Clinical features and resolution of food protein–induced enterocolitis syndrome: 10-year experience

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Background: Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy. FPIES diagnosis is frequently delayed because of the absence of classic allergic symptoms and lack of biomarkers.
Objective: We sought to characterize the clinical features and resolution of FPIES in patients evaluated in our practice.
Methods: Subjects 6 months to 45 years of age with FPIES were prospectively recruited for oral food challenges (OFCs). Medical records were searched to identify the subjects who did not participate in OFCs.
Results: Among 160 subjects, 54% were male; median age at diagnosis was 15 months. We performed 180 OFCs to 15 foods in 82 subjects; 30% of the study population had FPIES confirmed based on OFC results. The most common foods were cow's milk (44%), soy (41%), rice (22.5%), and oat (16%). The majority (65%) reacted to 1 food, 26% reacted to 2 foods, and 9% reacted to 3 or more foods. The majority were atopic, and 39% had IgE sensitization to another food. Thirty-nine (24%) subjects had positive specific IgE levels to the food inducing FPIES. Among children with specific IgE to cow's milk, 41% changed from a milk FPIES to an IgE-mediated phenotype over time. The median age when tolerance was established was 4.7 years for rice, 4 years for oat, and 6.7 years for soy. Median age when milk tolerance was established for subjects with undetectable milk-specific IgE levels was 5.1 years, whereas none of the subjects with detectable milk-specific IgE became tolerant to milk during the study ($P = .003$).
Conclusion: FPIES typically resolves by age 5 years. Milk FPIES, especially with detectable food-specific IgE, can have a protracted course and eventually transition to acute reactions.
(J Allergy Clin Immunol 2014;134:382-9.)

Key words: *Food protein–induced enterocolitis syndrome, allergic enterocolitis, food protein–induced enterocolitis, food allergy, milk allergy, soy allergy, rice allergy, oat allergy, natural history*

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that usually presents in young infants and manifests as profuse repetitive vomiting and lethargy, typically occurring 2 to 4 hours after ingestion of the offending allergen and occasionally followed by diarrhea 5 to 10 hours later.[1-3] Chronic exposure manifests as intermittent emesis and chronic diarrhea with blood, mucus, or both and can result in failure to thrive and hypoalbuminemia.[4] Cow's milk and soy, followed by rice and oat, are the most common causes of FPIES in the United States, although there are reports of reactions to many other foods, including egg, poultry, beans, vegetables, and seafood.[5-11] FPIES has been described in adults, usually related to shellfish ingestion.[12,13] Prevalence estimates of FPIES are limited to a single report from Israel that found 0.34% of infants with FPIES attributable to cow's milk; the same population included 0.5% with IgE- mediated cow's milk allergy.[14]

FPIES is underrecognized, and the diagnosis is not straightforward. Skin prick test (SPT) responses or serum allergen-specific IgE antibody results are typically negative.[2,13] Considering that FPIES pathophysiology is presumably T cell mediated,[15] patch tests have been proposed for diagnosing FPIES.[16] However, we and others have shown that atopy patch tests to common food allergens had poor utility in the follow-up management of FPIES.[6,12,17] US food allergy guidelines[18] recommend using the medical history and oral food challenge (OFC) results to establish a diagnosis of FPIES. A confirmatory OFC is considered unnecessary when the typical symptoms occur within 2 to 4 hours after food ingestion (particularly more than once), there is no alternative explanation for the symptoms, and the child remains well if the food is eliminated from the diet.[2] Data on the resolution of FPIES are lacking, particularly for solid foods.

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Supported in part by UL1 TR-000067 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health. L.S.F. was supported by the Jaffe Foundation Fellowship Award, and K.M.J. was supported in part by the Leff Family Grant.

