



Geographical Variations in Food Protein-Induced Enterocolitis Syndrome

Sonsoles Infante, MD, PhD^{1,2,*}
Paula Cabrera-Freitag, MD, PhD^{1,2}
Cristina Morales-Cabeza, MD³
Alberto Alvarez-Perea, MD, PhD^{1,2}

Address

^{*,1}Paediatric Allergy Unit, Hospital General Universitario Gregorio Marañón,
Madrid Spain
Email: sonsoles.infante@salud.madrid.org

²Gregorio Marañón Health Research Institute (IiSGM), Madrid Spain

³Allergy Unit, Hospital Infantil Universitario Niño Jesús, Madrid Spain

Published online: 22 October 2019

© Springer Nature Switzerland AG 2019

This article is part of the Topical Collection on *Food Allergy*

Keywords Food allergy · FPIES diagnosis · Food protein-induced enterocolitis syndrome · FPIES · Gastrointestinal food allergy

Abstract

Purpose of Review Food protein-induced enterocolitis syndrome (FPIES) is considered a rare, non-IgE-mediated food allergy that typically presents in infancy. As there is not a specific biological marker of the disease, diagnosis of FPIES is based on typical symptoms that improve once the offending food is removed from the diet. The most common causative foods are cow's milk, soy, and rice. For years, we have thought that the typical symptoms and the triggering foods were the same around the world.

Recent Findings The epidemiological data are scarce and variable but recent studies suggests that FPIES is not as rare as it is thought but rather misdiagnosed. The clinical symptoms and the offending foods vary depending on the geographic area. Perhaps because different phenotypes might exist due to dietary habits, race, or ethnicity.

Summary FPIES symptoms and causative foods are not the same around the world. It is important to know our population in order to reach a correct and early diagnosis of our patients.

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy that typically presents in infancy, with repetitive protracted vomiting that begins 1–4 h after food ingestion. Vomiting is often accompanied by lethargy and pallor and can be followed by diarrhea. Some patients have an isolated fever peak and severe cases can progress to hypothermia, methemoglobinemia, acidemia and hypotension, and mimicking sepsis [1••].

It is considered a rare disease. That, perhaps, is due to the fact that until the 70s, this entity had not been formally recognized or defined [2], as there was no adequate codification until October 2015 when the code K52.2 was implemented in the tenth revision of the International Classification of Diseases (ICD-10).

The epidemiological data are scarce and variable. To date, few epidemiological studies have been carried out. One of the most important is the one done by Katz et al.

[3]. They included 13,019 newborns over a 2-year period, and they found an accumulate incidence of milk-FPIES of 0.34%, whereas for milk-IgE-mediated allergy, the incidence was 0.5%. One of the limitations of this study is that no other causal foods of FPIES were included. In 2017, the Australian group published a study including all the new cases of FPIES in children under 24 months in a period of 2 years. They found an incidence of 15.4 new cases/100,000 children/year [4••]. The PREVALE study, carried out in a single center in Spain, found an incidence of FPIES of 0.7% which is higher than previously described [5••]. Finally, a recent cross-sectional study, carried out in the United States of America (USA) found a self-reported lifetime prevalence of physician-diagnosed FPIES of 0.28% [6]. These data suggest that FPIES is not as rare as we think but rather underdiagnosed.

Clinical Manifestations

The typical symptoms of FPIES are protracted and delayed vomiting that are often accompanied by lethargy, pallor, and diarrhea and that fits for the acute presentation of FPIES. Acute FPIES symptoms appear within 1–4 h after the ingestion of the offending food, diarrhea appears later, between 5–10 h. The symptoms disappear in the next 24 h. Children are well between episodes and they have normal growth. There is another clinical presentation, which is known as chronic FPIES and is less well characterized. It has been only reported in infants younger than 4 months of age, fed with cow's milk (CM) or soy-based infant formula [1••]. The symptoms occur over several days or weeks and do not have clear relationship with the offending food. Children have intermittent vomiting and/or diarrhea, failure to thrive, or poor weight gain. The severe form can develop dehydration, metabolic acidosis, and hypovolemic shock. The symptoms disappear within 10 days or a fortnight once the offending food is removed from the children's diet.

