American Academy of Allergy Asthma & Immunology

Oral Food Challenge for FPIES in Practice—A Survey: Report from the Work Group on FPIES Within the Adverse Reactions to Foods Committee, FAED IS, AAAAI

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BACKGROUND: Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy diagnosed via history and/or an oral food challenge (OFC).
OBJECTIVE: To determine allergists' approach to FPIES OFCs.
METHODS: A web-based survey was e-mailed to 1100 randomly selected American Academy of Allergy, Asthma and Immunology members.
RESULTS: A total of 132 individuals responded (12% response rate). A total of 95.5% (n = 105) of respondents perform OFCs in their practice, but only 58.7% (n = 71) perform FPIES OFCs. The median number of FPIES OFCs in children was reported as 3 per year (range, 0-76); all but 1 respondent (2.5%) had not performed any FPIES OFCs in adults. The most common FPIES OFC foods were cow's milk, rice, lightly cooked egg, oat, soy, baked milk, and baked egg. The decision to offer FPIES OFCs was based on the severity of past reactions, the patient and family's desire, and the patient's age. FPIES OFCs were most commonly performed in an outpatient setting, with placement of peripheral intravenous access depending on the severity of past reactions and with a serving appropriate for age divided into 3 equal portions administered over 30 minutes. There was significant variability in the approach to conducting FPIES OFCs. Most respondents (87.4%, n = 127) indicated that specific guidelines for performing FPIES OFCs would be helpful.
CONCLUSIONS: Our study highlights the discordance in allergists' practices performing OFCs for IgE-mediated food allergy compared with FPIES. The lack of universal agreement on the optimal way to perform OFCs in FPIES demonstrates the need for future studies to develop a

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma and Immunology
ED- Emergency department
FPIES- Food protein—induced enterocolitis syndrome
ICU- Intensive care unit
IV- Intravenous
OFC- Oral food challenge

standardized protocol for FPIES OFCs. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:3608-14)

Key words: *FPIES; Food protein—induced enterocolitis syndrome; Oral food challenge; OFC; Food allergy; Diagnosis*

BACKGROUND

Food protein—induced enterocolitis syndrome (FPIES) is a non—IgE-mediated food allergy with diagnosis reliant on a characteristic history of delayed, repetitive vomiting 1 to 4 hours after ingestion of the allergenic food. Biomarkers to confirm disease are unavailable; therefore, if clinical history leaves the diagnosis unclear, oral food challenges (OFCs) can be helpful to confirm the diagnosis.[1] OFCs are also recommended to evaluate resolution of FPIES.

The care of patients with FPIES has been complicated by poor provider-level awareness of the diagnosis and management of patients with FPIES. A 2014 survey of American Academy of Allergy, Asthma and Immunology (AAAAI) members assessing trends in provider management of patients with FPIES found that approximately one-third of responding allergists had poor familiarity with FPIES.[2] The respondents also reported considerable variation in practice and management style regarding diagnosis and management including a poor utilization of OFCs.

Our survey sought to explore if a lack of a universally accepted standardized protocol for FPIES OFCs is another complicating factor to the care of patients with FPIES. A number of protocols for FPIES OFCs have been published with particular variability in the number of servings and total amount of protein administered. Although international consensus FPIES guidelines recommend administration of the challenge food at a dose of 0.06 to 0.6 g of food protein per kilogram body weight (g protein/kg body weight) with 4 to 6 hours of observation,[1] a recent study reporting a new modified approach to FPIES OFCs cited 7 different published protocols.[3] Thus, the considerable variation in protocols can pose an additional challenge to allergists when performing FPIES OFCs.

The aim of the present study was to determine allergists' current approach to conducting an FPIES OFC in pediatric patients. Specifically, we sought to characterize indications, locations, frequency, foods, methods including dose calculation, treatment of OFC reactions, and observation times. This article describes our survey results and provides a review of the literature.

