

Food protein–induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children



Marta Vazquez-Ortiz, MD, PhD^{a,b,*},
Adrianna Machinena, MD^{a,*}, Olga Dominguez, MD^a,
Montserrat Alvaro, MD, PhD^a,
Katty Calvo-Campoverde, MD^a, María Teresa Giner, MD^a,
Rosa Jiménez-Feijoo, MD, PhD^a, Jaime Lozano, MD^a,
Mònica Piquer, MD^a, Marcia Dias, MD^a,
María del Mar Folqué, MD^a, and
Ana María Plaza, MD, PhD^a

Clinical Implications

- In this cohort of Spanish children, food protein–induced enterocolitis syndrome (FPIES) to fish and egg resolves in most cases, with 75% resolution by age 5 years. FPIES to multiple or uncommon foods and IgE sensitization were rare. Geographical particularities are essential to guide local practice in FPIES.

TO THE EDITOR:

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy still with significant knowledge gaps. Considerable differences have been described for different geographical areas involving key features that may influence clinical practice, such as the type and number of implicated foods and natural course of the disease.^{1–4} Cow's milk is the leading trigger in series from different countries^{1–3} except Australia, where rice is the main cause.⁴ The available data are skewed toward the large series from the United States,^{1,2} where FPIES to multiple foods and IgE sensitization to other foods appear to be common, ranging from 40% to 78%. Also, FPIES to foods rarely causing IgE-mediated food allergy, such as rice, oats, sweet potato, peas, or chicken, is not uncommon.¹ These findings have led to recommendations to delay or avoid certain foods when weaning children with FPIES.⁵ Whether these restrictions are appropriate in other populations is not well understood. Also, in American series an overlap with chronic gastrointestinal symptoms is reported in up to 64% of milk or soya-FPIES cases¹ and so-called atypical FPIES occurs in up to 1 in 4 children,¹ especially for cow's milk. That is a shift from acute FPIES to IgE-mediated allergy to the culprit food with poor prognosis regarding resolution, suggesting a role for IgE testing in FPIES. Again, to which extent these observations apply to other populations is not well known.

Regarding prognosis, very few studies have provided data on tolerance development based on repeated challenges—the criterion standard for diagnosis.^{1,4} FPIES to cow's milk, soya, or rice are considered transient, although differences have been described across regions. Less is known about the natural course of FPIES to egg or fish, which are believed to be more persistent,

with resolution in only a minority of cases.^{3,4,6–8} Given the knowledge gaps and geographical differences, there is no definitive consensus on when to perform such challenges.

In the present study, we aimed at describing FPIES characteristics and prognosis in children from a single tertiary centre in Barcelona, Spain.

Children aged 0 to 18 years diagnosed with acute FPIES between June 2008 and December 2013 at Sant Joan de Déu Hospital, Barcelona, were included retrospectively. The diagnosis was established when all Powell's criteria were met: (1) exposure to the incriminated food elicits repetitive vomiting, diarrhea, or both within 4 hours without any other cause; (2) symptoms are limited to the gastrointestinal tract; (3) avoidance of the offending protein results in symptoms resolution; and (4) a standardized oral food challenge or isolated reexposure elicits typical symptoms.