By definition, FPIES is a non-IgE-mediated food allergy. However, there is a third clinical manifestation called atypical FPIES [7]. This presentation may appear in a small percentage of patients with either acute or chronic FPIES. These patients have specific IgE (sIgE) against the causal food, either at the beginning or during the course of the disease. The rate of patients with atypical FPIES is variable, depending on the series. It seems to have a protracted course and children run the risk of developing IgE-mediated symptoms.

In Eastern countries, such as Japan, symptoms frequently appear in breastfeeding newborns. Bloody stools that are rare in Western countries are frequent in Japan, as is the positive sIgE and the peripheral eosinophilia [8•].

Table 1. Geographical variations in food protein-induced enterocolitis syndrome.

	Europe	USA	Asia	Australasia
Incidence	0.36–0.7%	0.28%	0.34%	15.4/100,000/years
Main offending triggers (in descending order)	CM/fish Egg Rice Wheat Chicken Corn Lentils Soy	CM Soy Rice/oats Egg Vegetables Fruits Fish	CM Soy (Korea) Rice Sesame (Israel) Peas Turkey Lentils	Rice CM Egg Oats Chicken
Clinical presentations	Acute: frequent Chronic: rare Atypical: rare but often associated with CM-FPIES	Acute: frequent Chronic: less frequent (CM or soy) Atypical: rare but often associated with CM-FPIES	Acute: frequent Chronic: frequent Atypical: frequent Exclusive breast-fed infants	Acute: frequent Chronic: rare Atypical: rare, most with egg-FPIES
Main symptoms (in descending order)	Vomiting (81–100%) Pallor (15–89.2%) Lethargy (17–88.3%) Hypotension (0–77%) Hypothermia (6.35%) Diarrhea (especially in CM-FPIES) Bloody stools in chronic FPIES	Vomiting (> 95%) Diarrhea (7%) Hypotension (5%) Pallor (5%) Cyanosis (5%)	Vomiting (0–100%) Bloody stools (0–100%) Diarrhea (18.2–56.3%) Peripheral eosinophilia (> 50%) Fever (0–20%) Shock (10–15%)	Vomiting (100%) Lethargy (75–85%) Pallor (67–78%) Floppiness (70%) Diarrhea (24–35%) Hypotension (16%) Hypothermia (10–24%) Bloody stools (6%)
Severity of the Symptoms	Mostly mild and moderate Severe symptoms mostly associated with solid foods	Mostly mild and moderate	Mostly mild and moderate	Mostly mild and moderate with CM or soy Severe in cases of rice-FPIES
Single-FPIES	Frequent	Frequent	Frequent	Frequent
Multiple-FPIES	Rare	Frequent (CM, soy and rice or oats) FPIES to 3 or more foods	Rare (CM and soy)	One-third of the patients FPIES to two foods
Age of tolerance	CM around 2 yo Fish and rice around 5 yo	CM around 5 yo Grains around 4 yo Soy around 6 yo	CM around 12 months Soy around 6–8 months Solid foods around 3 yo	CM around 2 yo Soy and rice around 3 yo Fish and egg over 5 yo
Adults FPIES	Reported	Reported	Not reported	Reported

CM cow's milk, FPIES food protein-induced enterocolitis syndrome, y years, yo years old. Note: The percentage corresponds to the ranges published in the different studies considered in this review. In those cases where only one number appears, it refers to a single study



Fig. 1. Main triggers of FPIES in each continent, ranked according to the available data.

Thus, clinical manifestation is highly variable. Signs and symptoms that can be considered typical in certain areas should be reckoned atypical in other, especially when considering eastern and western countries.

Offending Foods and Prognosis

In the same fashion, variability is the norm in terms of offending foods. Any food can trigger FPIES. However, there are geographical differences and some food are more prevalent than others. The development of tolerance varies by the type of food trigger and the country of origin. The geographical variations are summarized in Table 1 and the main triggers of FPIES in each continent are represented in Fig. 1.

FPIES in Europe

In 1939, Gert Von Sydow described the first series of patients in whom the ingestion of cow's milk proteins developed exclusively gastrointestinal symptoms. This "atypical" manifestation was called "congenital cow's milk idiosyncrasy" and would set the foundations of further understanding what we know as FPIES [9•].

Interestingly, the interest in this new entity seems to fade in Europe until the last 15 years, when most of the European studies have been published.