METHODS

A 32-question anonymous online survey (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) was created by the study authors who are the members of the AAAAI work group on FPIES OFCs within the Adverse Reactions to Foods Committee. This was administered via Survey Monkey (Portland, Ore) by the AAAAI to a random 1100 subset of its 4370 domestic and international members, and it was disseminated in the summer of 2019. Survey response attrition occurred selectively because of use of skip logic, and multiple responses were allowed for selected items. This study was approved by the AAAAI Board of Directors.

The relationships between the different types of OFC outcomes and other characteristics were analyzed by calculating the odds ratio and confidence intervals using a univariate or multivariate logistic regression.[4] All tests were performed with STATA (version 11.0 for Windows; STATA Inc., College Station, Texas).

RESULTS

The survey was emailed twice to 1100 allergists. A total of 132 individuals responded (12% response rate); 78.8% (n = 104) were from the United States and 87.7% (n = 115) were board certified in Allergy and Immunology (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Approximately half of respondents were in practice for 11 to 30 years (53.8%, n = 71) and in a private practice setting (51.5%, n = 68). The median number of pediatric patients seen in the last 12 months with symptoms consistent with FPIES was 12 (range, 0-100) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Among the allergists who manage patients with FPIES, 53.8% (63 of 117) perform allergy testing in the evaluation of FPIES. Among those who perform allergy testing in the evaluation of FPIES, the following tests were reported: skin prick testing 92%, serum food-specific IgE measurement 59.4%, intradermal testing 3.1%, and basophil activation test 3.1%. Approximately half (53.1%) of respondents perform OFCs in the evaluation of FPIES. The majority of the respondents (95.5%) perform OFCs for IgE-mediated food allergy in their practice, whereas fewer (58.7%, n = 71) perform FPIES OFCs. In the last 12 months, the median number of FPIES OFCs performed in children <18 years was 3 (range, 0-76), with responses as follows: 35 (57%) performed 1 to 10, 12 (20%) performed 11 to 50, and only 2 (3%) performed 51 to 100. All but 1 respondent (2.5%) had not performed any FPIES OFCs in adults. The most commonly performed challenges in children were to cow's milk (82.1%), rice (42.9%), lightly cooked egg (41.1%), and oat (37.5%), followed by soy, baked milk, baked egg, and wheat (Figure 1). When deciding whether to perform an OFC for FPIES, the most important factors were the severity of past reactions, followed by the patient's age and the patient and family's desire to reintroduce the food, and uncertainty about diagnosis (Figure 2, *A*).

Location

The location where FPIES OFCs are performed varied significantly. Over half (60%) of the respondents indicated that they perform FPIES OFCs in the regular office area (including outpatient clinics attached to a hospital), whereas around 37% reported hospital locations (which included infusion centers in a hospital, inpatient procedure units, and medical day units). One-third qualified that the location depends on the severity of past reactions and 17.5% on the patient's age. Only 3 (5%) perform FPIES OFCs in the emergency department (ED), 1 (2%) in the home setting, and although the intensive care unit (ICU) was not an answer choice in the survey, respondents could choose "other" and freely respond, but ICU was not reported (Figure 2, *B*).