At diagnosis clinical data were collected: age, sex, family history, allergic comorbidities (other food allergies, atopic dermatitis, respiratory allergy), food(s) causing FPIES, and type of symptoms at onset. Skin prick test (SPT) and specific IgE level measurements to the culprit food were performed at diagnosis. For SPT, standardized extracts (Laboratorios Leti, Barcelona, Spain) and 1 mm lancets (Stallergenes, Paris, France) were used. The results were read after 15 minutes using the Prick Film method (Immunotek, Madrid, Spain). Specific IgE levels in serum were measured by ImmunoCAP (ThermoFisher, Uppsala, Sweden), with 0.1 KU/L being the inferior detection limit. Tolerance to all other groups of foods was evaluated by direct questioning. Children were advised to wean as per normal, that is, not delaying or avoiding any foods beyond the culprit one. Follow-up open food challenges to the culprit food(s) were performed 18 to 24 months after the last known reaction, except for fish (36-month interval) on the basis of anecdotal experience suggesting later resolution. Children who failed the first challenge underwent subsequent challenges at 18- to 24-month intervals if no accidental reactions had occurred. Children with fish-FPIES were challenged to the same fish species triggering the initial reaction. Other fish species were not tested. For challenges, an age-appropriate portion (0.3 g/kg and 3 g as maximal dose, as in previous studies^{1,9}) was divided into 3 equal doses given at 90-minute intervals if no reaction occurred, except for cow's milk in which 7 consecutive doses were given at 90-minute intervals. Patients were admitted to the ward for 24 hours and an intravenous access was placed before start. Powell's criteria modified by Sicherer⁹ were used to determine a positive challenge outcome. Blood pressure was measured at baseline, before each dose, and every 10 to 20 minutes in the event of a reaction. Data related to challenges were collected (age, tolerance rate, and for positive challenges eliciting dose, type of symptoms, and time to symptoms onset). Intravenous saline (20 mL/kg) was given for hypotension, lethargy, or persistent vomiting.

Variables were described as appropriate. Comparative analysis among data from different foods was performed using parametrical and nonparametrical tests as appropriate. Tolerance development over follow-up was analyzed using Kaplan-Meier survival estimator, including comparative analysis among different foods using log-rank test. The event of interest was

TABLE I. Clinical characteristics at diagnosis and at first follow-up challenges in a cohort of 81 children with FPIES from Barcelona, Spain

Clinical characteristics	Culprit foods triggering FPIES					
	Any food	Fish	Cow's milk	Egg	Rice	Corn
Characteristics at onset						
Number of patients (% of patients, no.)	100% (81 of 81)	54.3% (44 of 81)	25.9% (21 of 81)	9.8% (8 of 81)	7.4% (6 of 81)	2.5% (2 of 81)
Sex: male (% of patients, no.)	53% (43 of 81)	52.2% (23 of 44)	57.1% (12 of 21)	25% (2 of 8)	83.3% (5 of 6)	50% (1 of 2)
Age at diagnosis (mo), median (IQR)	9 (5-12)	10 (9-12)	2 (1-5)	12 (10-12)	5.5 (4-7.2)	5.5 (4-7)
Symptoms (% of patients, no.)						
Vomiting	95.1% (77 of 81)	97.7% (43 of 44)	85.7% (18 of 21)	100% (8 of 8)	100% (6 of 6)	100% (2 of 2)
Lethargy	67.9% (55 of 81)	77.3% (34 of 44)	47.6% (10 of 21)	62.5% (5 of 8)	83.3% (5 of 6)	50% (1 of 2)
Pallor	49.4% (40 of 81)	43.2% (19 of 44)	52.4% (11 of 21)	37.5% (3 of 8)	83.3% (5 of 6)	100% (2 of 2)
Diarrhea	42% (34 of 81)	29.5% (13 of 44)	71.4% (15 of 21)	37.5% (3 of 8)	33.3% (2 of 6)	50% (1 of 2)
Hypotension	0	0	0	0	0	0
Characteristics at first food challenge						
Age (mo), median (IQR)	37 (25-49.5)	44.5 (33.2-50)	21 (15-31)	36.5 (30.5-60.7)	26.5 (7.7-51.7)	8 (7-9)
Tolerance rate	59.2% (48 of 81)	47.7% (21 of 44)	71.4% (15 of 21)	87.5% (7 of 8)	50% (3 of 6)	100% (2 of 2)
Symptoms at positive challenges (% patients, no.)						
Vomiting	90.9% (30 of 33)	91.3% (21 of 23)	83.3% (5 of 6)	100% (1 of 1)	100% (3 of 3)	NA
Lethargy	48.5% (23 of 33)	39.1% (9 of 23)	83.3% (5 of 6)	100% (1 of 1)	33.3% (1 of 3)	NA
Pallor	27.3% (9 of 33)	21.7% (5 of 23)	50% (3 of 6)	0	33.3% (1 of 3)	NA
Diarrhea	15.2% (5 of 33)	8.7% (2 of 23)	50% (3 of 6)	0	0	NA
Hypotension	0	0	0	0	0	NA
Need for IV fluid resuscitation (% patients, no.)	57.6% (19 of 33)	56.6% (13 of 23)	50% (3 of 6)	0% (0 of 1)	100% (3 of 3)	NA
Time to symptoms onset (h), mean $\pm$ SD	5 $\pm$ 1.08	5.04 $\pm$ 1.06	5.3 $\pm$ 1.33	4.8 $\pm$ 0	4 $\pm$ 0	NA
Eliciting dose (% patients reacting, no)						
First dose	0	0	0	0	0	NA
Second dose	36.4% (12 of 33)	43.4% (10 of 23)	16.7% (1 of 6)	0	33.3% (1 of 3)	NA
Third dose	51.5% (17 of 33)	56.5% (13 of 23)	16.7% (1 of 6)	100% (1 of 1)	66.7% (2 of 3)	NA
Fourth dose	3% (1 of 33)	NA	16.7% (1 of 6)	NA	NA	NA
Fifth dose	9% (3 of 33)	NA	50% (3 of 6)	NA	NA	NA

