM FPIES, while there are some doubts about solid culprit foods, such as fish. In fact, fish FPIES can occur after the ninth month and even after the twelfth month. Some episodes have been reported even in adolescents and adults and the culprit food were crustaceans. So this criterion should not be strictly applied, but our limit of 2 years seems to be more appropriate.

Second criterion: 'Exposure to the incriminated food elicited repetitive vomiting and/or diarrhea within 4 h without any other cause for the symptoms'

In 2012 Leonard *et al.* suggested that food ingestion has to be repetitive and that the elicited symptoms are generic gastrointestinal, not specifically vomiting and/or diarrhea. However, we do not agree with these changes. In fact, as it is stated in the fifth criterion (see below), at least two episodes are necessary to make the definitive diagnosis. Moreover, FPIES has to be suspected (not diagnosed) even if only a one episode occurred, so the need for repetitive ingestion specified by Leonard *et al.* [1] could divert doctors' attention from a possible diagnosis of the syndrome. We would rather focus on symptom duration, which is usually short in time. In fact, patients take 6–8 h to recover and at the end of all, they appear as if nothing wrong has happened. This last one is

a unique characteristic of FPIES, and it can not be found in other diseases, not IgE-mediated which could gloss over this syndrome as acute gastroenteritis but also surgical abdomen and sepsis. We would also highlight that vomiting is undoubtedly the prevalent symptom accompanied by hyporeactivity and pallor, as opposed to diarrhea, which is a secondary and inconstant aspect of the syndrome. It would be inaccurate to make a FPIES diagnosis if the patient presents with diarrhea without vomiting, although the conjunctions 'and/or' do not seem to underline the difference.

Third criterion: 'Symptoms limited to the GI tract'

It is difficult to believe that hypotonia, hyporeactivity and pallor are related to a GI problem. These symptoms could be rather caused by hypotension, which may be a consequence of fluid loss with vomiting. We think that they are most probably triggered by a toxemia deriving from a cytokine blood invasion, related to an allergic inflammation state. So we do not agree with the third Powell [2] criterion; we prefer Leonard *et al.*'s criterion [1], which requires the absence of symptoms compatible with an IgE-mediated reaction. For example, repetitive vomiting and hyporeactivity presenting 2 h after the ingestion of food, accompanied by hives, should mistrust a FPIES diagnosis, because hives as well as asthma and rhinitis are typical manifestations of an IgE-mediated allergy. However, we will discuss hereinafter the FPIES pathogenesis, which is an interesting and innovative aspect of this syndrome.

Fourth criterion: 'Avoidance of the offending protein from the diet resulted in resolution of symptoms'

Leonard *et al.* [1] do not change anything of this criterion, which is the cornerstone of every FA diagnosis and there are no exceptions for FPIES. It is untouchable.

Fifth criterion: 'A standardized food challenge or isolated re-exposure elicited the typical symptoms'

Leonard *et al.* [1] also do not change anything about this criterion. Even if this standard is considered necessary for FPIES diagnosis, it is not always observed in clinical practice, as doctors are scared

Table 2. Diagnostic criteria of FPIES.

Powell, 1986 [2]	Leonard <i>et al.</i> , 2012 [1]	Miceli Sopo <i>et al.</i> , 2013
Less than 9 months of age at initial presentation (reaction)	Less than 9 months of age at initial diagnosis	Less than 2 years of age at first presentation (frequent feature but not mandatory)
Exposure to the incriminated food elicits repetitive vomiting and/or diarrhea within 4 h without any other cause for the symptoms	Repeated exposure to causative food elicits gastrointestinal symptoms without alternative cause	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 less than 6 h
Symptoms limited to the GI tract	Absence of symptoms that may suggest an IgE-mediated reaction	Absence of symptoms that may suggest an IgE-mediated reaction
Avoidance of the offending protein from the diet results in resolution of symptoms	Removal of causative food results in resolution of symptoms	Avoidance of the offending protein from the diet results in resolution of symptoms
A standardized food challenge or isolated re-exposure elicits the typical symptoms	Re-exposure or oral food challenge elicits typical symptoms within 4 h	Re-exposure or oral food challenge elicits typical symptoms within 2–4 h. Two typical episodes are needed to deliver the definitive diagnosis

