

Oral Food Challenge in Food Protein-Induced Enterocolitis Syndrome by Fish: Is There Any Room for Improvement?

Sonsoles Infante^{a, b} Guadalupe Marco-Martín^c José Manuel Zubeldia^{a, b, d}
Victoria Fuentes-Aparicio^{a, b} Alberto Alvarez-Perea^{a, b} Paula Cabrera-Freitag^{a, b}
Cristina Morales-Cabeza^{a, b} Lydia Zapatero^{a, b}

^aPaediatric Allergy Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ^bGregorio Marañón Health Research Institute (IISGM), Madrid, Spain; ^cAllergy Unit, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain; ^dBiomedical Research Network on Rare Diseases (CIBERER)-U761, Madrid, Spain

Keywords

Fish · Food allergy · Food protein-induced enterocolitis syndrome · Oral food challenge

Abstract

Background: Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food hypersensitivity usually due to cow's milk or soy. Among the solid foods, rice is one of the most causative foods worldwide, but it varies depending on the geographic area. In the Mediterranean countries, fish is one of the most important triggers of FPIES. There is not a specific biological marker for the disease that allows us to confirm the diagnosis or to predict when tolerance to the offending food has been achieved, so all patients with a FPIES diagnosis undergo an oral food challenge (OFC) at least once. The OFC is a risky procedure and many patients develop severe symptoms. **Objective:** We sought to evaluate the safety of a new OFC protocol in children with fish-FPIES. **Methods:** A retrospective study was performed over a 22-year period (1996–2018). We compared two methodologies used in the OFC: Method 1 that consisted in giving several doses during the same day versus Method 2 that consisted in giving a unique dose per day on 2 or

three non-consecutive days. **Results:** A total of 75 positive OFC with fish done in 40 children were included. Forty-three (57.3%) OFC were performed following Method 1 and 32 (42.7%) with Method 2. The severity of the symptoms of the OFC done with Method 1 was mostly moderate (41.9%) followed by severe (39.5%) and mild (18.6%). The adverse reactions with Method 2 were mostly mild (68.8%) and only 18.8 and 12.5% presented moderate or severe symptoms, respectively. **Conclusions:** OFC performed in children with fish-FPIES are risky and many patients develop moderate or severe symptoms after this procedure. We propose a new protocol that has demonstrated to improve safety.

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Introduction

Food protein-induced enterocolitis syndrome (FPIES) has become an emerging disease during the last two decades. It is considered a non-IgE-mediated food allergy and is characterized by recurrent delayed vomiting, diar-

Edited by: H.-U. Simon, Bern.

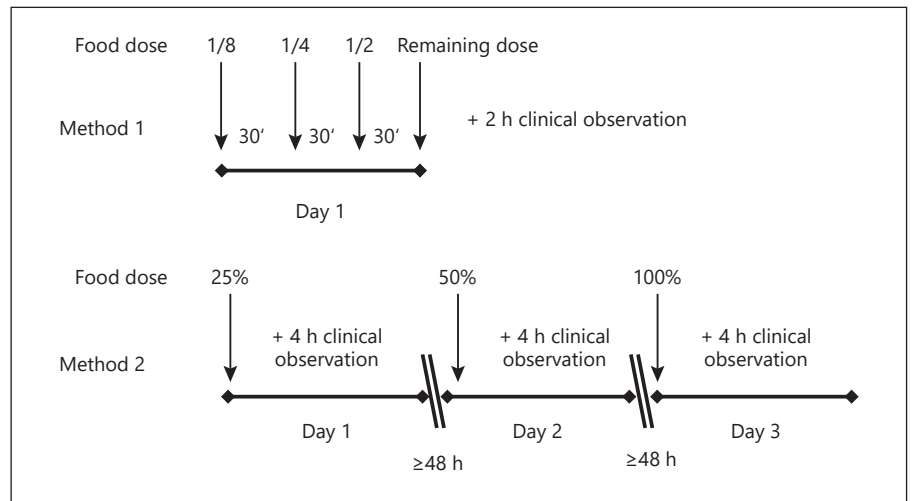


Fig. 1. Comparison of the methodologies used in OFC.

rhoea, lethargy, pallor, hypotension, and may progress to a state of dehydration and hypovolemic shock. The symptoms generally begin within 1–4 h after ingestion. Diarrhoea may develop after 5–10 h of ingestion and could last for up to 24 h after exposure. Manifestations resolve usually within 24–48 h after elimination of the causative food.