The majority of the studies have been carried out in Southern Europe. In Spain, several retrospective observational studies have been conducted, most of them involving a single tertiary center [10–12•]. There is only one multicenter study led by the Gastrointestinal Allergy Working Group of the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (SEGHPN). In this retrospective study, one hundred twenty patients were included over a 1-year period. CM was the most frequent causative food, followed by fish, egg, and rice. Eighteen patients (15.7%) had positive specific sIgE for the offending food,

most of them to CM and only two to egg. All acute FPIES patients included fulfilled the major criteria of the International consensus guidelines [1••]. Acute FPIES patients (92.5%) showed a high prevalence of pallor (89.2%) and lethargy (88.3%), and 54.1% presented diarrhea within the next 24 h. Bloody stools were most common in chronic FPIES but were found in up to 9.9% of the children with acute FPIES. Only 7 children (6.3%) developed hypothermia. The symptoms at onset were mostly mild and moderate. The severity of the symptoms was analyzed for each offending food, and they found that half of the rice-FPIES cases were severe, compared to a 21% for fish, 20% in CM, and 7.6% for egg. Multiple-FPIES was uncommon, and the majority of the patients (84.2%) reacted to one single food group [13••]. Vázquez-Ortiz et al. found that lethargy was more frequent in FPIES caused by rice, fish, and egg than in FPIES due to CM. Diarrhea appeared more often with CM than with other foods. Most children with FPIES to fish or egg developed tolerance at 60 and 63 months, respectively. Tolerance development was earlier for CM-FPIES (50% at 29 months) [12•].

In Italy, Sopo et al. estimated that FPIES accounted of approximately 19% of cases of food allergy. The offending foods, as in Spain, were CM, fish, and egg, and most of the children (85%) reacted to a single food. Positive sIgE to the triggering food was only found in two children (3%) with CM-FPIES. Vomiting, pallor, and hypotension were the most frequent symptoms and diarrhea only appeared in half of the patients [14].

Ludman et al. found an incidence of FPIES, in a tertiary London Pediatric Allergy Service, of 0.36%. Vomiting and diarrhea were the mainly symptoms at onset, followed by hypothermia, lethargy, and gray appearance. Most patients presented symptoms of acute FPIES, only 4 of the 54 children included developed symptoms of chronic FPIES. The most common eliciting food was CM followed by fish, egg, soy, and wheat. Thirty percent of the patients reacted to more than one food type, 70% had CM as one precipitant [15]. This data is similar to that observed by Sopo et al. [14] in which 15% of the cohort reacted to more than one trigger but lower than those reported in the USA [16]. Fish have been reported as the main trigger of acute FPIES in Southern Europe [12•, 17], and recent studies reported that there is no need to avoid all fish because some of them, like canned tuna and swordfish, could be tolerated by these patients [18•].

In European patients, acute FPIES seems to be more frequent than chronic FPIES. The main symptoms are vomiting, pallor, and lethargy, and the severity appears to correlate with the offending food. Diarrhea is more frequent in children with CM-FPIES than with other foods. Most of the patients react to a single food as it happens in other Western countries [13••, 14, 18•]. FPIES in exclusively breast-fed infants is rare in Europe [19, 20]. Coexistence of atopic diseases, such as atopic dermatitis (AD), rhinoconjunctivitis and asthma have been reported in children with FPIES [12•, 21]. However, no statistical significance has been found in patients with FPIES compared with those without FPIES [7].

FPIES in the United States of America (USA)

There is limited, wide-scale epidemiological information regarding FPIES in the Americas. There are no studies focusing in Central or South American countries.

In fact, all data available is originated in the USA.

In a recent cross-sectional population-based survey, conducted between October 2015 and September 2016 to a sample of 53,575 US households, lifetime prevalence of physician-diagnosed FPIES was estimated to be 0.28% (0.24–0.33%) [8•]. However, the study has several limitations as it was not conducted to estimate FPIES prevalence. Patients were asked if they had ever been diagnosed by a physician with FPIES, but no information about the diagnostic criteria used were given, and whether oral food challenges were performed to confirm diagnosis. Moreover, self-reported data are always a limitation.

As happens in Europe, coexistence with other atopic diseases, especially AD is common, as well as IgE-mediated allergy to other foods, although these data are variable [16, 22–24•].

The causative foods vary between North and South States. CM and soy are the most commonly offending FPIES triggers in up to 40% reported case series of the Northeast of the USA, followed by grains, with rice being the most frequent one [16, 22, 24•]. Egg and fish appear to be less frequent triggers of FPIES than in other countries [12•, 16, 17, 25].