of its consequences since during the acute phase the child may feel very unwell. This is the reason why many allergists refuse to perform an OFC if they are aware of the occurrence of only one typical episode. Adding to all this, parents often refuse to re-expose their babies to the suspected food. Many cases of FPIES diagnosis based on a single and severe episode were even published in literature [3,4], but we do not agree with this attitude, as there can be a high risk of wrong diagnosis and a consequent elimination of important foods from the patient's diet. On the contrary, we believe that the best way to make a correct diagnosis is the presence in the patient's clinical history of at least two typical episodes, one of which could be a failed OFC. Unlike Powell [2] and in agreement with Leonard *et al.* [1], we do not believe that the ingestion of culprit food must necessarily be isolated. In summary, we think that the fifth Powell [2] and Leonard *et al.* [1] criterion has to be respected. From practice to theory: Bridget performed an OFC, as she presented only one typical episode, while Ernst did not do the same, as he experienced FPIES symptoms three times.

The diagnostic delay and the increase of new diagnoses: is it a contradiction?

Ernst's story shows how a delay in FPIES identification, until a third episode, is not so rare. Fortunately, in the last 5 years there has been more information about this syndrome, so that doctors are more aware of it. In our experience, 10% of children presented almost four episodes before the diagnosis was made and a few of them had even ten adverse reactions before a solution was found. A few years ago, we ourselves were wrong, and you will read about what happened to Katie in 2004 below.

Katie's story: she was misunderstood

On many occasions the baby vomited repetitively within 2 h of fish ingestion, especially sole fish. SPTs performed with sole commercial extract and fresh sole (both cooked and raw) were negative. Katie was admitted to the DH to perform an OFC with cooked sole; she ingested about 30 g of fish but refused to continue. Two and a half hours after the ingestion, Katie started to vomit and presented with pallor and sweating. We did not think of FPIES; we thought it was a sort of psychological aversion toward fish, so we suggested to give her sole fish at home, but in a hidden form. Fortunately Katie's parents didn't follow that advice.

The story of Katie allows us to emphasize that the diagnosis of FPIES can be made if this syndrome is known, otherwise not. This is the case for all other diseases. Anyway, even though pediatricians do not easily suspect FPIES, often causing a diagnostic delay, the number of diagnoses is notably increasing. Australians were the first to become aware of FPIES [3], but now we are too [5]: in 2008 our diagnoses tripled, compared to the annual mean of the previous four-year period, and in the following years, the number of new diagnoses remained stable. This phenomenon can be considered a sort of paradox, that is: on one hand doctors do not seem to consider FPIES a lot, on the other hand it seems they think of it too much. Such a strange contradiction could be explained, at least in Italy, considering that knowledge of FPIES in the pediatric allergic field has spread in few years,

thanks to congresses, scientific journals and discussion forums. Primary-care pediatricians, who are the ones in direct touch with children and their parents, have been receiving this information more recently. There is still too much to do, as shown in the next story, which exemplifies other interesting aspects of FPIES.

FPIES differential diagnosis

Victor's story: why is everything over me?

Victor ate for the first time a homogenized fruit baby food containing 3% ground rice when he was five months old. He was fed with the same baby food, increasing its dose, for a week, until one day, 2 h after the food ingestion, he started to vomit repetitively (4–6 vomits), became pale and hyporeactive and also started to suffer from diarrhea. Due to his serious clinical condition, Victor was hospitalized for a few days with a diagnosis of acute gastroenteritis. Fifteen days later the baby ate two teaspoons of rice cream and 2 h after the ingestion, presented with the same symptoms of the previous episode. He was re-hospitalized and once more doctors believed the cause was gastroenteritis. During the time spent in the hospital, when Victor recovered completely, he was fed with rice cream and Victor had a third episode presenting with vomit, pallor, hyporeactivity and diarrhea. On that day he was examined by a pediatrician with expertise in allergies and so was finally issued the diagnosis of FPIES caused by rice. Rice-specific IgEs were negative.

