

Food Protein–Induced Enterocolitis Syndrome Food Challenges: Experience from a Large Referral Center



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What is already known about this topic? Food protein–induced enterocolitis syndrome (FPIES) is under-recognized, leading to delayed diagnosis. The diagnosis is often made clinically, especially when episodes recur. To confirm diagnosis or to assess tolerance, oral food challenges (OFC) can be performed.

What does this article add to our knowledge? This review of FPIES OFC is one of the largest single-center patient cohort to date. We review our experience with protocol and safety.

How does this study impact current management guidelines? A 1-dose protocol followed by home introduction appears to be safe and can minimize challenge time.

BACKGROUND: Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that is diagnosed based on clinical findings, but can be confirmed with oral food challenge (OFC). OFC is more often performed to assess the development of tolerance. Most studies describing OFCs in FPIES are limited in size.

OBJECTIVE: We sought to describe our experience with OFCs using our FPIES protocol. Patients were given one-third of serving size with a 4-hour observation period, followed by home titration to full dose.

METHODS: We conducted a retrospective chart review of patients who underwent OFC via the FPIES protocol from 2014 to 2017. Data regarding the history of reaction, age at the time of challenge, and reactions during challenge or with home introduction were collected.

RESULTS: A total of 169 OFCs were completed under the FPIES protocol, in 119 patients to 19 different foods. Thirty challenges (18%) were positive, with 17 challenges (10%) during

initial challenge and 13 (7.7%) during home dosing. Most reactions during initial challenge required intravenous fluids (IVF), but hypotension was uncommon. One hundred thirty-nine (82%) OFCs were negative with home introduction, indicating tolerance to the challenged foods. The mean age of passing a challenge to milk, soy, and grain was earlier than that of other solid foods. **Conclusions:** Our data suggest that our FPIES OFC protocol is safe. Early administration of IVF may prevent the development of hypotension. It is difficult to stratify the risk of severe or delayed reaction based on patient characteristics, and more data are needed to identify those appropriate for home introduction. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:444-50)

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Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that is characterized by delayed vomiting and diarrhea, and in the chronic form can lead to malnutrition.¹ These clinical features are nonspecific and lead to under-recognition, misdiagnosis, and delayed diagnosis.

FPIES is a clinical diagnosis and can be confirmed via oral food challenge (OFC), but challenges may be unnecessary if symptoms recur after ingestion of the food.² More commonly, OFCs are performed to assess the development of tolerance to the food. The age at which tolerance is achieved varies by country and food.³⁻¹⁰ In addition, FPIES OFCs are often performed under medical supervision due to the possibility of severe reactions and hypotension.

At Children's Hospital of Philadelphia, we receive referrals for FPIES, and over time, many are scheduled for food challenges. In this review, we describe challenges and outcomes for patients

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Abbreviations used

ED- Emergency department
FPIES- Food protein–induced enterocolitis syndrome
ICU- Intensive care unit
IV- Intravenous
IVF- Intravenous fluid
OFC- Oral food challenges
SD- Standard deviation

over a 3-year period. We also review our current challenge protocol for FPIES OFCs, with a focus on safety.

METHODS

Patient identification

We performed a retrospective chart review using electronic medical records (Epic Medical System, Madison, Wis) of patients who underwent OFCs via the FPIES protocol at Children's Hospital of Philadelphia during a 3-year period from September 2014 through August 2017. Patient histories were reviewed for age, sex, implicated foods, age of onset, and symptoms prompting food challenge. OFC-related data were also collected, including age at the time of challenge, cumulative dose of food, outcome of challenge, timing to reaction, treatment of positive challenges, disposition, and presence of late reaction. Patients who were unable to complete the food challenge dosing in its entirety were excluded. This review was approved by the Institutional Review Board of Children's Hospital of Philadelphia.