In Blackman's cohort of the Southwestern region of the USA, rice was the most common food trigger (53%), surpassing CM (49%). They also identified a significant number of their patients (40%) reacting to fruits, with banana (24%) and avocado (16%) being the most frequent, reinforcing the observation that FPIES is a heterogenous disorder with significant geographic variations [24•].

Multiple-FPIES is more frequent in the USA than in other parts of the world. Caubet et al. reported that the majority of FPIES subjects (65%) reacted to 1 food, 26% reacted to 2 foods, and 9% reacted to 3 or more foods [23]. Ruffner et al. [16] identified 30% of patients reacting to 3 or more foods, whereas in the Southwestern area of the USA, 51% have FPIES to 3 or more food triggers [24•]. Children with either CM or soy-induced FPIES can also react to both foods and have an increased likelihood of reacting to a solid food, most commonly rice or oats [16, 23, 24•, 26]. On the contrary, in the few reports of FPIES to egg and peanut, no coexistence to other FPIES were found [16, 22, 27].

In acute FPIES, vomiting is the most common symptom, reported in more than 95% of cases [16, 23, 24•], and diarrhea seems to be rare, appearing only in 7% of the patients after an OFC [23]. A more severe phenotype, including hypotension, pallor, and/or cyanosis is less frequent, affecting around 5% of patients with acute FPIES [16].

Chronic FPIES has only been reported in children younger than 4 months of age who were fed with CM- or soy-based formula [1••, 2, 23].

As happens in Europe, FPIES caused by solid foods seems to develop more severe reactions than CM and/or soy-FPIES [26].

The majority of patients with FPIES have negative skin prick test responses and undetectable sIgE to the suspected food at the time of their initial diagnosis [8•, 16, 23, 26]. However, Caubet et al. reported 24% of subjects with FPIES having sIgE to the FPIES food, and 82% of those children had FPIES to CM, soy, or both. In this study, the presence of sIgE to CM was a risk factor for persistence of CM-FPIES beyond 3 years of age. Interestingly, 41% of these patients with CM-FPIES and detectable CM-sIgE developed symptoms of IgE-mediated food allergy during the follow-up and none of them became tolerant to CM [23].

Ruffner et al. demonstrated that children with FPIES to milk and soy had reactions at a significantly younger age of onset at 7.0 ± 0.7 months compared with 12.1 ± 1.1 months for the solid foods ($p < .007$). They did not find any significant difference for the age of resolution of liquid vs solid FPIES (32.9 ± 0.95 months and 42.1 ± 3.8 months) [16].

This finding was later confirmed by Caubet et al. who compared 50 children with solid food FPIES with 92 children with CM-FPIES, soy-FPIES, or both observed over the same time period. The median age at the onset of solid food FPIES was significantly greater ($p < 0.001$) compared with the CM-FPIES, soy-FPIES, or both groups. The median age when tolerance was documented either by an OFC or by a parental report of food reintroduction at home was 4.7 years for rice, 4 years for oat, and 6.7 years for soy, and the median age of CM-FPIES resolution was 5.1 years [23].

FPIES in Asia

FPIES in this huge continent is only covered by studies performed in Israel, Japan, and Korea. The only prospective epidemiological study in Asia was carried out by Katz et al. [3]. They found an incidence of CM-FPIES of 0.34% and these authors reported that born by cesarean and having a Jewish mother were risk factors for developing FPIES. However, these risk factors have not been confirmed in further studies.

Cow's milk, soy-based infant formulas and rice are the most common causal foods of FPIES. Soy is especially frequent in Korea, often associated with CM-FPIES (up in 43% of patients), but it has a better prognosis and an earlier resolution than in other countries [28–32]. Solid foods such as peas, turkey, chicken, or lentils have been also reported [31]. Sesame seeds seem to be an emerging trigger of FPIES in Israel, as it is usually introduced into child's diet as a paste called "Tahini" or as a sesame-based confection called "halva" [33].