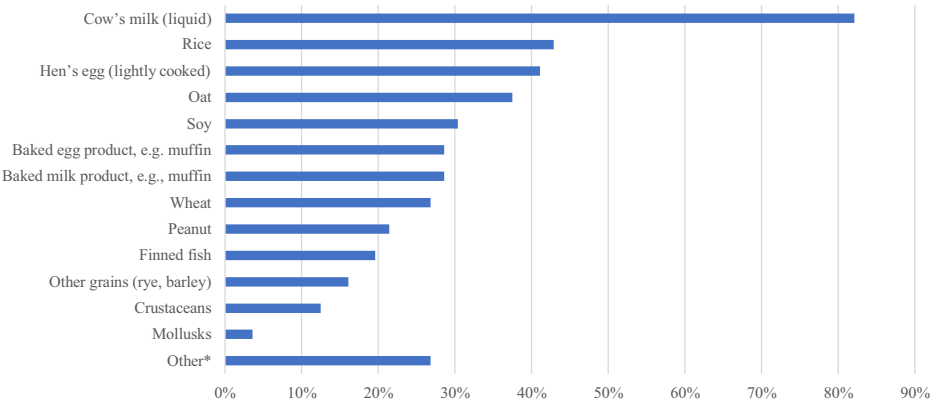

FIGURE 1. Foods administered during FPIES OFCs in the past 12 months (N = 56). *Avocado, beef, corn, kiwi, pork, squash, sweet potato, and tree nuts. *FPIES*, Food protein–induced enterocolitis syndrome; *OFC*, oral food challenge.

Peripheral intravenous access

In response to the question regarding placement of the peripheral intravenous (IV) access before starting FPIES OFCs, 41.3% reported that their decision is based on the severity of the past reactions, whereas 27% reported always securing peripheral IV line (Figure 2, *C*).

Total OFC dose

Regarding the selection of the total OFC dose, 37% reported using a regular serving of food appropriate for age, whereas 32.3% reported calculating the total dose of challenge food based on g protein/kg body weight (Figure 3, *A*).

Dosing regimen

For dosing regimens, the variables involved include the total dose administered, how that dose is portioned, and time interval between administration of dosing portions. The total dose administered can be given as either the regular serving size for the patient's age, or less than the regular serving for age. In those who initially administer a dose of food that is less than the regular serving for age, 36.5% proceed to a full serving after 2 hours, 30.1% allow for gradual build-up to full serving at home, 13.5% perform another OFC with a full dose serving, and 19.2% report other approaches. Regarding dose portions and time intervals, 33.3% divide the total dose into 3 equal portions administered over 30 minutes, 19.1% divide the total dose into 5 incrementally increasing portions administered every 10 to 15 minutes, and 23.8% administer 1 to 2 portions (Figure 3, *B*).

Treatment of the reactions during OFCs

Ondansetron is used for treating symptoms during FPIES OFCs by 38.7% of the respondents, whereas 8.1% never use ondansetron. The remainder base the decision whether to use ondansetron on the severity of the symptoms, the patient's age, and the severity of the past reactions. Ondansetron is administered intravenously by 46.3%, orally by 25.9%, and intramuscularly by 5.6%; the remainder use some combination of routes, depending on access and severity of symptoms. Systemic steroids are never used to treat symptoms during FPIES OFCs by 45.8% and always used by 8.5% of the respondents, whereas the remainder base the decision to use steroids on the severity of symptoms and the patient's age and other factors. If systemic steroids are used during FPIES OFCs, 60% administer them via IV route, 36.7% orally, and 3.3% via intramuscular injection. When asked if hospital admission is required for patients with symptoms during FPIES OFCs, 55% responded that it depends on the severity of the symptoms as well as past reactions and the patient's age; 43.3% never admit to hospital, whereas 3.3% always admit.

Time to discharge following FPIES OFCs

The majority (60.7%) reported observing asymptomatic patients for a total of 4 hours from the beginning of the OFC; however, the remaining respondents provided a wide range of observation times, from 2 hours from the beginning of the OFC to 6 hours and even 24 hours. Following a symptomatic FPIES OFC, the majority (62.9%) benchmark the time from the resolution of symptoms, between 2 and 6 hours, whereas 14.9% use the beginning of the challenge as the reference point for observation before discharge.

We ran single and multilogistic regression to identify the characteristics of the respondents that might determine their behaviors. We found no statistically significant associations. For example, the *P* values (95% confidence intervals) for association between placement of IV line before the challenge and type of practice were $P = .148$ (0.98; 1.13); years in practice, $P = .674$ (0.25; 2.44); number of food challenges, $P = .614$ (0.99; 1.00); and number of OFCs performed, $P = .159$ (0.91; 1.01). However, our study may be underpowered to detect the significant differences.