Disease definition

Patients with bloody stools that resolved with milk and/or soy avoidance directly or through breast milk and were otherwise well were classified as having food protein–induced allergic proctocolitis and excluded. We used the following proposed criteria from the international consensus guidelines for FPIES to interpret OFCs and to differentiate acute and chronic FPIES: subjects with intermittent food exposures and delayed emesis within 1–4 hours and/or diarrhea within 5–10 hours were classified as having acute FPIES, whereas subjects with daily ingestion of the food with intermittent emesis, chronic diarrhea, poor weight gain, or malnutrition were classified as having chronic FPIES.¹¹

Food challenge protocol

All patients underwent open food challenges in our day hospital unit. Intravenous (IV) catheters were placed in the majority of patients at the provider's discretion based on clinical parameters such as history, food challenged, and time lapse since index reaction. In some cases, parental request influenced the decision to place an IV. Our FPIES food challenge protocol was updated in July 2016 in an effort to standardize our approach across multiple providers. Before this update, patients received a 2-dose challenge, receiving a cumulative of one-quarter to one-third serving size for age. After July 2016, food challenges were performed by a 1-dose protocol: administration of one-third of serving size for age. After a 4-hour observation period, patients were discharged with detailed written instructions for home titration. Although individual practices varied slightly by provider, families were generally instructed to increase the dose every 3 days over 9 to 12 days. Sample home titration is detailed in Table I. For example, the family of a 4-year-old would be

TABLE I. Home titration dosing

	9-d titration	12-d titration
Days 1-3	1/3 serving size	1/3 serving size
Days 4-6	2/3 serving size	2/3 serving size
Days 7-9	Full serving size	3/4 serving size
Days 10-12	—	Full serving size

TABLE II. Serving size for age by food (challenge dose was 1/3 of serving size for age)

Age (y)	Liquid food	Solid food
<1	1/2 to 3/4 adult serving size	1/4 to 1/2 adult serving size
1-2	3/4 adult serving size	1/2 adult serving size
2-6	3/4 adult serving size	3/4 adult serving size
>6	Adult serving size	Adult serving size

instructed to give 2 oz of milk on days 1-3, 4 oz of milk on days 4-6, and 6 oz of milk on days 7-9. Telephone follow-up was done at the end of the titration period to check for adherence to the written plan and for any late-phase reactions or reactions with home introduction. OFCs were considered positive if patients reacted in the hospital or with home introduction and negative if patients had no reactions to a full serving size. Serving sizes for age were derived in consultation with a dietician based on USDA MyPlate adult serving size and are detailed in Table II with sample challenge doses by age and food in Table III.¹²

Age of resolution

Patients were considered to have outgrown FPIES if they had a history of reaction to the index food and tolerated the hospital challenge and full home introduction.

When determining age of resolution, challenges performed as a precaution secondary to FPIES to other foods were excluded. Patients undergoing multiple challenges to the same food were considered to have outgrown FPIES at the age they passed. Kaplan-Meier survival analysis was performed to estimate the probability of outgrowing FPIES by age. Patients who failed challenges were censored at the age of their OFC.

RESULTS

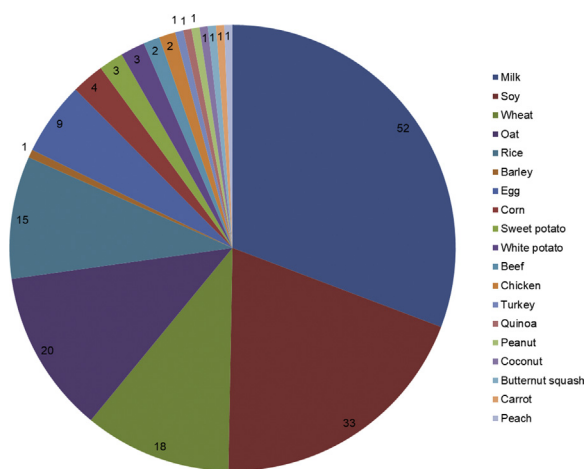
We identified 169 OFCs that were completed for the history of FPIES at Children's Hospital of Philadelphia during the study period. These OFCs were conducted in 119 subjects, to 19 different foods (Figure 1). Thirty challenges (18%) were positive, of which 17 challenges (10%) were during initial challenge and 13 challenges (7.7%) were during home introduction. In 139 challenges (82%), patients tolerated initial challenge and home introduction. One hundred twenty-six (75%) challenges were performed in patients with a prior history of FPIES reaction to the index food and 43 (25%) challenges were performed to foods that had been avoided as a precaution. Baseline patient characteristics are shown in Table IV, number of foods causing FPIES in Figure 2, and pass rates for the most commonly challenged foods in patients with and without a prior history of reaction to index food in Table V.

