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Archives de Pédiatrie xxx (xxxx) xxx

Contents lists available at ScienceDirect

Archives de pédiatrie

journal homepage: www.elsevier.com/locate/arcped

Research paper

Food protein induced enterocolitis syndrome: French practices assessment in children

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ARTICLE INFO

Keywords:
Food protein-induced enterocolitis
Oral food challenge
Food allergy
Survey
Practice

ABSTRACT

Background: Food protein-induced enterocolitis syndrome (FPIES) is a specific non IgE-mediated food allergy. The international consensus guidelines defined diagnosis criteria and management plan in 2017.
Objectives: To assess practices regarding FPIES in France and in French-speaking countries, according to those guidelines.
Methods and Setting: We carried out a 22-question online survey to assess practices of specialised physicians (paediatricians, allergists, gastroenterologists, members of 2 French-speaking learning societies and/or working at hospitals in paediatric allergy units) following patients with FPIES between August 2019 and February 2022.
Results: We received 92 replies to our survey, mostly from hospital practitioners following less than 10 patients with FPIES. Oral rehydration solution and/or Ondansetron were largely prescribed in the emergency kit (61/72, 84.7 % and 47/72, 65.3 % respectively). 20 practitioners declared never prescribing an emergency kit. There was some confusion when distinguishing between FPIES and an IgE-mediated food allergy, as suggested by the unnecessary prescription of an antihistamine (18/72, 25.0 %) and/or epinephrine (11/72, 15.3 %) in the emergency kit. An explanatory FPIES emergency management letter to physicians in case of allergic reactions was provided in 83.7 % (77/92) of patients. Oral food challenge (OFC) practices varied greatly concerning doses: most respondents used several doses (52/92, 56.5 %) during the same day (33/52, 63.4 %). Eleven responders (12.0 %) used the same protocol as for an IgE-mediated food allergy.
Conclusion: Our survey showed that practices of FPIES management in France are generally aligned with the international consensus guidelines. There are still pending issues to be standardised, such as the emergency kit prescription and its contents, as well as OFC management strategies. This work confirms the need for continuous training of physicians regarding FPIES management. Further guidelines are needed to improve standardisation of FPIES management.

1. Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a specific non IgE-mediated food allergy, with a prevalence rate estimated between 0.015 and 0.7 % [1]. FPIES has recently been diagnosed more frequently [2], likely due to an improved knowledge of it. International consensus guidelines, published in 2017, recognises two forms of FPIES [3]. Acute FPIES is characterised by recurrent delayed vomiting in the 1- to 4-hour period after ingestion of the triggering food, without classic IgE-mediated symptoms as well as at least 3 of the following minor criteria: a second or repeated episodes of emesis after consuming the same food, a similar episode after eating a different food, extreme lethargy, notable pallor, need for emergency room visit, need for intravenous fluid, hypotension or hypothermia. Chronic FPIES is harder to characterise, and includes chronic vomiting, diarrhoea, and failure to thrive. Symptoms should improve with exclusion of the triggering food

Abbreviations: ACU, Ambulatory care unit; APT, Atopy patch test; CMP, Cow's milk protein; FPIES, Food protein-induced enterocolitis syndrome; IV, intravenous; OFC, Oral food challenge; PVA, Peripheral venous access; SPT, Skin prick test.

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https://doi.org/10.1016/j.arcped.2024.12.003
Received 19 April 2024; Received in revised form 23 September 2024; Accepted 8 December 2024

from the diet.

There are no validated biomarkers to confirm diagnosis or assess tolerance, and oral food challenges (OFC) are often necessary [4]. The international consensus guidelines recommend a dose of 0.06 to 0.6 g of the triggering food protein per kilogram of body weight, in 3 equal doses over 30 min and then patient monitoring for at least 4 to 6 h. Experts also advise establishing intravenous access for the OFC [3]. However, this OFC protocol is not consistently used by specialists [5] as it is debated due to the administration of repeated doses in a short time, although most reactions are typically delayed.