Utilization of the 2017 FPIES guidelines

The majority (86.6%) report being familiar with the FPIES guidelines, and 75.4% reported using the document in their practice. The majority reported that specific guidelines for performing FPIES OFCs would be helpful. Figure 4 presents the topics of most interest, with the dosing schedule (85.5%), criteria for selecting patients for FPIES OFCs in the office (84%), calculating the total OFC dose (83%), and contraindications to OFCs (80%) being the top priorities.

DISCUSSION

We report the first data from the allergy community on the conduct of OFCs for FPIES in children. It is clear from the literature that FPIES knowledge and management practices

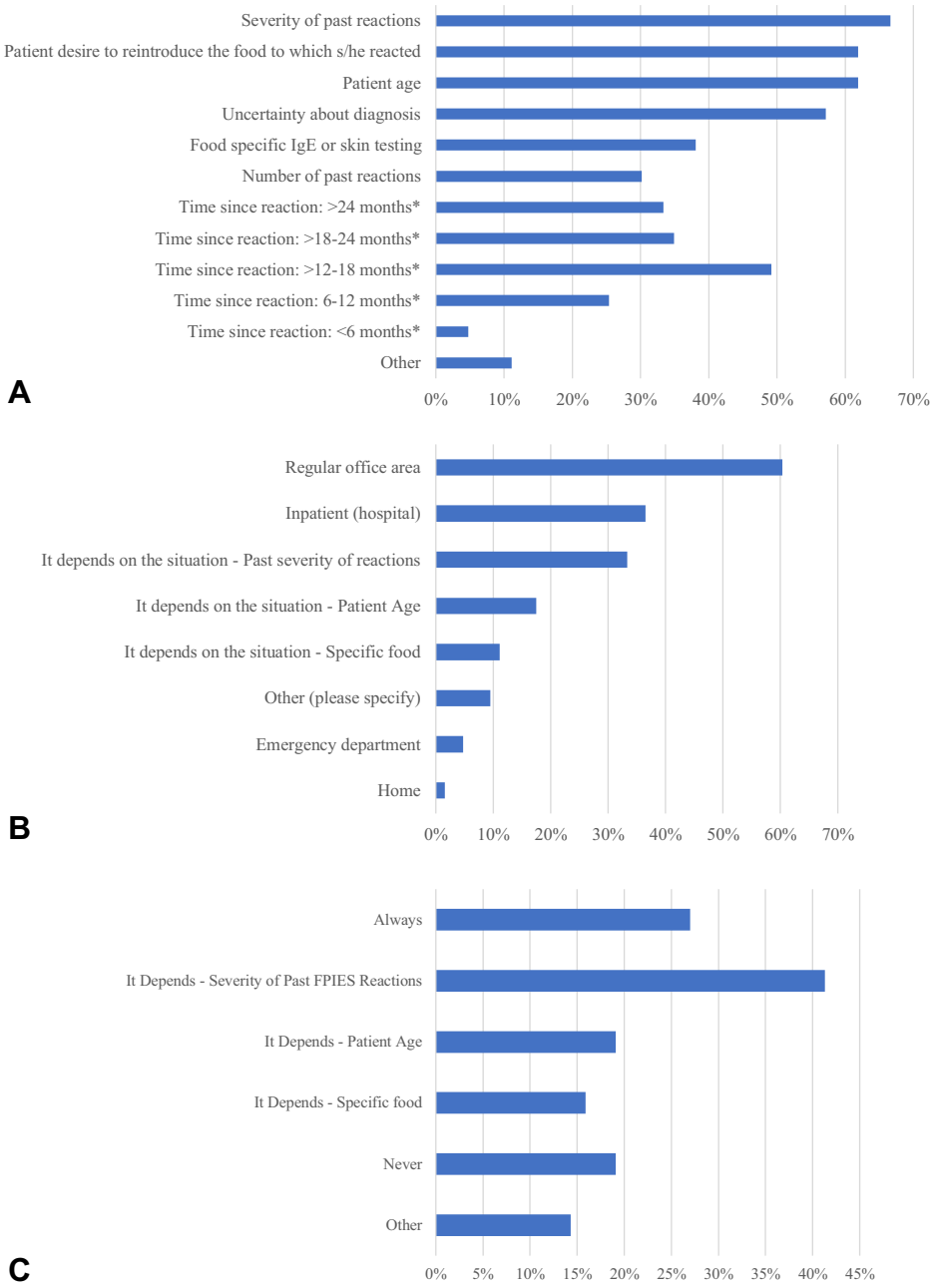

FIGURE 2. Technical details of FPIES OFC conduct. (**A**) Criteria used to decide to perform an FPIES OFC (N = 63). *Time period since the most recent reaction to the food considered for the OFC. (**B**) Location where the FPIES OFC is performed (N = 63). (**C**) Placement of a peripheral intravenous catheter before the OFC (N = 63). *FPIES*, Food protein–induced enterocolitis syndrome; *OFC*, oral food challenge.

among allergists vary greatly. Our study supports this conclusion. We observed significant heterogeneity of approaches to choosing a location of OFC, securing peripheral venous access, total dose, and dosing schedule. The decision to offer FPIES OFCs was predominantly based on the severity of past reactions and the patient's age. FPIES OFCs were most commonly performed in an outpatient setting, with placement of peripheral IV access depending on the severity of past reactions and with a serving appropriate for age divided into 3 equal portions administered over 30 minutes. However, within each domain between 40% and 75% of responders reported using a different approach, highlighting lack of the widely recognized standard FPIES OFC protocol. Studies on this topic have previously demonstrated poor utilization of OFCs in FPIES,[2] which was reinforced by our findings that almost all respondents perform OFCs for IgE-mediated food allergy in their practice (95.5%), but only 58.7% perform OFCs for FPIES. Of those who perform FPIES OFCs, 35 (49%) describe their practice setting as academic, and 28 (39%) are in a private setting. Even in the respondents frequently performing OFCs (42.6% who responded that they