Perhaps Asia is one of the most singular continents regarding FPIES. Clinical manifestations, especially in Japanese patients, present important differences with respect to other populations. In fact, the Japanese guidelines for food allergy state that the classification of this type of food allergy proposed in the USA, cannot be introduced in Japan because there are many cases in this country that do not meet the proposed criteria [30]. Contrary to Western countries' reports, in Japan, symptoms occur mostly in neonatal period in exclusive breastfeeding infants [34]. Although most patients develop vomiting or diarrhea, bloody stools are present in up to 47% of the patients and normally occur 24 h after the ingestion of the offending food. Food-sIgE antibodies are positive in up to one-third of the CM-FPIES patients [9•, 35]. Peripheral blood eosinophils are often elevated, and stool mucous eosinophils are found especially in bloody stools [9•]. It seems that there is a correlation between the degree of eosinophilia and the incidence of vomiting and bloody stools [34].

Nomura et al. [36•] described four subtypes of FPIES in neonates and infants distinguished by their initial symptoms. They classified the patients using only two variables that were vomiting and bloody stools at the onset: Cluster 1 included patients with vomiting and bloody stools, Cluster 2 included patients with exclusively vomiting, Cluster 3 were patients neither vomiting nor bloody stools, and Cluster 4 were patients with bloody stools without vomiting. The authors found some differences between these clusters, such as the birth

weight which was significantly lower in Cluster 3, and the onset of the symptoms that was later in Cluster 2. In this study, 37% of the patients had positive CM-sIgE, without statistically significant differences among the clusters. They conclude that an early diagnosis is easier using this classification and improve the likelihood of achieving a correct diagnosis in babies under 6 months of age [9•]. Perhaps, this proposal could fix the problem, shared with other countries, that gastrointestinal allergies are poorly described in Japanese textbooks and literature. So, physicians have to rely on reports from Western countries and, as clinical features of the patients differ, reaching a correct diagnosis can be difficult [9•].

Coexistence of other FPIES is rare, being the most frequent association CM and soy-FPIES (8.7%), as is coexistence with other atopic diseases, such as AD [38].

Age of resolution seems to be earlier than in USA. Nomura et al. and Katz et al. reported that 88% of the children outgrew their FPIES at 24 months of age [3, 9•]. Similar results were shown by Hwang with CM and soy-FPIES tolerance rates of 63.3% and 91.7% at 10 months, respectively. Based on these results, it should be accepted to perform an oral food challenge with CM when the child has 12 months of age and around 6–8 months of age for soy [29]. Resolution of FPIES due to solid foods seems to occur later (> 3 years old) [32].

FPIES in Australasia

Few studies have focused on the epidemiology of FPIES in Oceania. Moreover, most of them have been set in the Australian continent and led by the same group, which is behind 5 out of the 6 papers published in the area [4••, 37–40]. As a matter of fact, only one of them looks into data outside of Australia, including information from New Zealand [41].

The first work was published in 2009 by Mehr et al. It was a retrospective, descriptive study, which reported their experience after 16 years following a cohort of 35 children with acute FPIES. All of them had debuted in infancy, under 12 months of age, with a slight male predominance. Most patients (57%) had other atopic diseases (most frequently, AD and IgE-mediated food allergy) [37]. These characteristics have been confirmed in subsequent studies [25], including a more recent prospective population-based survey, conducted through the Australian Paediatric Surveillance Unit, and including data from 230 patients submitted by general and subspecialist pediatricians. This study did not find sex predilection and calculated an incidence of FPIES during the 2012–2014 period of 15.4/100,000 births/year [4••].

Nevertheless, incidence of FPIES in Australia seems to be increasing and does not seem to be caused by greater awareness of its existence by pediatricians. Actually, one of the main conclusions of the first study from the Australian continent was that mismanagement, misdiagnosis, and delayed diagnosis were common for children with FPIES [37]. These findings were confirmed by a 2018 study, which examined non-IgE allergic gastroenteritis admissions in Australia and New Zealand. They observed an increase from 6.8 admissions/100,000/year to in 1998–2000 to 26.5/100,000/year in the 1998–2014 period. Due to the limitations of coding, other related conditions could not be differentiated in the latter study. However, since most of these cases were infants under 12 months, it seems fair to assume that most were due to FPIES. The authors did not find differences between Australia and New Zealand [41].

Remarkably, rice has been observed to be the main trigger of FPIES among the Australian pediatric population [25]. The characteristics of that subgroup of patients with rice-caused FPIES were further explored in an article published in 2009, where the authors reported that severity of rice-triggered FPIES tended to be higher than those caused by CM or soy [38]. Remaining causative agents, in descending order, are rice, CM, egg, oats, and chicken [4••]. Chicken is another trigger of FPIES which has been described to be differential in Australia. Chicken FPIES seems to occur earlier in Australia, compared with the USA. This has been associated with the recommendation by Australian feeding guidelines to introduce chicken earlier than American guidelines [25].

