

RESEARCH LETTER

A modified oral food challenge in children with food protein-induced enterocolitis syndrome

Simona Barni¹  | Lucrezia Sarti¹ | Francesca Mori¹ | Lucia Liotti² | Neri Pucci¹ | Elio Novembre¹

¹Allergy Unit, A. Meyer Children's Hospital, Florence, Italy

²Pediatric Unit, Hospital of Senigallia, Senigallia, Italy

Correspondence

Simona Barni, Allergy Unit, Meyer Children's Hospital, Viale Pieraccini 24, 50139 Florence, Italy.

Email: simonabarni@hotmail.com

To the Editor,

Acute food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy that typically presented with repetitive protracted vomiting that begins 1-4 hours after ingestion of the culprit food.¹ OFC is extremely useful for determining whether FPIES has been outgrown 12-18 months after the last episode. According to the International Guidelines,¹ the OFC protocol entails the administering of the challenge food at a dose of 0.06-0.6 g per kilogram of body weight in 3 equal doses over 30 minutes followed by a 4- to 6-hour observation. It is generally recommended not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid) as a full dose but there is no reference advising capping the cumulative OFC dose.

As FPIES symptoms are delayed, we doubt that giving several doses within 1 hour leaves enough time to determine whether the first dose alone would have caused reactions.

This retrospective study was conducted from January 2016 to June 2018 in children diagnosed with FPIES at two Italian paediatric allergology centres. Before April 2017, the diagnosis of FPIES was based on Leonard criteria,² since April 2017, the diagnosis of FPIES was made if patients fulfilled the criteria of the latest International Guidelines.¹

We adopted a different OFC protocol consisted in administering 25% of the full dose, calculated as 0.3 g of food protein per kilogram of body weight, and in the absence of adverse reactions, the remaining dose 4 hours later, followed by another 4 hours of observation (Figure 1). If the patient had a previous history of severe reactions, a lower dose of 0.06 g protein/kg body weight was used.

Moreover, we did not observe the limit of 3 or 10 g, respectively, of protein or total food.

The aim of our study was to observe whether the initial dose is sufficient for eliciting symptoms.

A detailed clinical history, the offending food, age and symptoms at onset were recorded.

Skin prick tests (SPTs) were performed in all children using commercial allergen extract (Alk Abellò) and fresh food with the prick-by-prick technique when the commercial allergen extract was not available. The skin tests were performed at the time of diagnosis and before performing the OFC. Serum-specific IgEs (s-IgEs) to the trigger food allergens were determined using a fluorescent enzyme immunoassay (ImmunoCAP system-Thermo Scientific) with a positive cut-off point set at 0.1 KU_A/L.

After the publication of international consensus,¹ when the criteria were not met, children with FPIES underwent diagnostic OFC as soon as possible after recovering from the reaction. An OFC was performed with the trigger food from 12 to 18 months after the last FPIES episode to verify whether tolerance to the offending food had been achieved. An intravenous access was always secured. The OFC was considered positive, and the reactions were classified as mild, moderate and severe according to diagnostic criteria¹ for the interpretation of the OFCs. Written informed consent was obtained from the children's parent for all procedures performed. The study was approved by the Hospital's Ethics Committee. Descriptive data were expressed as mean values $\pm$ standard deviation (SD).

1 | RESULTS

Forty-eight patients were enrolled (25 females [52%]; 23 males [48%]). Fifty-one reactions were reported. Forty-five (93.7%) patients presented FPIES to a single food and 3 (6.3%) patients to multiple foods. The age of the first reaction was 5.4 ± 3 months (range 1-11 months), and the age of FPIES diagnosis was 12.7 ± 16.4 months (range 1-93 months) with a mean number of episodes before FPIES diagnosis of 1.8 (range 1-6). Cow's milk (CM) represented the most common trigger food, with reactions observed in 21 patients

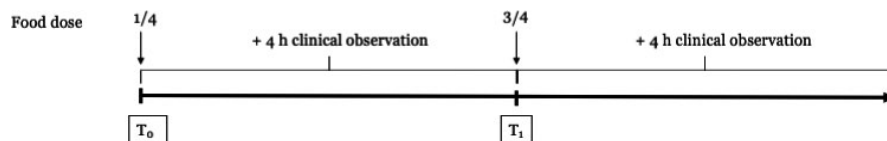


FIGURE 1 Protocol of oral food challenge

followed by fish in 10 patients, grains in 9 patients and egg in 7 patients. Two patients reacted to beef, one to bean and one to pear (Figure 2).