IQR, Interquartile range; IV, intravenous; NA, not applicable/available.

defined as a negative challenge outcome (ie, tolerance development). PASW Statistics 18 (SPSS Inc, Chicago, Ill) was used. A 2-tailed *P* value of less than .05 was considered significant. Written informed consent was obtained from parents/guardians. Local Ethics Committee approved the study.

Eighty-one patients were diagnosed with acute FPIES and fish was the main trigger (54.3%, 44 of 81; Table I). Fish species involved were hake (19 of 44), sole (9 of 44), monkfish (7 of 44), canned tuna (4 of 44), salmon (2 of 44), swordfish (1 of 44), fresh tuna (1 of 44), and dogfish (1 of 44). Mean age at symptoms onset was 9 months (interquartile range, 5.5-12). All patients presented with FPIES to 1 food only, except 1 child who reacted with acute FPIES to cow's milk, beef, and chicken on separate occasions. Children with FPIES to rice were tolerant to corn and vice versa, as well as to gluten-containing grains. No cases of FPIES to oats, wheat, soya, fruits, or vegetables were registered. No patient had chronic symptoms to the culprit food before presenting with acute FPIES. All children had negative SPT result and specific IgE to the culprit food at diagnosis. Only

1 child (1.2%) had another food allergy (IgE-mediated allergy to banana). Thirty-five children (42.7%) had a positive family history of atopy, 15 (18.3%) had atopic dermatitis, and 2 (2.4%) had respiratory allergy.

All children underwent reintroduction challenges over follow-up. Tolerance development curves and rates are shown in Figure 1 and Table E1 in this article's Online Repository at www.jaci-inpractice.org. The cumulative probability of tolerance development for any food was 25% at age 33 months (95% CI, 26.1-39.9), 50% at age 50 months (95% CI, 45-55), and 75% at age 60 months (95% CI, 52.1-67.9). Most children with FPIES to fish or egg developed tolerance (75% resolution at 60 months [95% CI, 49.5-70.5] and 63 months [95% CI, 47-79], respectively). Tolerance development was detected at an earlier age for milk than for fish-FPIES, suggesting faster resolution (50% at 29 months [95% CI, 17.2-40.8] vs 50% at 54 months [95% CI, 46.9-61.1], log-rank test *P* = .001), although children were not challenged at equivalent intervals. No other differences were found among other foods regarding tolerance development.