Most patients are sensitized to only 1 food trigger, but co-sensitization has been described in up to one-third of Australian patients [42].

As expected, the majority of children with FPIES have negative skin prick tests and sIgE. However, Australian researchers have described that FPIES triggered by egg was frequently accompanied by positive skin tests to egg white [39]. In fact, atypical FPIES, with positive skin prick tests or sIgE to the causative agent, has been associated with delayed acquisition of tolerance, especially in the case of CM-triggered FPIES [40].

Most Australian patients overgrow their FPIES. The first retrospective study by Mehr et al. found that over 80% of patients with sensitivity to soy and rice had lost it by the age of 3 years [37]. This finding was confirmed later by an additional study from the same group, which observed that 73% of their patients were tolerant at the age of 2 years. However, the food triggering FPIES had an influence in the prognosis of the disease. While 96% of CM-sensitive children and 100% of rice-sensitive children tolerated them by 2 years of age, overcoming FPIES caused by egg and fish was less common (25% at 5 years) [40]. Still, the reproducibility of these results is limited by the fact that these retrospective studies are based on open food challenges, which were not performed at regular intervals. Although transformation from FPIES to IgE-mediated food allergy has been described in other areas of the world [43, 44, 45•], we have been unable to find specific data for patients in Australasia.

FPIES in Africa

There is lack of information regarding FPIES in this continent. There are no studies about incidence or prevalence and, as far as we know, there is only one report describing 5 cases of non-IgE-mediated food allergy. Within these 5 children, four of them were finally diagnosis of having allergic proctocolitis, and the last one was diagnosis of allergic enteropathy [46]

FPIES in Adults

For years, we have thought that FPIES was a childhood disease; however, recently some cases of FPIES in adults have been reported. Adult-FPIES (A-FPIES) is less recognized than in children and even more misdiagnosis. Perhaps adults just avoid the offending trigger and do not seek medical attention.

There is only one prospective study, carried out by González-Delgado et al. [47], in a single center in Spain. Twenty-five patients over a 10-year period were included. The median age at the onset was 28 years (IQR 20.5–38). All of them

had exclusively gastrointestinal symptoms after ingesting seafood. Abdominal pain was the main symptom and reported in all cases, followed by vomiting (76%) and diarrhea (64%). Crustaceans were the most frequent causative food followed by fish. Eleven oral food challenge were performed in 8 patients in order to confirm if tolerance to the offending food have been achieved. Four patients overgrew their FPIES, three after a mean period of 3 years and one 21 years later.

In previous retrospectives studies [48, 49], seafood was the most common offending trigger of A-FPIES followed by dairy products, wheat, and egg in the USA and followed by egg in Australian population. Abdominal pain was reported by the majority of patients while vomiting and diarrhea were present only in half of the American patients.

Further studies in this unexplored manifestation of the disease are needed.

Conclusions

FPIES is considered a rare non-IgE-mediated food allergy, but it is probably not as rare as we thought, and we don't know what the role of the IgE in this disease is.

Some aspects of FPIES patients are well identified. However, there are still gaps in our knowledge of the disease, most notably incidence of chronic presentation of the disease and prognosis, including prospective interventional studies focusing on outgrowing and transformation of FPIES into IgE-mediated food allergy, especially in the case of atypical presentations and characteristics of adults with FPIES.

There are remarkable geographical differences in both clinical manifestations and offending triggers, suggesting that different phenotypes might exist, perhaps due to race or ethnicity, or dietary habits. This heterogeneous presentation may favor misdiagnosis of the disease. We have to know our population in order to reach a correct and early diagnosis and try to avoid unnecessarily restricted diets.

Finally, it is important to highlight that almost all the studies have been carried out in developed countries. There is a remarkable gap of information of the epidemiology of the disease in developing countries where poor socioeconomic conditions may turn FPIES into an especially life-threatening disease.