The most frequent offending foods are cow's milk and soy. Among the solid foods, rice is considered one of the most common causative foods worldwide [1], but it varies depending on the geographic area. In the Mediterranean countries, such as Spain or Italy, fish is the most important solid food trigger of FPIES [2–5].

Development of natural tolerance in patients with cow's milk- or soy-induced FPIES has been reported to occur at an earlier age than tolerance in patients with other FPIES. The average reported age of tolerance to solid food is 42 months [6], and for fish-FPIES it is about 5 years of life [7].

Nowadays, there is not a specific biological marker for the disease that allows us to confirm the diagnosis or to predict when tolerance to the offending food has been achieved. This is the reason why all patients with FPIES should undergo an oral food challenge (OFC) at least once. The OFC is not risk free and many patients develop severe symptoms after this procedure. There is no generally accepted protocol to perform the OFC, and several ways to do it have been described [4, 7, 8]. The International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome recommends administering the challenging food at a dose of 0.06–0.6 g, usually 0.3 g of the food protein per kilogram of body weight, in 3 equal doses over 30 min.

A total of 3 g of protein or 10 g of total food for an initial feeding should not be exceeded and the patient should be observed for 4–6 h. Lower starting doses or longer observation periods or both should be considered in patients with a history of severe reactions [6].

Despite the variety of protocols described, there are no studies analysing safety. We sought to evaluate the safety of a new OFC protocol in children with a diagnosis of FPIES induced by fish.

Patients and Methods

A retrospective study was performed over a 22-year period (1996–2018). We included all positive OFC performed in children with FPIES by fish at our Paediatric Allergy Unit from January 1996 to March 2018.

We compared two different methodologies used in the OFC. Before 2015, the so-called Method 1 consisted in giving several doses over 30 min during the same day. Initially, a dose equal to 1/8 (12.5%) of the serving size per age was given, then a 1/4 (25%), 1/2 (50%), and finally the remaining of the whole meal. The last dose was followed by a clinical observation period of 2 h. Since 2015, we performed the OFC in 3 non-consecutive days, the so-called Method 2. The first day a unique dose of 25% of the serving size per age was given followed by a 4-h clinical observation. If the children remained asymptomatic for the next 24 h, 48 h later a 50% of the serving size per age was served followed by a 4-h observation, and if they still remained asymptomatic for the next 24 h, we gave them a normal serving size per age on the third non-consecutive day (Fig. 1). When the patients had a history of mild reactions or if an alternative fish, different from the offending one, was tested, the OFC was performed within 2 days. On the first day a dose of 40% of the serving size per age was given and if it was well tolerated, and remained asymptomatic for the next 24 h, a new OFC with the normal serving size per age was then performed.

Outcome measures studied were: the age when the OFC was performed, severity of the symptoms, and need to be transferred to the emergency department or hospitalization. The severity of the symptoms was established following the criteria of the International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome: mild symptoms (1–2 episodes of emesis without lethargy); moderate symptoms (more than 3 episodes of emesis and mild lethargy); and severe symptoms (more than 3 episodes of emesis, with severe lethargy, hypotonia, or cyanotic appearance).

The Fisher exact test was used for comparisons between groups and Holm correction in the case that multiple comparisons were made. A multinomial logistic regression model was constructed to analyse those factors related to severity of reactions. Variables with a statistical significance in univariate model were included in the regression model and differences with a $p < 0.05$ value were considered statistically significant.

Results

A total of 189 OFC were performed in 71 children. A total of 75 of the OFC were positive in 40 children. Forty-three (57.3%) OFC were performed during the period from 1996 to 2015 following Method 1, and 32 (42.7%) were performed during the period from 2015 to 2018 following Method 2. Ten children underwent both OFC procedures.

The median age of the children that were challenged by Method 1 was 36 months (IQR = 25–48), whereas the median age in Method 2 was 60 months (IQR = 29.5–84) ($p = 0.016$). Hake was the most frequently used fish in the OFC in both groups, in 67.4% of the cases of Method 1 and in 78.1% of Method 2.

In all the positive OFC performed with the Method 1, except in two of them, the symptoms started after the complete serving size per age was given, while only in 6 (18.75%) the OFC performed with Method 2, the symptoms appeared after the whole meal was eaten. Most of the OFC performed with Method 2 (81.35%) were positive on the first day when the children had only consumed 25% of the serving size per age.