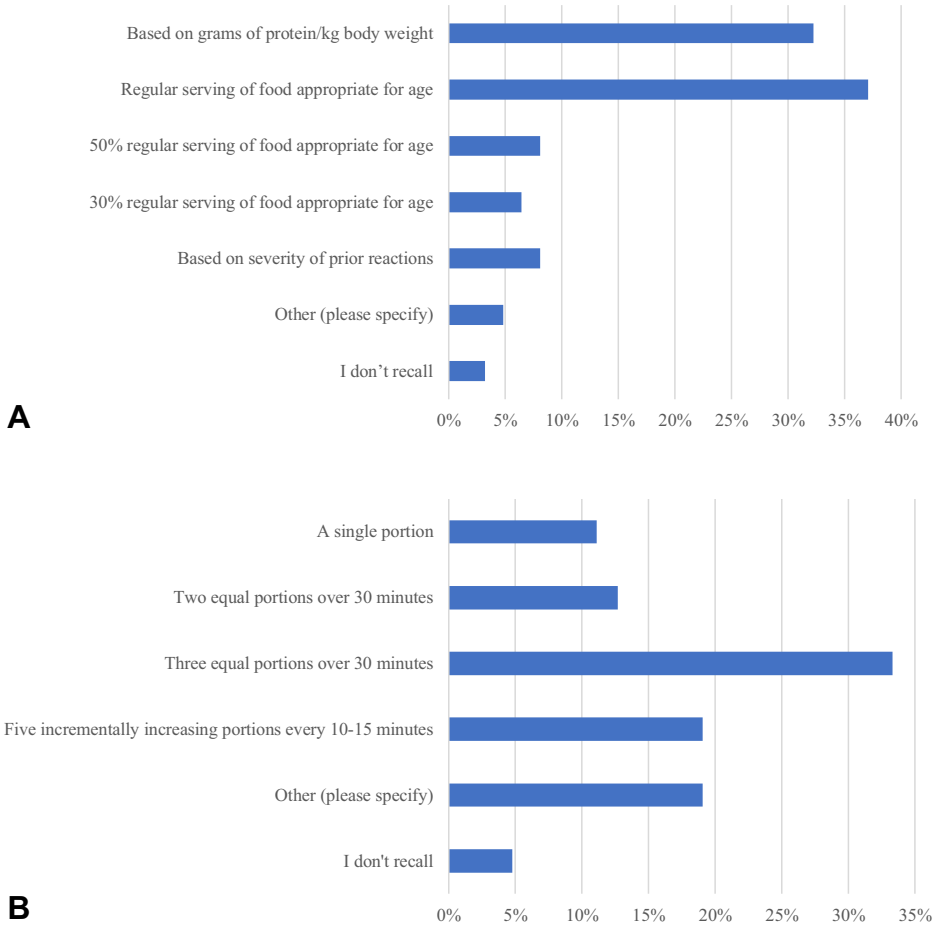

FIGURE 3. Details of challenge food administration during the FPIES OFC. (**A**) Determination of the total dose to be administered during the FPIES OFC (N = 62). (**B**) Quantity and intervals of administration of food during the FPIES OFC (N = 63). *FPIES*, Food protein–induced enterocolitis syndrome; *OFC*, oral food challenge.

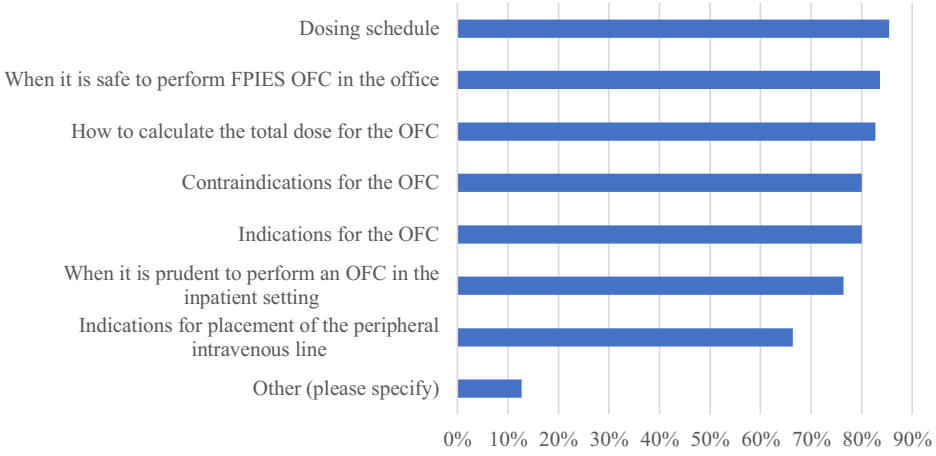

FIGURE 4. Interest in topics and content to be included in future guidelines (N = 110). *FPIES*, Food protein–induced enterocolitis syndrome; *OFC*, oral food challenge.

perform between 101 and 200 OFCs in 1 year for either FPIES or non-FPIES), none (0%) of these were FPIES OFCs. This highlights the discordance among allergists' utilization of OFCs for IgE-mediated food allergy, compared with FPIES. One potential explanation for this is a lack of standardization of FPIES OFC protocols, supported by our finding of 87.4% (n = 127)

agreeing that specific guidelines for performing FPIES OFCs would be helpful. Current guidelines leave it to the physician's discretion to modify OFC regimens as the total dose and dosing regimen for FPIES OFCs have not been systematically studied.[1]

There are well-established OFC protocols for the management of IgE-mediated food allergy that are widely available both for research purposes and clinical care for various age groups.[5-7] However, these are not necessarily transferable to the management of FPIES, a distinct entity for which the total dose and dosing regimen for performing OFCs has yet to be systemically studied. Although many protocols for FPIES OFCs have been published, these remain highly variable and are not validated by large studies. This can be difficult for a provider to interpret and subsequently implement in practice. To emphasize the lack of consensus and highlight differences in approaches to FPIES OFCs in the literature, we provide a review of the current literature.