Despite multiple OFC protocols having been published since 2017 [6–15], clear recommendations are still lacking regarding action plan and emergency management at home or school in the event of an acute reaction to accidental food exposure [3,16].

The aim of this study was to assess practices regarding FPIES in France and in French-speaking countries, amongst a specialised population of allergists and paediatricians, in accordance with the 2017 guidelines [3].

2. Material and methods

An online questionnaire was created in July 2019 using Google Forms©. It included 22 questions, regarding practice types, number of patients with FPIES under a physician's care, provision of an emergency letter and kit for managing an acute episode and details on the OFC protocol (including age, location, access to fluid resuscitation, doses and administration, duration of monitoring, compliance with guidelines, management of reactions and timeframe before the next OFC). The survey is outlined in the **Supplementary Appendix S1**. It was sent to members of the learned societies of Allergology (Société Française d'Allergologie), as well as paediatric hepatology, gastroenterology, and nutrition (Groupe Francophone d'Hépatologie Gastro-Entérologie et Nutrition Pédiatrique). It was also directly sent to several French hospitals between August 2019 and February 2022. Replies were analysed with Google Forms© and are presented in absolute values and percentage figures generated using Microsoft Excel software. Fisher's exact tests were used for analysing the contingency tables with GraphPad Prism (GraphPad Software version 10.1.2).

3. Results

3.1. Demography

Our questionnaire was sent to 930 members of learned societies and 30 paediatric departments, yielding 92 completed responses. They mostly identified as paediatricians ($n = 63$, 68.5 %, including 4 paediatric gastroenterologists), allergists (27.2 %, $n = 25$, included 9 pneumologists and allergologists) or both paediatricians and allergists (34.8 %, $n = 32$). The remaining 4 were gastroenterologists ($n = 2$) or general practitioners ($n = 2$). Most participating doctors were hospital practitioners (65.2 %, $n = 60$). We gathered replies from various regions in France ($n = 84$) and a few French-speaking countries ($n = 8$, countries: Algeria, Belgium, Morocco, and Switzerland). The majority reported having fewer than 10 patients with FPIES currently in their care (54.3 %, $n = 50$) or 10 to 50 patients (40.2 %, $n = 37$); and 5 participants indicated having more than 50 patients with yet unresolved FPIES in their actual practice.

3.2. Emergency kit

Most doctors reported prescribing an emergency kit: either consistently (39.1 %, $n = 36$) or only in cases of a previous severe reaction (39.1 %, $n = 36$). Only 21.7 % ($n = 20$) of participants never prescribed an emergency kit. When an emergency kit was prescribed, it included oral rehydration solution (84.7 %), ondansetron (65.3 %), corticosteroids (50.0 %), antihistamine (25.0 %) and epinephrine (15.3 %), alone or in association (Table 1). The majority of responding physicians (83.7 %) routinely provided their patients with a letter outlining management of an acute reaction in emergency room, whereas 2.2 % of them only provided this letter to patients who had suffered a previous severe reaction. Finally, 14.1 % did not provide any letter to their patients.

3.3. OFC

OFC methodologies varied significantly but were almost always performed under a physician's supervision, meaning in an ambulatory care unit (ACU) (90.2 %), and in this case, always with peripheral venous access (PVA).

Before conducting OFC, specific IgE testing was reported by 89.1 % ($n = 82/92$) of respondents (always: $n = 43$; often: $n = 28$; sometimes: $n = 11$). Skin prick tests (SPT) were performed by 51.1 % ($n = 47/92$) of participants (always: $n = 14$; often: $n = 21$; sometimes: $n = 12$) and atopy patch testing (APT) by 3.2 % ($n = 3/92$) (always: $n = 0$; often: $n = 2$; sometimes: $n = 1$).