The severity of the symptoms of the OFC that were performed following Method 1 were mostly moderate ($n = 18$, 41.9%) followed by severe ($n = 17$, 39.5%) and mild ($n = 8$, 18.6%), while the symptoms of the OFC that were performed following Method 2 were mostly mild ($n = 22$, 68.8%) and only in 18.8% ($n = 6$) and 12.5% ($n = 4$) moderate or severe symptoms, respectively, developed ($p < 0.001$) (Fig. 2).

OFC performed following Method 1 had a 2.23 higher risk of developing moderate symptoms (RR; 95% CI: 1.0–

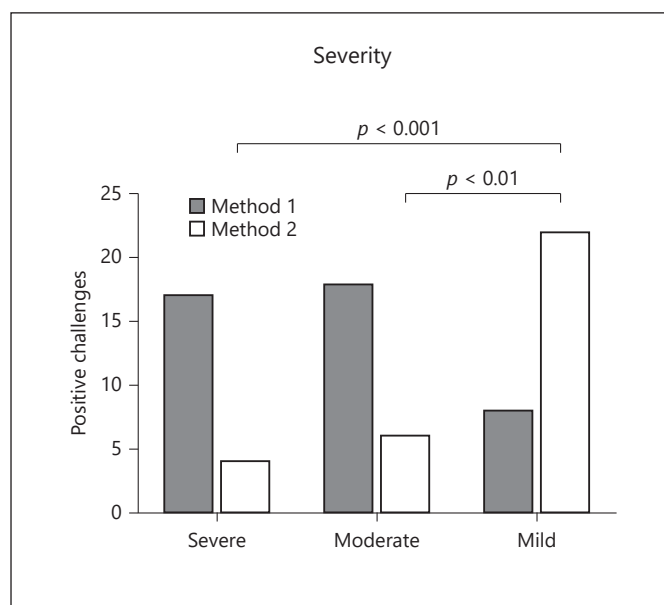


Fig. 2. Severity of the symptoms after OFC.

5) and a 3.16 higher risk of developing severe symptoms (RR; 95% CI: 1.2–8.5) compared to OFC performed following Method 2 ($p < 0.001$).

Following Method 1, patients had a higher risk of being transferred to the Emergency Department after the OFC ($n = 15$, 34.9%), (RR = 1.8; 95% CI: 0.8–4.2) or being hospitalized ($n = 3$, 7%) (RR = 1.1; 95% CI: 0.2–6.3) compared to Method 2 (18.8% [$n = 6$] and 6.25% [$n = 2$] respectively), although no statistical significance was found ($p > 0.05$).

Discussion

A variety of protocols for OFC in FPIES are reported in the literature. Powell [9] described the very first one in 1978, when she proposed a different methodology for milk and soy OFC and established the criteria for considering it positive. The challenge was done using 100 mL of formula when the infant was asymptomatic and had not received formula for at least 2 weeks. The challenge was considered positive if diarrhoea occurred within 24 h after the administration of a single challenge, if stools contained blood and leukocytes, and if an increase from pre-challenge values in the total polymorphonuclear leukocyte count greater than 4,000/mm³ was detected at 6–8 h post challenge. Later, the diagnosis criteria were

modified [10] but not the procedure of the OFC until 2005 when Sicherer [11] suggested to administer the dose gradually in 3 feedings over a period of 45 min, without exceeding 3 g of protein or 10 g of total food weight for a challenge. If there were no symptoms during the first 4 h, a second feeding was given, generally with a serving size amount and the child was observed for several more hours. In 2009, Nowak-Węgrzyn and Muraro [12] proposed a gradual increase of food protein intake over 1 h, and if no reaction occurred within 2–3 h, it was allowed to give a normal size per age of food. Katz et al. [13], in 2011, followed an OFC that was similar to the one used for IgE-mediated food allergies, increasing the dose every 30 min until the serving size per age was reached. Sopo et al. [3], in 2012, described three different protocols used in Italy. The first protocol consisted of the administration of 0.4 g/kg of the food protein divided into three equal doses over 3 h; if no adverse reaction occurred over the following 4 h, a whole meal of the trigger food was given, and clinical observation lasted for another 2 h. In the second protocol, a dose of food equal to 25% of the serving size per age was given, followed by a 4 h observation, then a dose equal to 50% of the serving size per age was given, and the whole meal was given the next day followed by another 4 h of observation. In the third protocol, a dose of food equal to 50% of the serving size per age was given followed by an observation period of 2 h and then a second dose equal to 100% of the serving size per age was given followed by an observation period of 4 h. These authors documented that most of their patients reacted after eating the whole meal, but they were successfully treated, without intravenous line in place, and they suggested customizing the OFC protocol. In this way, those cases with a history of mild reactions and in children above 4 years of age, a normal serving size amount per age could be given at once. However, in those cases with a history of moderate/severe reactions, OFC should be performed with caution, and the doses should be administered over 2 days with an intravenous line in place.