Compliance with Ethical Standards

Conflict of Interest

Sonsoles Infante declares that she has no conflict of interest. Paula Cabrera-Freitag declares that she has no conflict of interest. Cristina Morales-Cabeza declares that she has no conflict of interest. Alberto Alvarez-Perea declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. •• Nowak-Węgrzyn A, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive Summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2017;139:1111–26

This International consensus summarizes the knowledge of FPIES. Regrettably, most of the conclusions are only applicable to Western countries.

2. Powell GK. Milk and soy induced enterocolitis of infancy: clinical features and standarization of challenge. *J Pediatr.* 1978;93:553–60.
3. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol.* 2011;127:647–53.
4. •• Mehr S, Frith K, Barnes EH, Campbell DE. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012–2014. *J Allergy Clin Immunol.* 2017;140:1323–30

One of the most important epidemiological studies, carried out in Australia.

5. •• Alonso SB, Ezquiaga JG, Berzal PT, Tardón SD, San José MM, López PA, et al. Food protein-induced enterocolitis syndrome: increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol.* 2019;143:430–33

This study highlights that perhaps is not a rare disease.

6. Nowak-Węgrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein-induced enterocolitis syndrome in the US-population-based study. *J Allergy Clin Immunol.* 2019. <https://doi.org/10.1016/j.jaci.2019.06.032>.
7. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr.* 1998;133:214–9.
8. • Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. *Curr Allergy Asthma Rep.* 2012;12:297–303

Although is not a recent study, is one of the first that reported differences between Western countries and Eastern countries.

9. • Von Sydow G. Some cases of cow's milk idiosyncrasy. *Acta Paediatr Scand.* 1939;23:383

For history lovers. Where it all started.

10. Ruiz-García M, Escudero Díez C, Sánchez García S, Rodríguez del Río P, Ibañez MD. Diagnosis and natural history of food-protein induced enterocolitis syndrome in children from a tertiary hospital in

central Spain. *J Investig Allergol Clin Immunol.* 2014;24:354–6.

11. Vila L, García V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. *J Allergy Clin Immunol Pract.* 2015;3:621–3.
12. • Vazquez-Ortiz M, Machinena A, Domínguez O, Alvaro M, Calvo-Campoverde K, Giner MT, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by 5 years in Spanish children. *J Allergy Clin Immunol Pract.* 2017;5:521–5

Prognosis depends on the causative food and geographical location.

13. •• Díaz JJ, Espín B, Segarra O, Domínguez-Ortega G, Blasco-Alonso J, Cano B, et al. Food protein-induced enterocolitis syndrome: data from a multicenter retrospective study in Spain. *J Pediatr Gastroenterol Nutr.* 2019;68:232–36

Epidemiological studies are scarce so, all of them have some interest.

14. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy.* 2012;42:1257–65.
15. Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. *Ann Allergy Asthma Immunol.* 2014;113:290–4.
16. Ruffner M, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel J. FPIES: insights from review of a large referral population. *J Allergy Clin Immunol Pract.* 2013;1:343–9.
17. Douros K, Tsabori S, Feketea G, Grammeniatis V, Koliofoti EG, Papadopoulos M, et al. Restrospective study identified fish and milk as the main culprits in cases of food protein-induced enterocolitis syndrome. *Acta Paediatr.* 2019. <https://doi.org/10.1111/apa.14779>.
18. • Infante S, Marco-Martín G, Sánchez-Domínguez M, Rodríguez-Fernández A, Fuentes-Aparicio V, Alvarez-Perea A, et al. Food protein-induced enterocolitis syndrome by fish: Not necessarily a restricted diet. *Allergy.* 2018;73:728–32

This study highlights the needing to avoid unnecessarily restricted diets in FPIES patients.

19. Ntoupmpara M, Sotiriadou F, Fotoulaki M. Acute-on-chronic food protein-induced enterocolitis syndrome in an exclusively breast-fed infant. *Clin Case Rep.* 2019;7:71–3.