The age at the time of the first reintroduction of food varied depending on the type of food, mainly 12 to 18 months for cow's milk and after 24 months for solid food (Fig. 1). This timing was adjusted according to the child's age at the time of the first reaction and its severity; if the patient had positive specific IgE titres or at parents' request in case of a binding diet. There were no standardised challenge doses of food protein, which depended on weight, age, or either a fixed dose (Table 1). Most participants administered several doses (56.5 %), and in this case, often during the same day (63.5 %) and in minority over several days, either consecutively or not (Table 1). Eleven of them (12.0 %) used the same protocol as an IgE-mediated food allergy. The monitoring period was 3 to 6 h in 60.9 %, more than 6 h in 29.3 %, and less than 3 h for the remaining of attendees (Table 1). Only 46.7 % ($n = 43$) of participants stated that they followed the OFC positive criteria or OFC severity reaction defined by the international consensus.

In case of a successful OFC, physicians prescribed a gradual increase of continuous food protein doses at home for 91.3 % of responders. In the event of OFC failure, the timing schedule for the next OFC varied between 6 and 12 months (37.0 %, $n = 34$) and 12 to 18 months (32.6 %,

Table 1
Details of the replies.

	n (%)
Which of the following emergency kit contents? ($n = 72$) *	
Oral rehydration solution	57 (79.2 %)
Ondansetron	40 (55.5 %)
Corticosteroids	29 (40.3 %)
Antihistamine	12 (16.7 %)
Epinephrine	5 (6.9 %)
Which protocol for OFC? ($n = 92$)	
Dose depends on the weight	22 (23.9 %)
Dose depends on the age	20 (21.7 %)
Dose depends on both weight and age	22 (23.9 %)
Fixed dose (independent to weight or age)	12 (13.0 %)
several doses	52 (56.5 %)
dose: not applicable	16 (17.4 %)
If several doses: same day or not? ($n = 52$)	
On the same day	33 (63.5 %)
On consecutive days	11 (21.2 %)
On inconsecutive days	8 (15.4 %)
Duration of monitoring? ($n = 92$)	
0–3 h	1 (1.1 %)
3–6 h	56 (60.9 %)
>6 h	27 (29.3 %)
Variable	8 (8.7 %)
Dietary plan upon discharge? ($n = 92$)	
Gradual increase at home	84 (91.3 %)
Hospital increase	4 (4.3 %)
Other (not specified)	4 (4.3 %)

* Combined answers: "Always", "Often", and "Rarely".
OFC: Oral Food Challenge.