Significant differences can be found between FPIES OFC protocols in regard to dosing and timing of administration intervals. One of the earlier published protocols in FPIES prospectively studied cow's milk protein-induced FPIES in a cohort of 13,019 newborns born over a 2-year period (2004-2006) at a hospital in Israel.[8] Forty-four of these newborns were given diagnoses of FPIES (including 8 patients with FPIES who subsequently had IgE-CMA), whereas 28 patients fulfilled all FPIES clinical criteria and had a positive response on FPIES OFCs. This was the highest rate of OFC in any large published series of FPIES at that time. Their challenge protocol consisted of 6 doses, administered at intervals of 10 minutes for doses 1 and2, 20 minutes for doses 3 and 4, and 45 minutes for doses 5 and 6, for a maximum cumulative dose of 285 mL of cow's milk. The challenge protocol study design was suboptimal for determining the eliciting dose or time to reaction, because all doses were given within 4 hours or less, and symptoms started in <180 minutes after the last dose in 86% (24 of 28) of patients. This is in contrast to the largest European series on FPIES, which retrospectively evaluated 81 children with acute FPIES from 2008 to 2013 at a single hospital in Spain.[9] Challenges were also performed in an inpatient setting, but dosing consisted of giving 3 divided doses of age-appropriate portion (0.3 g/kg, 3 g maximal dose) at 90-minute intervals for certain foods and 7 consecutive doses at the same intervals for cow's milk. Fish was the main trigger (54.3%, 44 of 81), with 36.4% (12 of 33) patients reacting at the second dose and 51.5% (17 of 33) at the third. These studies demonstrate considerable variation in doses and administration intervals, and how these differences are important for accurate determination of time to reaction.

Another variable with dosing involves not only timing between doses but also determining the appropriate initial dose, eliciting dose, and observation time. Most recently, a retrospective study over a 22-year period (1996-2018) compared 2 methodologies for performing OFC in fish FPIES in an inpatient setting.[10] Method 1 consisted of giving 4 doses over 30 minutes, compared with method 2 that administered increasing doses every 48 hours: 25%, 50%, then a full serving. Method 1 resulted in 95% of patients reacting after all 4 doses were ingested (81.4% moderate-severe), compared with 81% of patients reacting after the 25% dose in method 2 (31.3% moderate-severe). A retrospective study over 2 years (2016-2018) at 2 Italian pediatric allergy centers sought to observe whether the initial dose in FPIES OFCs was sufficient for eliciting symptoms in 48 patients.[3] Their protocol administered 25% of the full dose (0.3 g protein/kg body weight, or 0.06 g protein/kg body weight for patients with a previous history of severe reactions), and if no adverse reaction occurred in 4 hours, then the remainder was administered followed by a 4-hour observation period. A total of 54 OFCs were performed; 19 (35.2%) were positive, all of which demonstrated onset of symptoms after 25% of the full dose. A total of 79% of reactions were considered moderate (n = 6, 32%) to severe (n = 9, 47%). No patients required intensive care, but 15 patients (78.9%) received ondansetron, 14 (73.7%) received corticosteroids, and 11 patients (57.9%) were given fluid therapy. Although these results suggest that a first dose of 25% of a full serving dose is sufficient for triggering symptoms, a high number of moderate-to-severe reactions occurred (79%) similar to method 1 of Infante et al[10] (81.4% moderate-severe), but higher than Infante's method 2 (31.3% moderate-severe). These studies emphasize the careful balance of determining the appropriate observation period and eliciting dose while minimizing the risk and severity of possible reactions when conducting OFCs.