Victor's story teaches us that FPIES is frequently confused with an acute gastroenteritis; actually, it can even be wrongly diagnosed as sepsis, acute abdomen, metabolic diseases and necrotizing enterocolitis. None of the abovementioned conditions resolves in a few hours from their onset, as FPIES does, and this is a very typical aspect of this syndrome. FPIES is also confused with anaphylaxis and both these diseases actually have the same duration but, as FPIES diagnostic criteria point out, there are no IgE-mediated signs and symptoms, such as urticaria and angioedema, in this syndrome.

FPIES pathogenesis and diagnostic tests

Katie's story teaches us something more: when we visited Katie we suggested to perform an atopy patch test (APT) with sole, even if at that time (2004) we did not know anything about FPIES. It was only in 2006 that Fogg published his study [6], which reported a 100% negative predicting value of APT in FPIES. This seemed very useful information, as we were able to exclude FPIES in all the children who had a single episode with a negative APT. Unfortunately a short time later Zapatero *et al.* [7] and Jarvinen *et al.* [8] proved the inefficiency of this test, so that APT could not be considered a relevant tool for FPIES diagnosis. Moreover, specific IgE research turned out not to be useful for the diagnosis because it is usually negative, with the exception of 5% of cases, which are defined as 'atypical', as they have positive specific IgE. Bridget, Ernst, Katie and Victor all had negative SPTs. This evidence supports the hypothesis that FPIES pathogenesis is cell-mediated and this is without doubt the most accepted immunopathogenetic theory; furthermore, some variations in blood cytokine levels, which are increasing for TNF- α

Box 1. Clues in favor of a specific IgE role in food protein-induced enterocolitis syndrome pathogenesis.

- There are some cases with positive specific IgEs against the culprit food, even if their levels are low.
- In one child,, during an episode of acute FPIES caused by rice, a plasmatic cytokinic trend similar to those of IgE-mediated allergic reactions was observed, with an increase of IL-4 and a decrease of IFN- γ [10].
- The fact that symptoms arise 2 h after the ingestion of the culprit food is not a typical feature either of classical IgE-mediated forms (the reaction usually appears long before 2 h) or of classical non-IgE-mediated forms (which usually manifest long after 2 h).
- Few patients (with positive specific IgE research) present a shift in symptoms from those of FPIES to those of gastrointestinal anaphylaxis [11].
- Regarding CM FPIES, there is a report about the capability of tolerating the culprit food if well-cooked (baked) [12].

CM: Cow's milk; FPIES: Food protein-induced enterocolitis syndrome.

and decreasing for TGF- β , were observed [9]. For these reasons, the idea to evaluate the diagnostic performance of APT, a skin test that aims to unveil a cell-mediated immune reaction, is correct; unfortunately, this test is not yet sufficiently standardized and reproducible. Anyway, someone is beginning to think that specific IgEs could play a role in FPIES and they suppose that they might be expressed only along the GI tract. In Box 1 we show the reasons that lead us to imagine that FPIES could have a combined pathogenesis, at least sometimes.

The last point of Box 1 could have a significant impact on young patients' quality of life. In fact, nowadays the chance of tolerating the culprit food if baked or well-matured (as parmesan 36 months) in the case of CM, has been demonstrated only for IgE-mediated FAs [13–15]. Cell-mediated FAs could not have this privilege due to their immunological mechanisms. However, we found that four out of seven children suffering from CM FPIES tolerated the culprit food if baked (e.g., cake or biscuits) [12]. If pathogenesis of FPIES is erected on an exclusive cell-mediated mechanism, tolerance versus the offending food well-cooked could not be possible in an active FPIES. In fact, denaturation of conformational epitopes, caused by high and prolonged temperatures, should not obstruct the antigen–receptor link, as happens in the majority of the cases of IgE-mediated allergies. In fact, T-cell receptors (TCRs) recognize antigenic peptides derived from proteins degraded and exposed on cellular surface of dendritic cells through link with MCH1 receptors present on own surface and not specific for that allergen, but independent from its structural conformation [16]. In conclusion, as Caubet *et al.* [9] wrote, it is not possible to exclude a possible IgE role in FPIES pathogenesis. We think that FPIES is a FA halfway between the IgE-mediated and cell-mediated forms and, moreover, that there are different phenotypes of FPIES. In some of them, IgE and related cytokines may play a significant role. However, we are aware that it may be a controversial theory and that authors' opinions on this may vary.