Challenges were positive, either during OFC or home introduction, in 13 of 52 challenges for milk (25%), in 4 of 33

TABLE III. Examples of FPIES powder dosing by age for common foods

Food	Milk	Soy	Rice	Oat	Wheat
Brand	Bob's Red Mill	Barry Farm	Barry Farm	Bob's Red Mill	Barry Farm
Protein	1 tsp = 1.16 g	1 tsp = 2.5 g	1 tsp = 0.05 g	1 tsp = 0.44 g	1 tsp = 0.33 g
Age (y)					
<1	1-1½ tsp	1/2-3/4 tsp	3¼-6½ tsp	1/2-3/4 tsp	3/4-1½ tsp
1-2	1½ tsp	3/4 tsp	6½ tsp	3/4 tsp	1½ tsp
2-6	1½ tsp	3/4 tsp	10 tsp	1 tsp	2¼ tsp
>6	2¼ tsp	1 tsp	12 tsp	1¼ tsp	3 tsp

FPIES, Food protein–induced enterocolitis syndrome.

**FIGURE 1.** The number of challenges performed to each food.**TABLE IV.** Patient characteristics (n = 169 unless otherwise noted)

Male	65 (55%, n = 119)
History prompting challenge	
Chronic FPIES	34 (20%)
Acute FPIES	92 (55%)
Never ingested	43 (25%)
Mean age at index reaction	7.9 mo (SD 9.3, n = 126)
Mean time to rechallenge	31.4 mo (SD 20.8, n = 126)
Mean age at challenge	37.1 mo (SD 25.1)
FPIES to multiple foods	76 (64%, n = 119)
IgE-mediated food allergy*	37 (31%, n = 119)

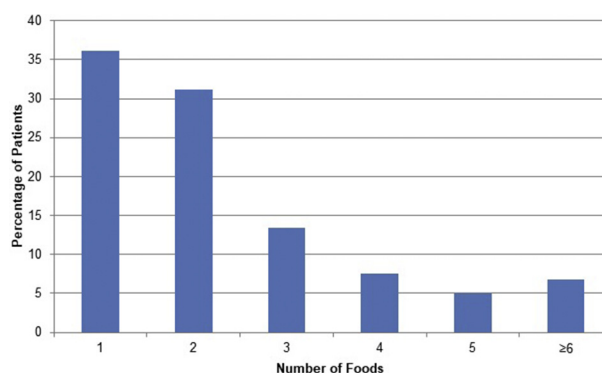
FPIES, Food protein–induced enterocolitis syndrome; SD, standard deviation.

*IgE-mediated food allergy to other foods.

challenges for soy (12%), in 6 of 54 challenges for grains (11%), in 1 of 4 challenges for corn (25%), in 2 of 3 challenges for sweet potato (67%), in 1 of 3 challenges for white potato (33%), and in 1 challenge for squash, turkey, and peanut (100%), and none of the challenges for egg, beef, chicken, quinoa, carrot, coconut, or peach (Figure 3).