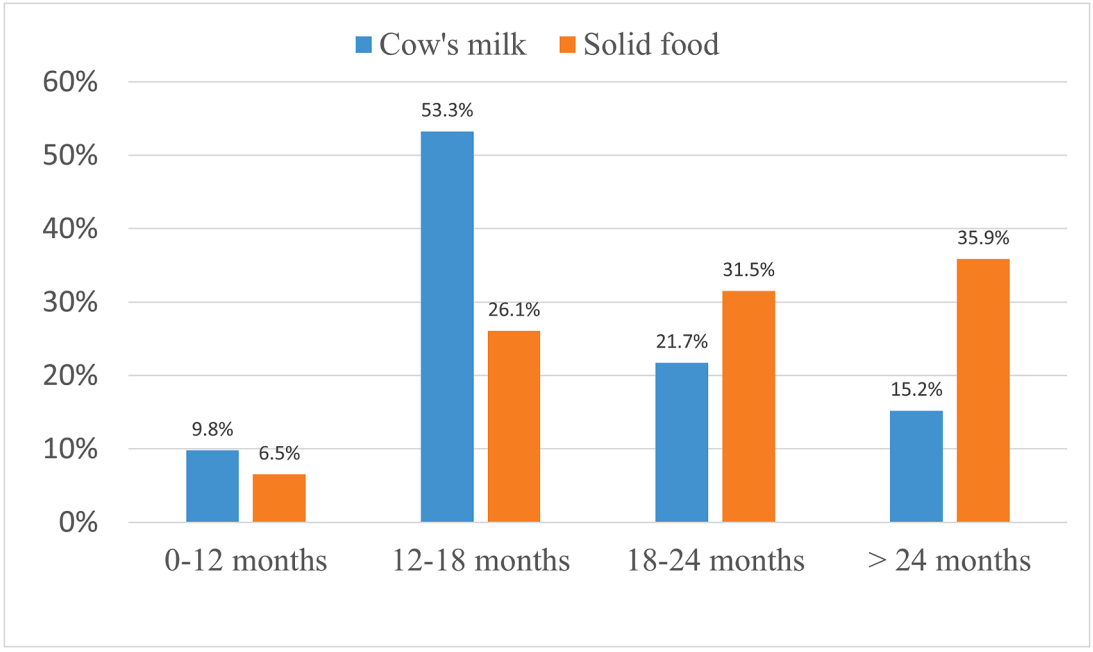

Fig. 1. Age at first reintroduction attempt.

$n = 30$). Few practioners responded that they waited less than 6 months (4.3 %, $n = 4$), or between 18 and 24 months (7.6 %, $n = 7$) before proposing a new OFC. Seventeen physicians (18.5 %) stated that these procedures should be adjusted according to the severity of the last reaction or according to the patient's age.

Milk was administered in heated form for 23.9 % (22/92) of participants.

3.4. Management strategies during OFC

Management strategies for OFC failure varied but were always tailored to the clinical severity of the reaction.

A blood test was frequently performed in case of clinical reactions by most physicians (66.3 %, $n = 61$). It was mostly serum electrolytes (47.8 %, $n = 29/61$) or a complete blood count (46.7 %, $n = 28/61$). Blood gases were only tested for in case of severe clinical reactions (30.4 %, $n = 28/92$).

Ondansetron and a serum saline bolus were the most routinely administered treatments (either according to severity of the clinical reaction: 52.2 % and 50.0 % or systematically: 40.2 % and 48.9 %) whilst the use of corticosteroids varied (Fig. 2). Most physicians reported never using an antihistamine (70.7 %) or epinephrine (78.3 %), but others indicated using them either "systematically" or "according to severity".

3.5. Comparison of answers according to the practitioner's experiments in FPIES

Practitioners treating more than 50 patients with FPIES ($n = 5$) "fully agreed" or "tended to agree" with providing an emergency kit, either always or according to the severity of clinical reactions severity, whereas it was not systematically used by physicians treating fewer than 10 patients ($n = 35/50$) or those with 10 to 50 patients ($n = 33/37$) (Table 2). Ondansetron was seldom prescribed by the most experienced practitioners. Corticosteroids were prescribed similarly in all groups: 30.0 % for the group treating fewer than 10 patients, 32.4 % for those