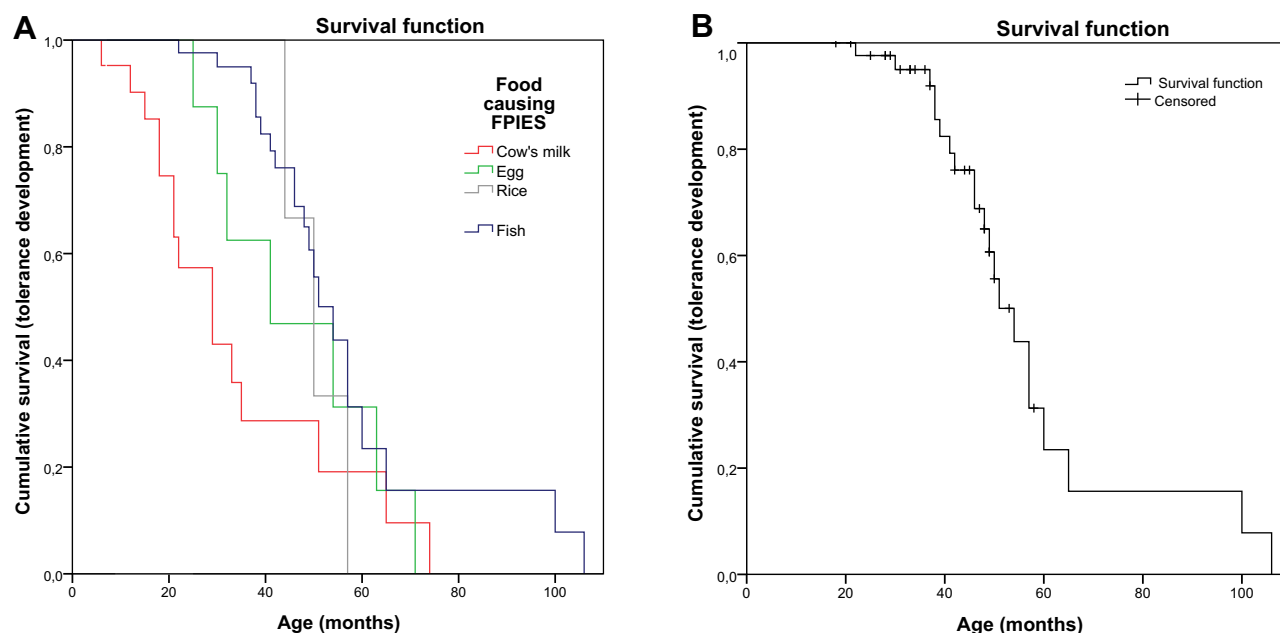


FIGURE 1. Kaplan-Meier estimate of survival showing tolerance development over time to the different culprit foods (A) and to any food (B) in a cohort of 81 children with FPIES from Barcelona, Spain.

Symptoms and other clinical data at onset and at challenge are summarized in Table 1. Diarrhea both at onset and at challenge was more frequent with cow's milk than with other foods ($P < .05$). At challenges, no patients experienced IgE-mediated immediate-type symptoms or hypotension or required pressors or intensive care unit admission.

To our knowledge, this study is the largest European series on FPIES reported, and one of the very few to provide data on tolerance development over follow-up based on repeated challenges. As main findings, fish was the main culprit food. FPIES to fish and egg resolved over time in most cases, with 75% cumulative probability of resolution at around age 5 years. FPIES to multiple foods was exceptional affecting only 1 case, as was having other food allergies. FPIES to less commonly allergenic foods, except rice and corn, was also rare. FPIES presented as an acute event in all cases, with no previous chronic symptoms. No children showed IgE sensitization to the culprit food or a change from FPIES to an IgE-mediated food allergy phenotype over time. These results are significantly different from other series, especially those from the United States,^{1,2} as described above. Fish-FPIES is rare in Australian and American cohorts and tolerance development was classically thought to be nonexistent.⁴ Recently, fish was identified as the leading cause of FPIES to solid foods in Spanish children.⁶ Our results further support this, showing that fish-FPIES is even more common than milk-FPIES in our region. In other European series, fish-FPIES is also common, but it accounts for only 12% to 15% of cases³ and tolerance development is also reportedly low (19%-36%).⁶⁻⁸ Methodological differences can partly explain this disagreement, for instance, reintroduction challenges being performed only in a minority of patients in these studies. Similarly, in a recent Australian study, only 25% of children with fish-FPIES or egg-FPIES developed tolerance and this occurred at a later age in comparison to FPIES to milk or rice.⁴ In contrast, in our cohort,

tolerance development to egg did not occur later than that to other foods.