Reactions with hospital challenge

Two reactions, both to milk, were associated with hypotension. The past history was of chronic FPIES in one patient and of

**FIGURE 2.** The number of foods causing FPIES reactions per individual. Each grain, fruit, vegetable, and meat counted as a single food. FPIES, Food protein–induced enterocolitis syndrome.**TABLE V.** Pass rate for foods in patients with and without a prior history of reaction to index food

	History of prior reaction		No history of prior reaction	
	No. of challenges	Pass rate (%)	No. of challenges	Pass rate (%)
Milk	46	72	6	100
Soy	19	84	14	93
Oat	17	76	3	100
Rice	14	86	1	100
Wheat	5	100	13	100
Egg	6	100	3	100

acute FPIES with hypotensive shock in the other patient with a history of prematurity and necrotizing enterocolitis with bowel resection.

In all positive challenges, symptoms of acute FPIES 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. All those children with onset of symptoms sooner than 120 minutes had negative skin prick testing to the index food, except 1 patient in whom it was not performed. This patient was challenged as a precaution and reacted at 105 minutes. Of 17 patients who had reactions consistent with FPIES, all developed vomiting and 3 (18%) developed diarrhea.

Of all the challenges performed, intravenous fluid (IVF) was administered to 14 patients (7.1%) and ondansetron was

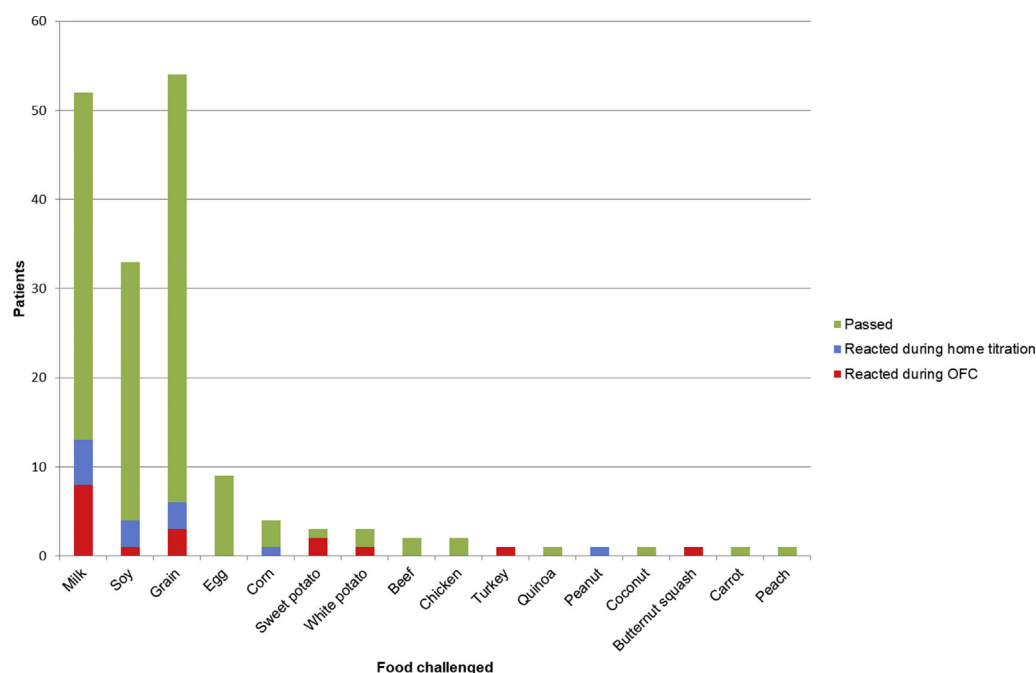


FIGURE 3. The outcome of hospital OFC and home titration to each food. *OFC*, Oral food challenges.

administered to 12 patients (6.1%). All patients who received ondansetron received it IV as adjunct to IVF, except for 1 patient without an IV who received an oral dose. Three patients did not require IVF and were able to be orally rehydrated.