Most frequent culprit foods

Bridget suffers from CM FPIES, Ernst and Katie from fish FPIES, Victor from rice FPIES. These four stories present us with the three most frequent culprit foods of FPIES. The predominant food is CM, with the exception of Australia, where rice is the most frequent. The latter is also the most common solid culprit food worldwide, unless in Italy where fish is the most relevant one. In the United States some studies were published reporting a double

reactivity to CM and soy in 50% of patients and this fact has led the suggestion for preventive dietary therapies [17] (we will discuss about this aspect next in the article). On the contrary, in Israel none out of 44 children affected by CM FPIES had any problem with soy [4]. In summary, there are some FPIES geographical differences, so that clinical approaches cannot be always the same. Some prudent dietetic attitudes that can be suitable in a particular geographical area could be wrong elsewhere. In addition to rice and fish, among some solid culprit foods identified were oat, barley, poultry, turkey, egg, peas, peanut, potatoes, fruits and shellfish. Recently, we also detected an episode of FPIES caused by corn [18], so this food can be added to the list.

In our study [5], CM was the culprit food in 67% of cases. Fish was involved in 12% of cases. Approximately three out of eight children suffering from fish FPIES also performed an OFC with types of fish different from the culprit one (the remaining children did not agree with this proposal) with the following results:

- A child affected by sole FPIES tolerated codfish and tuna;
- A child affected by codfish and sole FPIES tolerated salmon and swordfish;
- A child affected by trout and sole FPIES tolerated seabream, codfish and perch.

In summary, as happens in IgE-mediated fish allergy [19], it is possible that even in fish FPIES the patient is able to tolerate other types of fish and this fact is very important as, together with the baked food mentioned before, it can help improve patients' quality of life by expanding their food choices and making their diet less limited. So, it's now the time to discuss one of the most important management aspect of FPIES, the diet therapy.

Diet therapy, single and multiple

To date, nobody doubts that the culprit food has to be always and strictly eliminated from the patient's diet up to the spontaneous achievement of tolerance. This is a difference between FPIES and IgE-mediated FAs: the management of FPIES does not provide, as happens for some common IgE-mediated FAs, the possibility of initiating oral immunotherapy (OIT) in order to actively induce tolerance or at least desensitization [20]. OIT was never performed for FPIES, as spontaneous tolerance is achieved relatively soon, usually within the first 5 years of life: it's not worth exposing patients to the risks of OIT for such a short wait.

So, patients cannot ingest even small amounts of culprit food, as the minimum quantity which can cause an acute episode is still unknown, and it's very difficult to obtain this information due to the latency period of the symptoms; the patient always has the time to finish the meal before symptoms arise. We also do not know if small and frequently ingested amounts of food can cause chronic FPIES. So in case of FPIES, diet concerning the culprit food must be very strict and has no alternative.

Moreover, Sicherer has also proposed the elimination from the diet of other foods in addition to the culprit. In fact, this author suggests [17], in case of CM FPIES, to avoid ingesting soy and cereals and to delay the introduction of other solid foods, at least until the baby is one year old. In case of FPIES induced by solid food, he proposes avoiding the ingestion of cow milk, cereals, legumes and poultry, at least until the baby is 1-year-old. Of course, the preventive diet will be implemented only if the foods in question, at the time of diagnosis of FPIES, have not already been eaten without problems by the child. The suggestion is born from the observation of a clinical reactivity to these foods in children with CM FPIES or solid food FPIES in the USA in a series composed of 30–50 individuals [21,22]. However, Sicherer precises [17]: “These strategies represent only one of many possible courses of action and would require alterations in approach depending on numerous factors, including severity of previous reactions, clinical judgment, nutritional needs and patient preferences. Foods that are clinically tolerated should not be removed from the diet”. When the Italian [5], Australian [3] and Israeli [4] clinical series (a little less than 150 cases total) were published, it was observed that the occurrence of FPIES caused by many different foods in the same child (‘multiple FPIES’) was infrequent; in our experience this event happens at most in 2% of cases. In light of this recent information, we think that the probability of a multiple FPIES is too low to suggest multiple dietary restrictions for all children with FPIES to their debut.