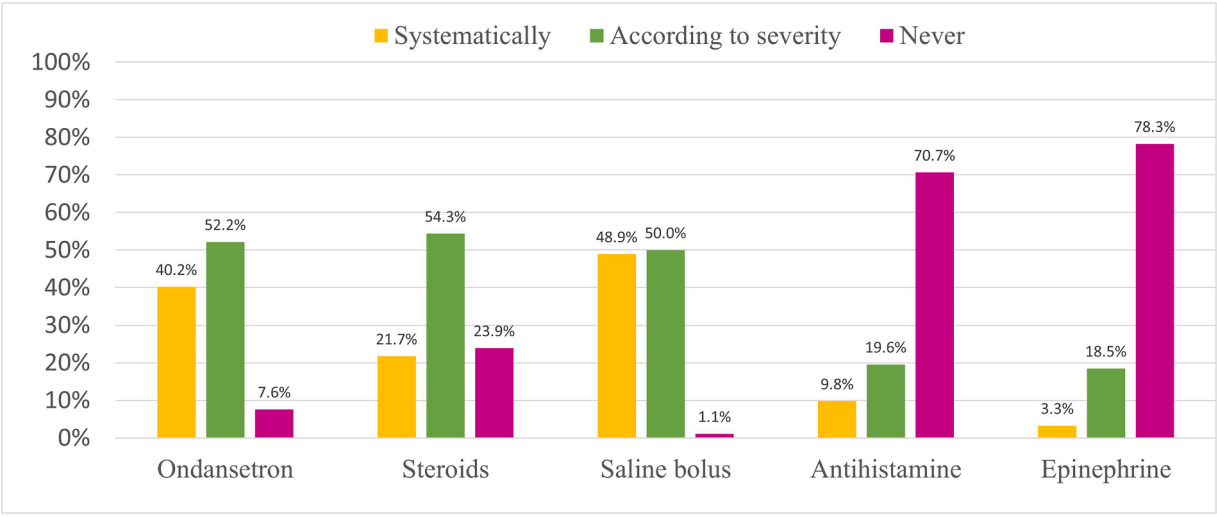

Fig. 2. Treatment strategies for allergic reaction during oral food challenge (OFC).

Table 2
Answers according to the practitioner's experiments in FPIES.

	<10 patients (n = 50)	10–50 patients (n = 37)	>50 patients (n = 5)	p-value
Prescription of an emergency kit? *				
Always	15 (30.0 %)	18 (48.6 %)	3 (60.0 %)	0.06
According to severity	20 (40.0 %)	15 (40.5 %)	1 (20.0 %)	
Never	15 (30.0 %)	4 (10.8 %)	1 (20.0 %)	
Emergency kit contents? #				
Oral rehydration solution	27 (54.0 %)	26 (70.3 %)	4 (80.0 %)	0.28
Ondansetron or anti-emetic	19 (38.0 %)	20 (54.1 %)	1 (20.0 %)	0.22
Corticosteroids	15 (30.0 %)	12 (32.4 %)	2 (40.0 %)	0.82
Antihistamine	7 (14.0 %)	5 (13.5 %)	0 (0 %)	>0.99
Epinephrine	4 (8.0 %)	1 (2.7 %)	0 (0 %)	0.54
Letter for emergency department?				
Always	40 (80.0 %)	33 (89.2 %)	4 (80.0 %)	0.07
According to severity	0 (0 %)	1 (2.7 %)	1 (20.0 %)	
Rarely or never	10 (20.0 %)	3 (8.1 %)	0 (0 %)	
Place for reintroduction of the triggering food? *				
At home	3 (6.0 %)	2 (5.4 %)	1 (20.0 %)	0.61
In office	2 (4.0 %)	2 (5.4 %)	0 (0 %)	
In hospital	45 (90.0 %)	33 (89.2 %)	4 (80.0 %)	
Saline bolus for acute reaction during OFC?				
Always	25 (50.0 %)	18 (48.6 %)	2 (40.0 %)	>0.99
According to severity	24 (48.0 %)	19 (51.4 %)	3 (60.0 %)	
Never	1 (2.0 %)	0 (0 %)	0 (0 %)	
Ondansetron for acute reaction during OFC?				
Always	16 (32.0 %)	20 (54.1 %)	1 (20.0 %)	**0.04**
According to severity	27 (54.0 %)	17 (45.9 %)	4 (80.0 %)	
Never	7 (14.0 %)	0 (0 %)	0 (0 %)	
Corticosteroids for acute reaction during OFC?				
Always	8 (16.0 %)	11 (29.7 %)	1 (20.0 %)	0.24
According to severity	27 (54.0 %)	19 (51.4 %)	4 (80.0 %)	
Never	15 (30.0 %)	7 (18.9 %)	0 (0 %)	
Antihistamine for acute reaction during OFC?				
Always	6 (12.0 %)	3 (8.1 %)	0 (0 %)	0.82
According to severity	11 (22.0 %)	7 (18.9 %)	0 (0 %)	
Never	33 (66.0 %)	27 (73.0 %)	5 (100 %)	
Epinephrine for acute reaction during OFC?				
Always	3 (6.0 %)	0 (0 %)	0 (0 %)	**0.04**
According to severity	11 (22.0 %)	6 (16.2 %)	0 (0 %)	
Never	36 (72.0 %)	31 (83.8 %)	5 (100 %)	

* Combined answers "Fully agree" and "Tend to agree"; # Combined answers "Always" and "Often". OFC: Oral Food Challenge; FPIES: food protein-induced enterocolitis syndrome; p-value from Fisher's exact tests.

with 10 to 50 patients and 40.0 % for the group with more than 50 patients (Table 2). An antihistamine and epinephrine were never prescribed in the group of experienced practitioners treating more than 50 patients, whereas the group treating fewer than 10 patients reported administering these drugs always or often in the emergency kit in 14.0 % and 8.0 % respectively (Table 2).