Five patients had persistent symptoms despite receiving fluid resuscitation and ondansetron and/or could not orally rehydrate and were transferred to the emergency department (ED). All of these patients had intractable vomiting and either accompanying lethargy or tachycardia. Three required hospitalization overnight, including 1 to the intensive care unit (ICU) (premature infant as above) due to persistent hypotension prompting trial of epinephrine. On arrival to the ICU, blood pressure improved without pressor support. However, the majority did not develop hypotension. All of the patients admitted received continuation of IVF. None of the patients required vasopressors and all were discharged the next day. Causative foods included milk, oat, and turkey. Clinical histories of these severe reactors are detailed in Table VI.

Reactions with home introduction

Thirteen challenges (7.7%) were completed in patients who tolerated initial challenge in the hospital, but had delayed reactions at home. Foods implicated were milk (5), soy (3), rice (2), oat (1), corn (1), and peanut (1). Most reactions were characterized by delayed diarrhea, though 3 had vomiting. One patient with vomiting presented to the ED, but did not require additional interventions. All occurred later in the day of initial challenge or within the first few days of home dosing. Seven patients had a history of acute FPIES, 5 patients with chronic FPIES, and 1 never ingested. The mean age at the time of challenge was 35 months (range, 19-71 months) and mean lapse in time to rechallenge was 29 months (range, 5-71 months). One patient had mild symptoms during OFC.

Age of resolution for food protein–induced enterocolitis

Milk. Forty-four individual patients completed OFC to milk with a history of FPIES to milk (2 patients had previously been challenged and 6 patients were challenged as a precaution). Thirty-three of these patients passed the initial challenge and home introduction. No patients were challenged at or before 12 months. We found that 28% of patients outgrew FPIES by 2 years, 53% by 3 years, 65% by 4 years, and 72% by 5 years (Figure 4). The mean age of passing a challenge to milk was 35 months ($n = 33$, standard deviation [SD] = 19.2).

Soy. Nineteen patients completed OFC to soy with a history of FPIES to soy (14 patients were challenged as a precaution). Sixteen of these patients passed the initial challenge and home introduction. No patients were challenged at or before 12 months. We found that 27% outgrew FPIES by 2 years, 52% by 3 years, 70% by 4 years, and 85% by 5 years (Figure 4). The mean age of passing a challenge to soy was 38.4 months ($n = 16$, SD = 22).

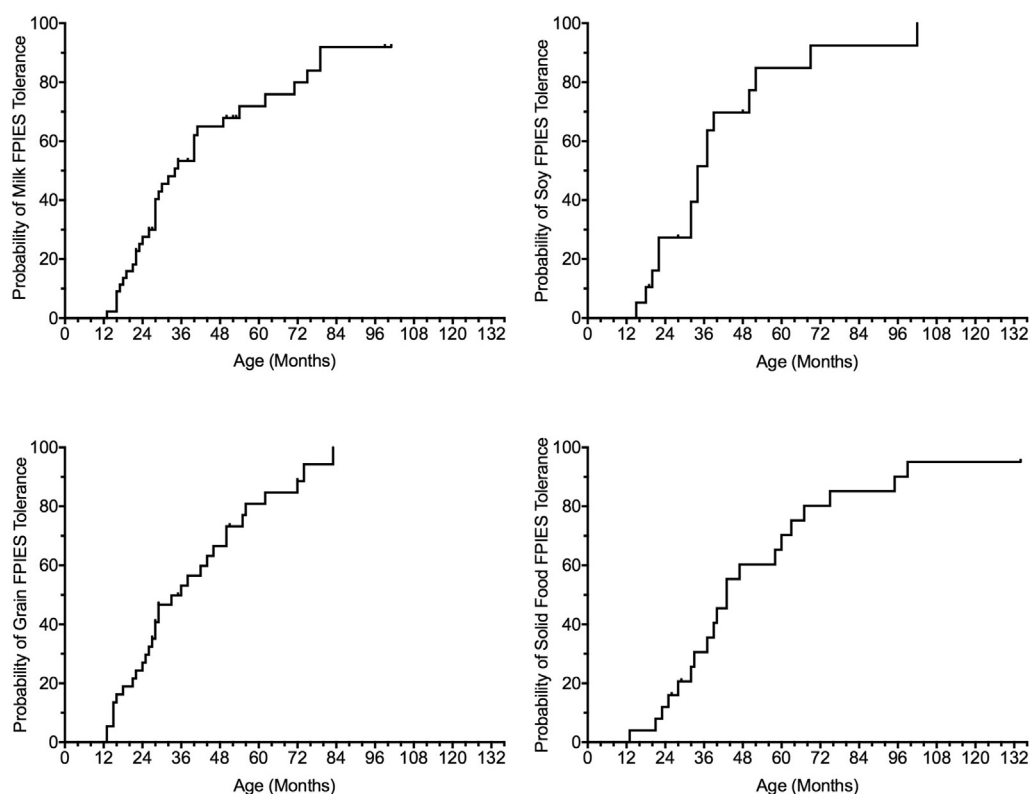
Grains. Thirty-seven individual patients completed OFC to grains (oat, rice, wheat, barley) with a history of FPIES to that grain (17 patients were challenged as a precaution). Thirty-one of these patients passed the initial challenge and home introduction. No patients were challenged at or before 12 months. We found that 27% outgrew FPIES by 2 years, 53% by 3 years, 67% by 4 years, and 81% by 5 years (Figure 4). The mean age of passing a challenge to grains was 35.7 months ($n = 31$, SD = 19.3).