These findings further support that FPIES characteristics vary in different regions and clinical practice should follow these local particularities, including when reintroduction challenges should be performed. Although Australian authors suggest deferring egg and fish challenges until age 5 years,⁴ we would not advise deferring egg challenges beyond age 3 years because around 50% of patients are tolerant by then in our region. Also, our results support our practice of weaning infants with FPIES with no restrictions beyond the implicated food, in contrast to recommendations by American and British authors.⁵ Likewise, repeating allergy tests over follow-up, as advised by some authors,¹ seems of limited value in our area. Finally, no children experienced hypotension at our challenges, whereas this affects up to 50% of cases in other series.^{1,3} The fact that we gave consecutive challenge doses at long intervals—every 90 minutes—might have contributed to a safer outcome. However, we cannot exclude that prompt fluid administration at challenges might have prevented hypotension or simply that FPIES might be milder in our population. Optimal challenge protocols for FPIES to ensure patients' safety need to be further studied.

Finally, the main limitation of the study is its retrospective design, which might have impacted the thoroughness of the data. Also, the fact that the initial reintroduction challenge to fish was performed later than that to other foods (36 vs 18-24 months) might have influenced our observation regarding later resolution for fish-FPIES. However, this is supported by similar findings by other groups.^{4,7}

In conclusion, our results provide further evidence on the geographical differences in FPIES phenotypes, with regard to triggers, characteristics, and tolerance development. This reinforces the need to consider local particularities to appropriately

guide practice in FPIES regarding reintroduction challenges, weaning advice, or usefulness of IgE testing as well as to adequately inform parents on prognosis.

We thank the Paediatric Allergy Nurses at Sant Joan de Déu Hospital for their excellent work when performing challenges and allergy tests. We thank Dr Paul Turner, Clinical Scientist at Imperial College London, for his invaluable comments on this manuscript.

^aPaediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

^bDepartment of Paediatrics, Imperial College London, London, United Kingdom

^cThese authors contributed equally to this work as first authors.

Conflicts of interests: M. Vazquez-Ortiz has received research support from Marie Skłodowska-Curie actions Research Fellowship funded by the Commission of the European Communities (reference 656878). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 2, 2016; revised December 21, 2016; accepted for publication December 28, 2016.

Corresponding author: Adrianna Machinena, MD, Passeig de Sant Joan de Déu, 2, Esplugues de Llobregat, 08950 Spain. E-mail: amachinena@sjdhospitalbarcelona.org.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.12.029>

REFERENCES

1. 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.
2. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013;1:343-9.
3. Sopo SM, Giorgio V, DelloIacono 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.
4. 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.
5. Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;14:255-62.
6. 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.
7. Sopo SM, Monaco S, Badina L, Barni S, Longo G, Novembre E, et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. *Pediatr Allergy Immunol* 2015;26:731-6.
8. González-Delgado P, Caparrós E, Moreno MV, Clemente F, Flores E, Velásquez L, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. *Pediatr Allergy Immunol* 2016;27:269-75.
9. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol* 2005;115:149-56.

TABLE E1. Kaplan-Meier estimate of survival showing tolerance development over time to the different culprit foods in a cohort of 81 children with FPIES from Barcelona, Spain

Culprit food	25th centile (95% CI)	50th centile (95% CI)	75th centile (95% CI)
Any food	33 (26.1-39.9)	50 (45-55)	60 (52.1-67.9)
Fish	46 (37.6-54.4)	54 (46.9-61.1)	60 (49.5-70.5)
Cow's milk	18 (12.8-23.2)	29 (17.2-40.8)	51 (27.8-74.2)
Egg	30 (21.6-38.4)	41 (15.3-66.7)	63 (47-79)
Rice	44	50 (40.4-59.6)	57
Corn	7	7	9