Management strategies during OFC also differed according to the number of patients in the physician cohort, particularly for ondansetron use, which was never used in 14.0 % of physicians with fewer than 10 patients with FPIES. Epinephrine was either used in all cases for acute reactions or according to the severity of said reaction in 23.0 % of practitioners with fewer than 50 patients, whereas it was never used by the most experienced physicians ($p = 0.04$) (Table 2).

4. Discussion

Our survey assessed practices regarding FPIES amongst a population of specialist physicians (paediatricians and allergists) from French-speaking countries, mainly working at hospitals. Knowledge of FPIES has improved, as shown by increased diagnoses in the last 20 years. Overall, most replies to our survey followed the recommendations, but some misconceptions still remained.

An emergency kit was usually provided for patients with FPIES in our cohort of specialists, although not in most cases. Currently, there is no consensus on the contents of the kit, which patients could be managed at home, and how they would be managed. A common prescription amongst our participants was a combination of oral rehydration solution and ondansetron, which has been shown to be effective in preventing dehydration during a reaction or vomiting in case of accidental exposure [3,17–19]. Use of ondansetron may have been limited by the off-label use and the need for a restricted prescription. Participants did not specify whether other anti-emetics were used. While corticosteroids were prescribed by almost half of the participants, there is no randomised controlled study confirming their efficacy in FPIES. Prescription of unnecessary and inappropriate antihistamines or epinephrine auto-injectors at home or school was reported by 19.6 % (18/92) and 12.0 % (11/92) of our respondents, respectively, especially amongst less experienced practitioners, consistent with previous surveys (antihistamine: 5–25 %; epinephrine: 16.3–28 %) [20–22]. These numbers were even higher regarding the treatment strategies for allergic reactions during OFC, with 29.3 % (27/92) and 21.7 % (20/92) of our respondents reporting the systematic or conditional use ("according to severity") of an antihistamine and/or epinephrine. They did not specify whether they used these treatments in case of history of atypical FPIES or IgE-mediated allergy. Epinephrine is not recommended for classical FPIES without a history of IgE-mediated allergy [3] as it will not alleviate symptoms of FPIES, and could theoretically be deleterious in case of hypovolemic shock. This specific point highlights that knowledge about FPIES, although improving, remains insufficient; thus there is a clear necessity to continue to train allergy specialists, as seen in a previous American survey performed in 2014 [21], as well as paediatricians and other non-allergist practitioners [20,22]. Redaction of French recommendations are currently underway to clarify the management of acute reactions in outpatient settings. Moreover, since FPIES is often misdiagnosed, several authors and the French Society of Allergology have recommended providing patients with an emergency letter, explaining symptoms and treatment in case of consultation in an emergency department [16,23], a practice largely followed by our cohort of physicians.

The wide variety of answers regarding the details of OFC (age, interval since the last reaction or failed OFC, quantity per dose and number of doses, duration of monitoring, heating) is not surprising given the diversity of published methodologies both before and since the international consensus of 2017 [3].

The ideal age to perform an OFC has been subject to considerable discussion, ranging from 12 to 60 months [7,24,25]. It varied between cow's milk and solid food in our survey responses. The interval to perform an OFC since the last reaction ranged between 6 and 18 months, often adjusted according to the severity of the previous reaction. Most studies recommend a minimum interval of 12 months [8,15,26]. We need to gather epidemiological data worldwide to improve the estimation of the age of acquisition of tolerance to a triggering food. To this end, a paediatric observatory for FPIES is being set up in France (NCT05528900).