20. Miceli Sopo S, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. *Int Arch Allergy Immunol*. 2014;164:137–9.
 21. Miceli Sopo S, Monaco S, Badina S, Longo G, Novembre E, Viola S, et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. *Pediatr Allergy Immunol*. 2015;26:731–6.
 22. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol*. 2006;17:351–5.
 23. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol*. 2014;134:382–9.
 24. • Blackman AC, Anvari S, Davis CM, Anagnostou A. Emerging triggers of food protein-induced enterocolitis syndrome: lessons from a pediatric cohort of 74 children in the United States. *Ann Allergy Asthma Immunol*. 2019;122:407–11
- FPIES symptoms and offending foods have differences even in the same country.
25. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2014;14:208–16.
 26. Nowak-Węgrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003;111:829–35.
 27. Caubet JC, Nowak-Węgrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Expert Rev Clin Immunol*. 2011;7:317–27.
 28. Ahn KM, Han YS, Nam SY, Park HY, Shin MY, Lee SI. Prevalence of soy protein hypersensitivity in cow's milk protein-sensitive children in Korea. *J Korean Med Sci*. 2003;18:473–7.
 29. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. *Arch Dis Child*. 2009;94:425–8.
 30. Ebisawa M, Ito K, Fujisawa T. Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology. Japanese guidelines for food allergy 2017. *Allergol Int*. 2017;66:248–64.
 31. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea and soy protein intolerance. *J Pediatr*. 1977;91:404–7.
 32. Levy Y, Danon YL. Food protein-induced enterocolitis syndrome. Not only due to cow's milk and soy. *Pediatr Allergy Immunol*. 2003;14:325–9.
 33. Ovadia A, Nahum A, Tasher D, Abiri S, Epov L, Kessel A, et al. Sesame: an unrecognized trigger of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract*. 2019;7:305–6.
 34. Kimura M, Shimomura M, Morishita H, Meguro T. Prognosis of infantile food protein-induced enterocolitis Syndrome in Japan. *Pediatr Int*. 2017;59:855–60.
 35. Yang M, Geng L, Xu Z, Chen P, Friesen CA, Gong S, et al. Severe food protein-induced enterocolitis syndrome to cow's milk in infants. *Nutrients*. 2015;8(1):1.
 36. • Nomura I, Morita H, Hosokawa S, Hoshina H, Fukuie T, Watanabe M, et al. Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms. *J Allergy Clin Immunol*. 2011;127(3):685–8
- Different clinical manifestations, very useful for an early diagnosis.
37. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics*. 2009;123:459–64.
 38. Mehr SS, Kakakios AM, Kemp AS. Rice: A common and severe cause of food protein- Induced enterocolitis syndrome. *Arch Dis Child*. 2009;94:220–3.
 39. Hsu P, Mehr S. Egg: a frequent trigger of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2013;131:241–2.
 40. Lee E, Campbell DE, Barnes EH, Mehr SS. Resolution of acute food protein-induced enterocolitis syndrome in children. *J Allergy Clin Immunol Pract*. 2017;5:486–8.
 41. Mullins RJ, Turner PJ, Barnes EH, Campbell DE. Allergic gastroenteritis hospital admission time trends in Australia and New Zealand. *J Paediatr Child Health*. 2018;54:398–400.
 42. Mehr S, Campbell DE. Food protein-induced enterocolitis syndrome: guidelines summary and practice recommendations. *Med J Aust*. 2019;210:94–9.
 43. Banzato C, Piacentini GL, Comberiati P, Mazzei F, Boner AL, Peroni DG. Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome. *Eur Ann Allergy Clin Immunol*. 2013;45:209–11.
 44. Miceli Sopo S, Monaco S, Cerchiara G, Bersani G. A very unusual case of food allergy, between FPIES and IgE-mediated food allergy. *Eur Ann Clin Immunol*. 2017;49:42–4.
 45. • Miceli Sopo S, Fantacci C, Bersani G, Romano A, Liotti L, Monaco S. Is food protein induced enterocolitis syndrome only a non IgE-mediated food allergy? *Allergol Immunopathol*. 2018;46:499–502
- FPIES is considered a non-IgE-mediated food allergy but is not always like that.
46. Afaa TJ, Afrane AK, Etwire V. Gastrointestinal food allergy in Ghanaian children: a case series. *Ghana Med J*. 2017;51:138–42.
 47. Gonzalez-Delgado P, Caparrós E, Moreno MV, Cueva B, Fernández J. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. *J Allergy Clin Immunol Pract*. 2019;7:670–2.

48. Tan JA, Smith WB. Non-IgE mediated gastrointestinal food hypersensitivity syndrome in adults. *J Allergy Clin Immunol Pract.* 2014;2:355–7.
49. Du YJ, Nowak-Wegrzyn A, Vadas P. FPIES in adults. *Ann Allergy Asthma Immunol.* 2018;121:736–8.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.