Victor's story: second episode

Victor is part of the abovementioned 2% patients suffering from multiple FPIES in our casistic; his story was not ended. When he was six months old he ate corn at home and at the second administration he showed his fourth FPIES episode. After a time, an OFC was performed in DH with lentils, potato and semolina wheat and Victor presented his fifth episode caused by wheat. At home, his mother gave him chickpeas and Victor had his sixth adverse reaction. In summary, if we had followed Sicherer's suggestions [17] this baby would not have shown three of his six FPIES episodes. However, as we have already said, the probability of encountering a child affected by multiple FPIES is quite low and considering our 55 clinical cases, Victor is the only one. So, we struck a compromise that somehow takes into account the suggestion of Sicherer [17]. In fact, we suggest patients perform a DH OFC with a mix of cereals, legumes and poultry, since the probability that the child tolerates such foods is very high. In this way we avoid an enlarged diet in children who actually do not need it. This was, for example, the advice

given to Bridget. We did not propose the same management to Ernst as, when he came to our attention, he had already eaten these foodstuffs without any problem. Moreover, especially for CM FPIES, in case of lack of breast-milk, there was a strong recommendation to give an extensively hydrolyzed casein formula instead of cow milk and to avoid soy milk ingestion. Nowadays, this prescription is declining and this is mainly due to the publication by Katz *et al.* [4], which reported that the majority of 43 children suffering from CM FPIES tolerated soy milk. In conclusion, it is certain that the culprit food has to be excluded from patient's diet until he spontaneously reaches tolerance, but it is not certain that further dietary restrictions are needed. So, in an attempt to improve the quality of life of the child with FPIES, we perform OFCs with a mixture of other foods hypothetically involved, without deleting them from the diet prejudicially. In the case of fish FPIES, we suggest OFCs with other types of fish, while in case of CM or hen's egg FPIES we propose challenges with the baked food. Of course, ours is a working hypothesis and studies are in progress to demonstrate its validity.

FPIES prognosis

How long does a dietary restriction have to be carried out? When do baby patients recover from FPIES? The majority of children achieve tolerance at the age of 3 years and only a few of them manifest this syndrome longer. In our series there is one 5-year-old child affected by active soy FPIES, while another one, who is six years old, suffers from active CM FPIES. In our experience [5], in cases of CM FPIES, tolerance was achieved at a mean age of 30 months; we also observed that children with CM FPIES have 60% probability of passing an OFC with the culprit food at 18 months. Other authors [423] reported even lower ages; according to Hwang *et al.* [23] there are many chances to be cured at the age of 1 year. Regarding FPIES induced by other foods, it is not possible to predict anything specific, unless the probability of achieving tolerance increases from the third year of life. We are used to performing an OFC year by year, until tolerance is achieved. Atypical cases of FPIES (so defined for their late insurgence, past the ninth month, and/or for the presence of specific culprit food IgE) could last more than typical ones and even run into an unusual destiny, as Micol's history teaches.

Micol: the chameleon FPIES

Since her birth, Micol had taken CM four-times. The first time, when she was ten days old, she vomited twice. Then, three times within the third and fourth months of life, 3 h after the ingestion of 30 ml of formulated milk, the baby started to vomit repetitively and presented with pallor, lethargy and diarrhea. 6–8 h after the symptoms started, Micol was fine. SPTs performed with casein, β -lactoglobulin and lactalbumin were negative, while fresh CM SPT was weakly positive (mean wheal diameter: 4 mm). We diagnosed atypical FPIES and from the age of 8 months, Micol consumed an extensively hydrolyzed formula of casein instead of CM as breast milk was terminated. At the age of 16 months, a