Differences also exist in relation to the location of where FPIES OFCs are performed, including inpatient, outpatient, or home settings. Although both of the aforementioned studies conducted FPIES OFCs entirely in an inpatient setting, one of the largest single-center US patient cohorts to date retrospectively reported their experience with a 1-dose protocol followed by home updosing.[11] Patients were fed one-third of serving size for age with a 4-hour observation period and then discharged with instructions to gradually build up to a full dose at home (generally increasing the amount every 3 days over 9 to 12 days). A total of 169 OFCs were completed in 119 patients; 30 (18%) were positive, with 17 (10%) of patients challenged reacting during the OFC and 13 (7.7%) reacting at home (all self-resolved except one who was evaluated in the ED but did not require additional management). These data demonstrate another consideration for providers of where to conduct FPIES OFCs and suggest that a 1-dose protocol followed by stepwise home introduction may be a safe approach that can minimize challenge time.

With such vast differences in these protocols and patient selection to undergo such a procedure, it is evident why optimal challenge procedures can be unclear to and underutilized by practitioners. As we are working toward a standardized FPIES OFC protocol, it is important that the physicians continue to exercise clinical judgment regarding the IV access, the timing of the OFC, and the total dose of the OFC. The duration of the post-challenge observation should remain at 4 hours. Other important variables to include in the clinical decision process are the age of the patient, time from the most recent reaction to the challenge food, and the severity of past symptoms as well as the triggering dose in the past reactions. Patients who reacted recently (less than 6 months ago) to a very low dose of food (eg, a bite or from cross-contact) with severe symptoms that required IV rescue in the ED or admission to the hospital are generally considered to be at higher risk for more severe reactions during an OFC. Such patients are better suited for an OFC in a more controlled setting, with IV access secured before the OFC and 2-step feeding, starting from a low dose, for example, 0.03 g protein/kg and followed by a second feeding on the same day or a different day.

There are several limitations to the present study. The overall response rate is low (although comparable to the average response rates to the online surveys), and the results might not be generalizable to the entire community of the US allergists or to

the allergists practicing in other countries. The response rates were lower for the more specific questions regarding FPIES OFC practices (such as determining total dose to be administered, quantity, and intervals of administration of food during FPIES OFCs). This may reflect the lower percentage of allergists who perform OFCs for FPIES compared with those for IgE-mediated food allergy, and should be noted as a source of potential respondent bias because allergists who responded are likely to be more interested in or familiar with managing patients with FPIES and guidelines. The survey focused on pediatric patients with FPIES; therefore, the findings may not apply to adult patients. Recall bias is also of potential concern, although we limited the reporting timeframe to the past 12 months to try to reduce recall bias. There may be other possible barriers contributing to the underutilization of OFCs in FPIES that were not addressed in our survey, including limited resources in practice settings, staff limitations (number of staff, training in IV placement, etc.), or physical space limitations.

CONCLUSIONS

FPIES knowledge and management practices among allergists vary greatly, and FPIES OFCs are underutilized. This might be attributed to a lack of universal agreement on the optimal way to perform OFCs in FPIES, suggesting the need for future studies to characterize the best approach to conducting an FPIES OFC. We propose that these studies and the available evidence be used to develop a standardized protocol for performing OFCs in the diagnosis and management of patients with FPIES.

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ONLINE REPOSITORY

TABLE E1. Characteristics of responding allergists

Demographic characteristics	N (n = 132 responses unless otherwise noted)	Percentage
Country of practice		
USA	104	78.8
Canada	6	4.6
Other	22	16.6
Board certified in Allergy and Immunology	115	87.8
No. of years in practice since completion of training		
5 or less	22	16.8
6-10	22	16.8
11-20	45	34.1
21-30	26	19.6
31+	17	12.7
Practice setting		
Private	68	51.5
Academic	45	34.1
Hospital-owned	7	5.3
Military	1	0.8
Other	11	8.3

TABLE E2. Number of pediatric patients evaluated in the last 12 months with clinical manifestations of food protein–induced enterocolitis syndrome

No. of patients	N (total n = 131)	Percentage
0	12	9.2
1-5	50	38.2
6-10	12	9.2
11-20	16	12.2
21-30	10	7.6
31+	5	3.8
Cannot recall	26	19.8