In 2013, Järvinen and Nowak-Węgrzyn [14] proposed to perform the OFC administering food (0.15–0.6 g protein/kg body weight) in 3 equal doses every 15 min and used a lower dose in patients with a history of severe reactions. If no acute symptoms occurred, patients were discharged home after 4 h of observation. Finally, in 2017, Vazquez-Ortiz et al. [7] administered 0.3 g/kg of the food protein (3 g as maximal dose) divided into 3 equal doses given at 90-min intervals if no reaction occurred and, in 2018, Vila Sexto [4] administered the full serving size per

age divided into 5 equal doses given every 20 min followed by 4 h of observation.

Due to this variety of protocols for OFC in FPIES, the International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome suggested in 2017 that the OFC should be performed administering the challenge food at a dose of 0.06–0.6 g, usually 0.3 g, of the food protein per kilogram of body weight in three equal doses over 30 min. They also recommended considering lower starting doses, longer observation periods between doses, or both, in patients with a history of severe reactions [6].

All the above described protocols are similar, with slight variations in the timing and in the amount of the protein given per dose. However, except in one of the three described by Sopo et al. [3], all of them reach the normal serving size per age at the same day.

In our study, before 2015, we followed a protocol (Method 1) comparable to the one proposed by Katz et al. [13] giving progressive increasing doses over 30 min until the children consumed a normal size per age. The last dose was followed by a 2 h observation and almost every child with positive OFC developed symptoms, mostly severe, when the whole meal was eaten. This protocol does not differ much from the one proposed in the last consensus [6]. With Method 1, if we calculate the amount of protein given as 0.3 g/kg of body weight, no dose exceeded 3 g of protein and they were given every 30 min. Since 2015, the OFC was performed in 2 or 3 non-consecutive days (Method 2). Each day a unique dose was given, and the children remained in observation for at least the next 4 h before they were discharged. The election of the number of days depended on the fish tested. If the OFC was performed with the offending fish or if the patient had a previous severe reaction, the OFC was performed in 3 days. However, if the OFC was with an alternative fish or if the symptoms had been mild, we performed it in 2 days. As we previously reported, children with FPIES due to fish could tolerate canned tuna and swordfish; therefore, when the OFC was performed with one of this fish, we did it on 2 non-consecutive days [15].

We questioned that perhaps the severity of the symptoms could be related with the kind of fish they were eating, that the severity of the symptoms depended on the age of the children, and that the severity of the symptoms could be influenced by the way we were giving the fish. So, we closely analysed those three variables that we thought could influence the severity of the symptoms.

Regarding fish, hake was the most frequently fish used in OFC in both groups and no statistical differences were