year after the last adverse episode, Micol performed and passed an OFC, ingesting 200 ml of CM without showing any symptoms, so we suggested to reintroduce CM into the child's diet. However, after 5 days of ingestion of CM without any other problems except a slight erythema in the perioral region, Micol presented with cough and vomiting 20 min after drinking 200 ml of CM. On the 7th day, 40 min after she finished her CM meal, the child presented with vomiting without coughing, and hives and rash appeared on the anterior surface of the body, which was the skin area that came in contact with vomit. Eating parmesan did not, however, cause symptoms. So, eight days after the first OFC, a second one was performed; SPTs were positive for fresh CM (mean wheal diameter: 5 mm), β -lactoglobulin (mean wheal diameter: 3 mm) e lactalbumin (mean wheal diameter: 4 mm), while the one with casein was negative. Micol consumed 220 ml of CM in one dose; some hives showed on the perioral area where some drops of milk dripped. 20 min after the child finished the CM meal, she presented with cough and vomiting; hives and erythema appeared also on the body surfaces that came in contact with vomit. In conclusion, in Micol's case, we observed a shift from FPIES to an IgE-mediated generalized reaction [11], where, however, the involvement of the GI tract remains important. This means that Micol was cured of FPIES – that is, she no longer presented symptoms compatible with FPIES when she ate CM again. Only a few days later the symptoms of IgE-mediated allergy appeared. And before 16 months of age, symptoms compatible with an IgE-mediated form had never presented. The two clinical expressions have never been contemporaneous. Similar stories were also reported by Katz *et al.* [24] and Kessel *et al.* [25] Micol's story can support, according to us, the hypothesis that there are different phenotypes of FPIES; in some cases the role of specific IgE becomes more important. But we want to emphasize once again that there is controversy surrounding this idea and mention that some researchers may not agree with this concept.

Acute management of FPIES

There are not many measures to take except giving iv. fluids and steroids. At this regards, Sicherer [17] wrote: "On the basis of the only partially understood pathophysiology of the immune response (T-cell-mediated) and observations of the clinical symptoms (lethargy, dehydration, shock), several suggestions can be made for emergency care that are based on response to treatments in studies reporting results of oral food challenges. If an ingestion is known to have occurred, the patient should be instructed to present to medical attention for observation. Intravenous fluid resuscitation may be needed. For patients with a history of severe reaction and onset of any symptoms, consideration should be given for administration of corticosteroids to quell a presumed T-cell-mediated reaction, and this treatment could be considered for any patient with more than minimal symptoms. From the words of Sicherer, it can be concluded that the treatment of acute episodes of FPIES is only a practice. In fact, there are no randomized studies demonstrating the usefulness of corticosteroids and, indeed, even of iv. fluids. On this topic, Powell [2] suggested that it could be safest to place

a venous access before starting an OFC, while more recently different measures were adopted. For example, Katz *et al.* [4] do not place any preventive venous line and they are used to treat patients who failed OFCs with oral rehydration. From 2008, we do not take any prophylactic measure either, as failed OFCs resolve spontaneously. We are of course always ready to take the necessary therapeutic measures, such as we did for Bridget. This less aggressive management does not produce any worst outcomes, compared to those of other Italian allergic centers [5] that conformed to all procedures stated by Powell [2]. On the other hand, the majority of acute FPIES episodes usually occur at home and these patients do not receive any medical assistance at all, just as Ernst experienced three times. According to the literature, and until now, FPIES did not cause any deaths. There still are many doubts about the utility of im. epinephrine, which is strongly recommended in case of anaphylaxis; we administered it only in two serious situations, one of which was Bridget's reaction. We felt that this was a useful measure, but they are only two cases. In this regard Sicherer writes [17]: "The reaction can include symptoms of shock that may presumably respond to epinephrine, but our experience has been that iv. hydration and steroids are the only medications typically required." We think that the role of epinephrine in the treatment of acute FPIES is not clearly known: at the current state of knowledge, it is not possible to exclude it. However, we wish to emphasize that the use of epinephrine in the therapy of acute FPIES is not part of the management officially suggested.