The use of a PVA was not a point of debate amongst our participants, with 100 % providing positive responses when an OFC was conducted in ACU. IV interventions are necessary for administering IV fluids and/or ondansetron and/or corticosteroids in case of moderate (≥3 emesis episodes, mild to moderate lethargy) to severe reactions (≥3 emesis episodes, severe lethargy, hypotonia, pallor) [1]. Reported OFC reactions involved IV intervention in 40.5 % to 95 % of cases [27,28]. There are no known predictive factors for severe reactions during OFC [6,29], except for prior severe reactions [30]. The latest expert

discussion on the use of PVA for FPIES OFC still supports establishing a PVA before initiating the OFC, without debate if there is a history of severe reaction, and after an optional shared decision-making process if there has been no previous severe reaction [1].

The majority of our participants (63.5 %) performed an OFC with multiple doses on the same day, consistent with international consensus [3]. Since then, numerous protocols for OFC have been published in the literature regarding dosing [6–15]. However, international consensus provides a broad range from 0.06 to 0.3 g of protein per kg of body weight [3]. For example, for a child weighing 10 kg, the amount of milk varied from 0.6 g (equivalent to 20 mL of cow's milk) to a maximum of 3 g (equivalent to 100 mL). Moreover, symptoms usually begin 120–155 min after ingestion of the triggering food [6,8,26], and administering several doses every 30 min may not be appropriate in FPIES. The most recent protocols prefer a single dose of one third [6] or one quarter [7] of a serving dose for the age, at hospital, or even a full serving dose in one day [8,12,15], followed by several hours of monitoring. Follow-up care involves gradually increasing the consumption of the triggering food at home or in the hospital, over several days, consecutively or inconsecutively, if the full dose was not administered on the first day [7, 13–15]. The rate of delayed failure of OFC is around 7.7 % to 18.7 % [6, 7] with less severe reactions if gradual increase occurs over several days compared to during the same day [7]. A standardised protocol for OFC in France is currently used in the French observatory for FPIES (NCT05528900), involving 25 % of the serving dose on the first day in hospital, followed by an increase at home with 50 % and 100 % of the serving dose on the 2 subsequent days, consecutively or inconsecutively. The protocol for OFC should be adapted, with gradual and supervised increase in dose on the first day, if the patient has atypical FPIES, i.e. positive specific IgE and/or SPT, with or without previous IgE-mediated symptoms. APTs before OFC are not very useful in FPIES and there is no recommendation for their use at any moment of the disease [1,3]. The duration of monitoring was also consistent with international consensus [3] and literature [6–10,12–15].

Almost one quarter of physicians stated they used heated milk for cow's milk FPIES, although the concept of establishing better tolerance with heated food, particularly for cow's milk, remains a working hypothesis still today [1] without an affirming randomised trial.

4.1. Limitations

The main limitations of our survey were the reliance on self-declared answers, the limited number of patients with FPIES per practitioner, that most physicians working in hospitals which induced a selection bias, and a low response rate (9.8 %, even though comparable rates are found in similar studies [21]). Moreover, participants were members of learned societies, which can hinder generalisation to non-allergists paediatricians or general practitioners.

5. Conclusion

This survey demonstrated that practices for managing FPIES in France as well as other French-speaking countries generally align with international consensus guidelines. There are still unresolved issues requiring standardisation, such as the prescription and contents of emergency kits, as well as the OFC management strategies. There was a confusion between IgE-mediated allergy and FPIES although the survey cohort were considered specialists. This corroborates the necessity for ongoing physician training in FPIES management. Additionally, learning societies should provide further guidelines to enhance the standardisation of FPIES management.

Supplementary Appendix S1: English translation of the survey.

Declaration of competing interest

The authors declare that they have no competing interest related to this work.

Acknowledgements

We would like to thank the GFHGNP and the SFA for their help in circulating the survey and all the physicians who took the time to answer.

The authors acknowledge ITC Traductions for the English language review.

Funding source

The authors received no financial support for the research, authorship and/or publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcped.2024.12.003.

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