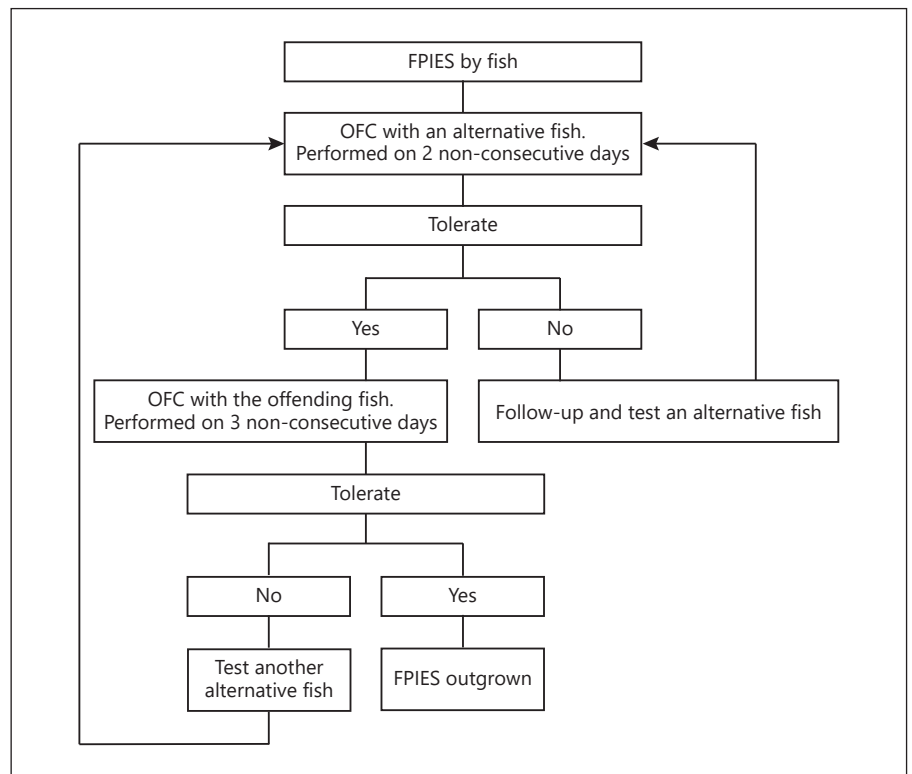


Fig. 3. Flow chart for the management of FPIES. OFC, oral food challenge; FPIES, food protein-induced enterocolitis syndrome.

Table 1. Fish used in OFCs

	Method 1 (n = 43)	Method 2 (n = 32)	p
Hake (<i>Merluccius merluccius</i>)	67.4%	78.1%	>0.05
Sole (<i>Solea solea</i>)	11.6%	ND	
Megrim (<i>Lepidorhombus boscii</i>)	9.30%	ND	
Cod (<i>Gadus morhua</i>)	4.65%	3.12%	>0.05
Canned tuna (<i>Thunnus albacares</i>)	2.32%	15.62%	>0.05
Sardine (<i>Sardina pilchardus</i>)	2.33%	ND	
Swordfish (<i>Xiphias gladius</i>)	2.32%	3.12%	>0.05

ND, not done.

found between the kind of fish used in the OFC (Table 1). With respect to age, although a statistically significant difference between the ages of the groups was found ($p = 0.016$), the multinomial logistic regression model showed that the age did not produce any bias in the severity of the symptoms. Finally, in relation to how the OFC was performed, our data showed statistical differences between Method 1 and Method 2. The new proposed protocol is safer than the previous one with a significant statistical

difference ($p < 0.001$) regarding the severity of the symptoms after challenge. Most of the children had mild reactions and the number of moderate or severe reactions was considerably lower (Fig. 1). That could be explained because most of the children (81.25%) developed the symptoms at the first day with a lower dose of the food while with the Method 1 most of them reacted when they had eaten the whole meal.

The OFC in FPIES is a time-consuming procedure and it is difficult to tell the minimal dose of culprit food that may cause an adverse reaction. The threshold dose could be a normal serving size or a very minute quantity, although it is thought that it is generally in the gram range [16, 17]. Sopo et al. [8] did not find any differences in the severity of the symptoms developed after the first dose or after the whole serving was given, so they suggested that the quantity of fish ingested did not appear to be correlated with the severity of the symptoms presented. However, our results support the idea that the symptoms do correlate with the amount of fish ingested. Our children had more mild symptoms than severe because most of them reacted the first day with a lower amount of fish. Furthermore, as symptoms in children with FPIES are delayed with a starting average time of 3 h, giving several doses over 30 or 90 min could be counterproductive be-

cause when the children develop symptoms, they have already eaten more than they really tolerate.

Regardless of which protocol is chosen, the OFC for FPIES is a lengthy procedure. Our new procedure takes more time than others but increases the safety.

Finally, as we previously reported, children with FPIES by fish tolerate better an alternative fish than the offending one [15]. In our experience, we propose a safer way to the general management of FPIES by fish (Fig. 3). We recommend challenging first with an alternative fish, different from the offending one, and performed the OFC on 2 or 3 non-consecutive days. In this way, we increase the safety of the procedure and diminish the risk of developing severe symptoms for the children. More studies are needed to be sure that the advantages of the new procedure that we propose are generally validated.

Conclusions

OFC performed in children with fish-FPIES are risky and many patients develop moderate or severe symptoms after this procedure. We propose a new protocol that has demonstrated that we could do it safer.

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Acknowledgements

We would like to thank all the parents and children included in this study and a special acknowledgment to our nurses Teresa Pérez, Patricia González, Francisca López, and M^a Dolores López for their hard work and exquisite management of these children over the years.

Statement of Ethics

This study was approved by our local Institutional Review Board and all the parents signed the corresponding informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

S.I. designed and supervised the research. G.M. analysed the data. S.I., J.M.Z., V.F., A.A., P.C., C.M. and L.Z. participated in acquiring all the study patients. All authors contributed to the writing of the manuscript and have given approval to the final version of the manuscript.