At last...FPIES register

We hope you would not miss the chance to suspect an FPIES diagnosis when you meet a patient suffering from it. To do this, the only things you need to know are the main FPIES diagnostic criteria, as for example the first four ones we discussed before (see TABLE 2); an allergist will take care of all the other specialist aspects of this syndrome such as the consequent diagnostic work-up, the definitive diagnosis and the correct dietary management. As often happens in medicine, there is still a gray zone in FPIES, including different methods of performing OFCs. Some authors, ourselves included, disagree a little with published methods [24]: oral challenge involves the administration of food protein, 0.15–0.3 g protein/kg body weight, up to a maximum of 10 g, in three doses over 30–45 min. For example, we do not understand why the established dose should be administered three times in 30–45 min if vomiting usually occurs 2 h after the beginning of ingestion. However, this is a very specialist aspect, which should interest only allergists, those few who are used to performing OFC in their daily clinical practice. Anyway, you will find some hints about this problem in our case review [5]. All the things we ignore about FPIES are inversely proportional to all we learnt about this syndrome. After all, the number of cases published at the end of 2012 do not exceed 400 units and this is not only due to the fact that FPIES is an uncommon disease (Katz *et al.* [4] registered CM-FPIES in 0.5% of newborns), but because it is not well-known and studied. To remedy this situation, we are going to set up the Italian FPIES Register. Our aim is to collect a significant

number of cases to throw light on new aspects of this syndrome; thanks to information gathered, a FPIES guideline could be outlined to follow in clinical practice. That's the meaning of 'from practice to theory'.

Expert commentary & five year view

FPIES is an old FA that has been rediscovered in recent years. It is probably modified in its clinical expression. In past years chronic forms prevailed, managed mainly by gastroenterologists. Today, perhaps due to a more aggressive management of mild disorders of the GI tract (regurgitation, mild diarrhea, poor weight gain) with frequent elimination of CM protein from infants' diet, acute forms definitely prevail. Today, we know a lot of epidemiological information: the prevalence of this syndrome, the foods involved and the type of clinical expression. However, many aspects remain to be fully investigated: the immunological pathogenesis, diagnostic laboratory investigations, the methodology of OFCs, the prognosis and some aspects of diet therapy. For example, nothing is known about the possibility of performing OIT with the culprit food for those FPIES patients who remain allergic past the fourth or fifth year of life. On the contrary, this is a concrete chance for those children suffering from IgE-mediated FAs.

In addition to the Italian FPIES Register, we hope that the constitution of other national registers is in progress, as they will

be useful to collect further information about FPIES. During the next five years, the method of performing OFCs should be improved to adapt them to the timing of FPIES symptoms. FPIES pathogenesis should be cleared, above all it would be significant to understand the specific IgE role, which could have great implications on acute episodes treatment. To improve patients' quality of life, it would be important to define multiple FPIES prevalence and identify some markers of this special phenotype, so that we could limit enlarged diets only to those patients who really need them. We will try to solve doubts about FPIES duration, especially for solid food FPIES, which is still less known, with the goal of giving a more precise prognosis to children and their families.

One thing is certain: in the last 30 years, our knowledge about FPIES has evolved and transformed. Who knows what lies ahead for the next few decades!

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Key issues

- Do not forget about FPIES. Try to avoid diagnostic delay, as FPIES incidence is probably increasing.
- A FPIES episode can be defined as 'typical' if it presents the following characteristics: symptoms arising 2–4 h after the ingestion of culprit food with repetitive vomiting, lethargy and pallor. Diarrhea can ensue and hypotension can develop in most serious cases. Another relevant FPIES feature is that symptoms resolve in few hours.
- Cow milk is the most frequent culprit food, while rice is the most frequent solid one.
- FPIES diagnosis is based on the occurrence of at least two typical episodes. If patient presents only one adverse reaction an OFC has to be performed.
- Acute FPIES therapy consists of administering i.v. fluids and steroid, even if the majority of cases resolves spontaneously.
- Surely, FPIES diet therapy consists of avoiding the ingestion of culprit food. The need for other dietary restrictions is not yet well defined.

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