Grain cross-reactivity. Eighteen wheat challenges were performed, 13 of which were performed as a precaution due to FPIES reaction to oat or rice. The mean age of challenge was 27

TABLE VI. Clinical history of FPIES reactions that required transfer to the emergency department

Patient	Gender	Food	Acute vs chronic FPIES	Age at index reaction (mo)	Age at OFC (mo)	Time lapse (mo)	Reaction
1	M	Milk	Acute	11	52	41	Emesis, weak, dizzy, hypotensive
2	M	Milk	Acute	8	22	14	Emesis, lethargy
3	M	Milk	Chronic	1	99	98	Emesis, weak, hypotensive
4	M	Oat	Acute	4	51	47	Emesis, diarrhea, tachycardia, pallor
5	M	Turkey	Acute	20	134	114	Emesis, tachycardia

FPIES, Food protein–induced enterocolitis syndrome; OFC, oral food challenge.

**FIGURE 4.** Probability of FPIES tolerance for milk, soy, grains, and other solid foods. FPIES, Food protein–induced enterocolitis syndrome.

months (range, 9–50 months). All patients tolerated initial challenge and home introduction.

Other. Twenty-four patients completed OFC to other foods to which they have had a prior FPIES reaction, which included egg (6), corn (4), sweet potato (3), beef (2), chicken (2), white potato, carrot, coconut, peach, peanut, turkey, and butternut squash (1 each). Nineteen of these patients passed the initial challenge and home introduction. No patients were challenged at or before 12 months. We found that 12% outgrew FPIES by 2 years, 31% by 3 years, 60% by 4 years, and 70% by 5 years (Figure 4). The mean age of passing a challenge to these foods was 44.9 months ($n = 19$, $SD = 23.6$).

DISCUSSION

We report on one of the largest cohort of patients undergoing FPIES OFCs to date. Although OFCs can be performed in FPIES to confirm the diagnosis or allergen if there is clinical uncertainty, we typically diagnose FPIES based on clinical

criteria, and perform OFCs to assess the development of tolerance.