The mean time latency from trigger food ingestion to the onset of symptoms was 131 ± 60 minutes (range: 60-180 minutes). The symptoms presented in 51 reactions were as follows: vomiting in all reactions (100%), lethargy in 40 (78.4%), pallor in 38 (74.5%), diarrhoea in 10 (19.6%), hypotension in 3 (5.8%) and hypothermia in 1 reaction (2%). Thirty-six out of 51 (70.5%) reactions were recovered with any treatment, 12 (23.5%) needed iv fluids, 2 (3.9%) ondansetron and 1 (2%) corticosteroid.

SPTs with the trigger food were conducted in all patients and were negative in 100% of patients; s-IgEs to the trigger foods were tested in 36 (75%) children and were negative in all cases.

A total of 54 OFCs were performed (4 patients performed 2 or more OFCs): 6 OFCs to confirm FPIES diagnosis and 48 to verify the tolerance. Nineteen out of 54 OFCs (35.2%) were positive (13 to test tolerance with the culprit food, 6 to confirm FPIES diagnosis). All the 19 failed OFCs showed the onset of symptoms after 25% of the full dose with a mean time latency of 136 minutes (range 60-230 minutes; median: 120 minutes; IQR: 105-165). The severity of reactions was as follows: 4 (21%) mild, 6 (32%) moderate and 9 (47%) severe. Ondansetron was necessary in 15 patients (78.9%), corticosteroids were administered in 14 (73.7%), fluid therapy was administered in 11 patients (57.9%), 2 patients (10.5%) did not receive any treatment, and no patients required to be transfer to the intensive care unit. The characteristics of the failed 19 OFCs are summarized in Table 1.

A variety of protocols for FPIES-related OFC have been published, differing in amount and number of doses and timing.³⁻⁹

In particular, Infante et al³ performed OFCs on 2 non-consecutive days: on the first day, the child was given a single dose slightly <50% of the serving age. If tolerated and the child remained free of symptoms for 48 hours, a full serving dose was offered. All patients were observed for 4 hours after each OFC.

Forty-five out of 60 patients (75%) passed the OFC, and the children who managed the first day of OFC tolerated the whole meal without any problems; in those who failed (25%), the symptoms were milder without specifying the time latency from the last dose.

Vazquez-Ortiz et al⁴ administered 0.3 g of protein/kg divided into 3 equal doses at 90-minute intervals, except for CM, in which 7 consecutive doses were given at 90-minute intervals.

None of the 81 challenged children reacted to the first dose, 36.4% (12/33) reacted to the second dose, 51% (17/33) reacted to the third dose, 3% (1/33) reacted to the fourth dose, and 9% (3/33) reacted to the fifth dose with a latency time to onset of symptoms of 5 ± 1.08 hours after the last dose.

Vila Sexto⁵ administered the full serving dose per age and size divided into 5 doses every 20 minutes. Patients were under observation for at least 4 hours.

Fogg et al⁶ reported a trigger dose of 0.15 g of protein/kg body weight in 15 (93.7%) of 16 cases of confirmed FPIES with a mean reaction time of 2.8 ± 0.8 hours after ingestion.

Katz et al⁷ used a challenge to cow's milk as follows: 10 minutes separated the first two doses (5 and 20 mL), 20 minutes separated the next two doses (30 and 60 mL) and 45 minutes separated the remaining doses (120 and 150 mL) with an observation time of 3 hours. Five out of 28 patients (17.9%) presented symptoms after 30-50 mL. Six out of 28 patients (21.4%) after 51-100 mL and 15 out