The total dose and dosing regimen for performing FPIES OFCs has not been systemically studied; thus, protocol and practices vary. The current international consensus guidelines recommend administering 0.06 to 0.6 g protein/kg of body weight, not to exceed 3 g protein or 10 g whole food, in 3 equal doses over 30 minutes, followed by a 4- to 6-hour observation period.¹¹ However, if the prior reaction is severe, a low dose is first administered, followed by 2 to 3 hours of observation, followed by full serving size and 4 hours of observation.¹¹ Our protocol, which was revised in 2016 as an effort to standardize our approach across multiple providers, differs. We administer one-third of the full serving size of food in 1 dose followed by a 4-hour observation period. If the patient tolerates the initial challenge, subsequent titration to an age-appropriate serving size is completed at home over the following weeks. This approach affords a shorter challenge time, with generally mild rates of reaction with home introduction. Except for 1 patient who was

observed in the ED, others were managed with supportive care at home. Therefore, we have found this protocol to be safe.

In our retrospective chart review, we reviewed 169 open FPIES performed in 119 patients for the history of acute or chronic FPIES. Recently, the international consensus guidelines proposed revised criteria for the interpretation of OFCs in patients with possible or confirmed FPIES that requires fulfillment of the major criterion of vomiting in the 1- to 4-hour period after ingestion of the food and absence of classic IgE-mediated skin or respiratory symptoms and 2 minor criteria: lethargy, pallor, diarrhea 5 to 10 hours after food ingestion, hypotension, hypothermia, or increased neutrophil count from baseline.¹¹ We interpreted challenges to be positive if they met the major criterion, but we did not require minor criteria to be met for several reasons: similar to other studies, diarrhea occurred in 50% or fewer of patients³⁻⁷; with the early use of IVF and ondansetron, the development of additional symptoms may have been prevented. Finally, complete blood counts were rarely collected. Our clinicians relied on delayed vomiting and/or diarrhea as the symptom to diagnose a positive OFC.

We found that 18% of challenges were positive either during challenge or home introduction, which is lower than the 41% positive challenges found in studies by Caubet et al⁶ and Sopo et al³ and 25% by Lee et al.⁸ Although a larger proportion of patients avoiding food as a precaution may lead to higher pass rates, Caubet et al,⁶ which is another large US cohort with a similar proportion of challenged foods, challenged a similar proportion of patients avoiding food as a precaution: 25% in their study compared with 22% in our review. Timing of challenge in both cohorts was 2.8 years. The difference in rates of reactivity may be explained by more stringent criteria to diagnose FPIES, as Caubet et al required standardized OFC or isolated re-exposure to elicit symptoms for their cohort. In addition, we generally wait at least 18 months after the last reaction to rechallenge to the index food, which may account for more patients having developed tolerance at the time of challenge.

Because up to 50% of positive OFCs might require treatment with IVF and approximately 15% of patients with acute FPIES reactions develop hypovolemic shock, our protocol includes establishment of IV access before OFC in the majority of patients.^{2,11} Of the 17 patients who developed acute FPIES reactions, 14 received IVF for repeated episodes of emesis, whereas 3 were orally rehydrated. Although oral rehydration has been successful for all OFCs in a group of patients with milk FPIES by Katz et al,⁴ our experience indicates that secure IV access should be considered for each patient undergoing challenge as most reactions may need fluid resuscitation. Currently, the decision to place an IV is recommended, but ultimately is at the discretion of the provider based on clinical parameters. Identification of risk factors for severe reactions may help identify patients who are high risk and require formal OFC versus those who are low risk and safe for home introduction. However, based on this limited cohort, risk stratification based on patient history is challenging. There is overlap of clinical features in those who required IVF and those who were able to orally rehydrate. Patients who required IVF were older than patients who did not require IVF during initial challenge or at home (mean, 51.8 months vs 31.9 months), but the clinical significance of this finding is unclear. A prior history of FPIES reaction requiring IVF did not consistently predict the need for IVF during OFC.

The number of foods causing FPIES did not predict the need for IVF. One patient with a history of severe reaction and pediatric ICU (PICU) admission required IVF and subsequent PICU admission, so IV placement in those with severe reactions should be strongly considered.