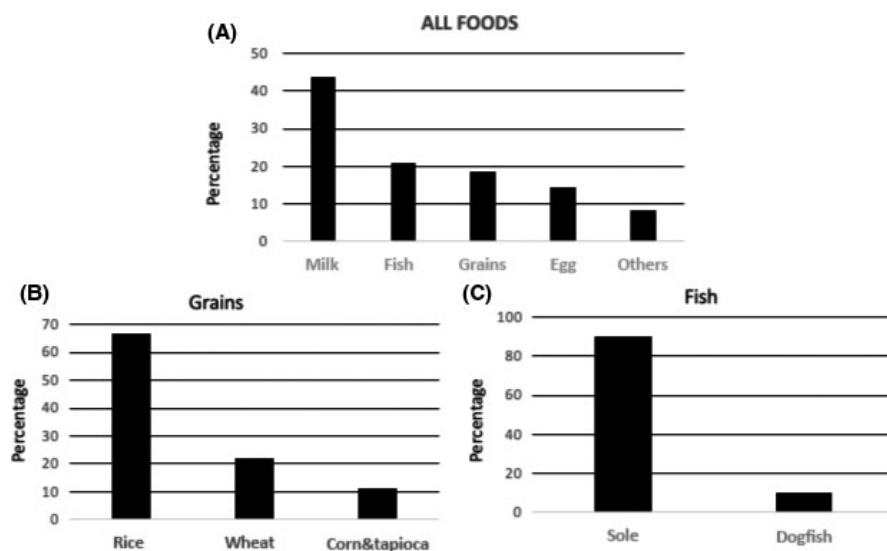


FIGURE 2 Foods that cause food protein-induced enterocolitis (FPIES) reaction. A, Foods are expressed as a percentage of patients with FPIES reaction to the given food. Meats, fruits and legumes are grouped into other category and included beef, beans and pear. B-C, FPIES reactions to individual foods expressed as percentage of patients for individual foods: B, grains and C, fish

TABLE 1 Characteristics of the 19 reactions observed during the OFCs

Sex	Trigger food (g of protein/100 mL or mg of food)	Type of OFC	Age at OFC (months)	Patient's weight (kg)	Multiplication coefficient	Serving dose (g or mL)	25% of the serving dose or reaction dose (g or mL)	Severity of reaction (Mi/Mo/S)	Time latency from last food dose (minutes)	Therapy during OFC (IV)
F	Milk form (2.2)	D	3	4.4	0.06	12 mL	3 mL	Mi	90	-
M	Cow's milk (3.15)	T	44	20	0.06	38 mL rounded to 40 mL	10 mL	S	150	Fl, O, C
M	Cow's milk (3.15)	T	32	14.2	0.06	28 mL	7 mL Taken dose: 2 mL	S	120	Fl, O, C
F	Milk form (2.2)	D	5	4.8	0.06	13.6 mL rounded to 12 mL	3 mL	Mi	180	-
F	Milk form (2.2)	D	7	7.6	0.3	100 mL	25 mL	S	150	Fl, O, C
F	Cow's milk (3.15)	D	14	10.5	0.3	100 mL	25 mL	S	60	Fl, O, C
F	Cow's milk (3.15)	D	18	10.8	0.3	100 mL	25 mL	S	180	Fl, O, C
F	Sole (15.24)	T	36	11	0.3	18.7 g rounded to 20 g	5 g	S	120	Fl, O, C
M	Sole (15.24)	T	30	14	0.3	28 g	7 g	Mo	230	Fl, O
F	Sole (15.24)	T	18	8.5	0.3	16 g	4 g	S	120	Fl, O, C
M	Sole (15.24)	T	60	20	0.3	40 g	10 g	S	90	Fl, O, C
F	Dogfish (16)	T	75	20	0.3	37.5 g rounded to 40 g	10 g Taken dose: 5 g	Mo	90	Fl, C
M	Rice (2.18)	T	36	17	0.06	48 g	12 g	Mo	60	Fl, O
M	Rice (2.18)	T	50	14	0.06	40 g	10 g Taken dose: 5 g	Mo	210	Fl, O
M	Rice (2.18)	D	7	7	0.06	20 g	5 g	S	120	Fl, O, C
F	Wheat (13)	T	60	25.5	0.3	60	15 g	Mo	120	C
M	Corn & tapioca (4.5)	T	16	11	0.3	73 g	18 g Taken dose: 1 spoon	Mi	120	O
M	Apple (0.27)	T	16	10	0.06	222 g	55 gaken dose: 6 g	Mi	230	Fl
F	Egg (12.5)	T	19	13	0.3	38 g	8 g	Mo	145	Fl, O

Abbreviations: C, corticosteroid; D, diagnostic; F, female; Fl, fluid; Form, formula; IV, intravenous; M, male; Mi, mild; Mo, moderate; O, ondansetron; OFC, oral food challenge; S, severe; T, to evaluate tolerance.

of 28 patients (53.6%) after 121 mL, with a latency time from the first dose to reaction of 3.7 ± 1.20 hours.

Wang KY et al⁸ utilized one-third of a serving size with a 4-hour observation period, followed by home titration to full dose over 9–12 days. Thirty (17.7%) out of 169 challenges were positive, with 17 challenges (10%) during the initial challenge and 13 (7.7%) during home dosing. In all positive challenges, symptoms of acute reaction occurred at least 85 minutes after dosing. In the majority (76%) of these positive OFCs, the symptoms started at least 120 minutes after dosing. Of all the 13 positive challenges at home, all occurred later in the day or within the first few days after the initial challenge.

Recently, Infante et al⁹ compared two methodologies used in the OFC for patients with FPIES to fish: the method 1 consisted in giving several doses (1/8 + 1/4 + 1/2 + the remaining of the whole meal) over 30 minutes during the same day vs method 2 that consisted in giving 25% of the serving size per age on day 1, 48 hours later, a 50% of the serving size per age and finally, after other 48 hours, a normal serving size per age on the third non-consecutive day. In 41 (95.3%) positive OFCs performed with the method 1, the symptoms started after the complete serving size per age was given, while only in 6 (18.7%) the OFC performed with method 2, and the symptoms appeared after the whole meal was eaten. Most of the OFC performed with method 2 (81.3%) were positive on the first day when the children had only consumed 25% of the serving size per age. The latency time from the dose to the onset of symptoms is not specified.

Choosing the most appropriate OFC protocol is complex, in fact, as the onset of FPIES symptoms is delayed, it is difficult to know the smallest symptom trigger dose. Patients can eat a whole serving dose before the onset of reactions, and however, it is not known whether the same reactions would have occurred even after a smaller dose of the trigger foods. We detected a trigger dose of 25% of the serving dose that could be appropriate and less time-consuming in most cases, even if it could be lower, as there are case reports of FPIES caused by cow's milk protein passed through breast milk.¹⁰

Not only our first dose is sufficient for triggering symptoms, but it can also provoke reactions as demonstrated by our results. Our protocol is safer than the method 1 of Infante et al⁹ which described 81.4% moderate-severe reactions, while is less safe than method 2 of Infante in fact the percentage of moderate-severe reactions is lower than ours (31.3% vs 78%) even if our protocol is less time-consuming.

In conclusion, our results, as the method 2 of Infante,⁹ show that a quarter of the full dose, as a trigger dose, is sufficient for eliciting reactions and that the temporal latency between the first and second dose should be longer than the 30 minutes as recommended by the current guidelines.

Given the lack of concordance in the optimal way to perform OFC in FPIES, multi-centre studies should be performed in the future to ascertain in particular number of doses and timing of administration

for each food. The limit of our study is the small number of patients and positive reactions. However, if our protocol were confirmed in a larger number of patients, the OFC would be less time-consuming than the current one, since only one dose would be sufficient to trigger the eventual reaction, and it could be a valid alternative to the one currently used.

CONFLICT OF INTEREST

The authors declare not to have any conflict of interest.

ORCID

Simona Barni  <https://orcid.org/0000-0001-5598-2740>

REFERENCES

1. Nowak-Węgrzyn A, Chehade M, Groetch ME, 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(4):1111–1126.
2. Leonard SA, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome. *Pediatr Clin North Am*. 2015;62:1463–1477.
3. Infante S, Marco-Martín G, Sánchez-Domínguez M, et al. Food protein-induced enterocolitis syndrome by fish: not necessarily a restricted diet. *Allergy*. 2017;73(3):728–732.
4. Vazquez-Ortiz M, Machinena A, Dominguez O, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. *J Allergy Clin Immunol Pract*. 2017;5(2):512–515.
5. Vila SL. Latest insights on food protein-induced enterocolitis syndrome: an emerging medical condition. *J Investig Allergol Clin Immunol*. 2018;28(1):13–23.
6. 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(5):351–355.
7. 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(3):647–653.
8. Wang KY, Lee J, Cianferoni A, et al. Food protein-induced enterocolitis syndrome food challenges: experience from a large referral center. *J Allergy Clin Immunol Pract*. 2019;7(2):444–450.
9. Infante S, Marco-Martín G, Zubeldia JM, et al. Oral food challenge in food protein-induced enterocolitis syndrome by fish: is there any room for improvement? *Int Arch Allergy Immunol*. 2019;121:1–7.
10. Vergara Perez I, Vila SL. Suspected severe acute food protein induced enterocolitis syndrome caused by cow's milk through breast milk. *Ann Allergy Asthma Immunol*. 2018;121(2):245–246.

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