Only 2 patients developed hypotension. Early administration of IVF may be helpful to prevent hypotension in patients with repeated episodes of emesis. Five patients developed intractable vomiting accompanied by lethargy and/or tachycardia, indicating the need for additional monitoring.

The use of ondansetron in FPIES food challenge has not been well established. Two small case series have suggested that IV and intramuscular ondansetron can lead to rapid resolution of symptoms during an acute FPIES reaction.^{13,14} A more recent retrospective review suggests that it is more effective than parental fluids and corticosteroids; however, no difference was found between patients who received ondansetron and no therapy, and therapies were not randomized.¹⁵ In our cohort, ondansetron was administered to 12 of 17 patients who developed emesis during their challenge, and as an adjunct to IVF in all but 1 patient. Despite receiving ondansetron, 5 patients did not have full resolution of their symptoms and 3 required hospitalization for persistent symptoms. This suggests that the success of ondansetron in acute FPIES reactions varies and emphasizes the role of fluid resuscitation as the cornerstone in the treatment of acute FPIES reactions. A prospective, randomized study is needed to draw more definitive conclusions about the efficacy of ondansetron in acute FPIES reactions.

The development of tolerance to foods in FPIES varies by food and by country.³⁻¹⁰ In our cohort, we found that the tolerance to cow's milk (CM), soy, and grains occurred at an earlier age than tolerance to other solid foods and that the majority resolved their FPIES by school age. CM and soy FPIES resolved around a mean age of 3 years, whereas Korean, Israeli, and Australian cohorts found earlier ages of resolution.^{4,8,9} In our practice, we wait approximately 18 months after the last reaction to rechallenge to the index food, which may account for older age at the time of challenge. In addition, because patients are not rechallenged at regular intervals, because of parents' reluctance to rechallenge, and because of the limited availability of OFC appointments, we acknowledge that the age at which patients clinically outgrow their FPIES may be earlier. Limitations also include limited patient follow-up, and uncertainty regarding age of resolution for those who failed OFCs.

Although the majority of children have FPIES to a single food, some children have FPIES to multiple foods.⁵⁻⁷ The proportion of patients with multiple food FPIES (Figure 2) demonstrate that most children have FPIES to 1 to 2 foods. Previous studies have reported that up to 50% of infants who react to 1 grain react to multiple grain types.^{7,10} Because of this risk, children who have FPIES to oat, rice, and barley may be advised to avoid other grains, notably wheat. In our cohort, 33% of challenges performed to grains were to wheat, and 72% of these challenges were performed as a precaution due to FPIES to other grains. None of these patients developed acute FPIES reaction. This suggests that patients with grain FPIES may have a low risk of having wheat FPIES, though it remains unclear whether these patients were tolerant of wheat at the time of diagnosis or developed tolerance while awaiting OFC. Therefore, perhaps home introduction of wheat may be considered in children older

than 12 to 24 months, as the mean age of challenge was 27 months (range, 9-50 months). Forty-three total challenges in our cohort were performed to foods that were avoided as a precaution, and 2 of these challenges (4.6%), to potato and soy, resulted in reaction. More data are needed to better characterize whether patients who are avoiding foods as a precaution can introduce foods at home, and at what age.

In summary, we reviewed 169 OFCs performed under the FPIES protocol over the past 3 years. Our data suggest that a 1-dose protocol followed by home introduction is safe. The predominant symptom characterizing acute reactions was vomiting, suggesting that early administration of IVF and ondansetron may prevent the development of other symptoms that are part of the diagnostic criteria. Ondansetron may be used as an adjunct to IVF but does not lead to complete resolution of symptoms. Although wheat is commonly avoided in patients with grain FPIES, our data suggest that avoidance may not be necessary, and reintroduction may be done at home in older children. Currently, it is challenging to risk stratify patients based on history and patient characteristics. More data on FPIES OFC patients are needed to better characterize those with reactions, so that patients who are safe for home introduction may be identified.

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