Disclosure of potential conflict of interest: J. C. Caubet is employed by Geneva University Hospitals. L. S. Ford has received research support from the Jaffe Foundation. K. M. Järvinen has received research support from the National Institutes of Health and has received royalties from UpToDate. S. H. Sicherer is a member of the American Board of Allergy and Immunology, has received consultancy fees from Food Allergy Research and Education (FARE) and Novartis, has received research support from the National Institute of Allergy and Infectious Diseases (NIAID) and FARE, and has received royalties from UpToDate. H. A. Sampson has received research support from the NIAID/National Institutes of Health and from FARE (including funding supporting clinical trials in milk and wheat allergy); is Chair of the PhARF Award Review Committee; has received consultancy fees from Allertein Therapeutics, Regeneron, and the Danone Research Institute; and has received lecture fees from Thermo Fisher Scientific, UCB, and Pfizer. A. Nowak-Węgrzyn has received research support from Nestlé, the NIAID, FARE, Merck (DSMB), Nutricia, and Stallergens; has received royalties from UpToDate; and has received lecture fees from Thermo Fisher Scientific. L. Sickles declares that she has no relevant conflicts of interest.

Received for publication February 20, 2014; revised April 4, 2014; accepted for publication April 8, 2014.

Available online May 28, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.04.008

Abbreviations used
ANC: Absolute neutrophil count
FPIES: Food protein–induced enterocolitis syndrome
IQR: Interquartile range
OFC: Oral food challenge
SPT: Skin prick test

The aim of our study was to characterize the clinical features and resolution of FPIES to improve the management of subjects with this condition.

METHODS

Study population

The research protocol was approved by the Mount Sinai Institutional Review Board. Written informed consent was obtained before enrollment. This study includes a mixed prospective and retrospective method of patient ascertainment. Subjects aged from 6 months to 45 years with FPIES were prospectively recruited for OFCs under the natural history of the FPIES protocol from the Mount Sinai Allergy and Immunology Clinic patient population (New York, NY) between 2001 and 2011. All subjects with suspected FPIES were offered participation; for those who declined OFCs, the medical records database at the Mount Sinai Allergy and Immunology Clinic was searched. The terms FPIES, food protein–induced enterocolitis syndrome, and enterocolitis were used to identify the subjects who chose not to participate in OFCs. These patients were followed clinically to assess the natural history of FPIES. The diagnosis of FPIES was based on Powell's clinical criteria[2,19]: (1) exposure to the incriminated food elicits repetitive vomiting, diarrhea, or both within 4 hours without any other cause for the symptoms; (2) symptoms are limited to the gastrointestinal tract; (3) avoidance of the offending protein from the diet results in resolution of symptoms; and (4) a standardized OFC or isolated re-exposure elicits the typical symptoms. Age of diagnosis was defined as the age at which the physician suspected a diagnosis of FPIES, which could have been before presenting at Mount Sinai. The age of resolution was determined with either OFCs or parental report of food introduction at home. Exclusion criteria included a history of immediate (<2 hours) allergic reactions with cutaneous symptoms, respiratory symptoms, or both to the suspect food and a biopsy-confirmed diagnosis of allergic eosinophilic gastroenteritis or allergic eosinophilic esophagitis.

Study procedures

During the study visits, subjects underwent SPTs with bifurcated needles (Allergy Labs of Ohio, Columbus, Ohio) with commercial food extracts (Greer Laboratories, Lenoir, NC), saline (negative control), and histamine (positive control); results were read between 10 and 15 minutes after the prick.[20] Serum food-specific IgE antibody levels were measured with UniCAP (Thermo Fisher, Portage, Mich), with a lower limit of detection of 0.35 kU_A/L and an upper limit of detection of 100 kU_A/L.

OFCs were performed after a minimum of 12 months after the most recent FPIES reaction to a specific food. A subset of subjects underwent periodic OFCs to the same food to evaluate possible resolution. In children with multiple food–induced FPIES, history of severe reactions to 1 food, or both, OFCs were sometimes done to foods that had never been ingested previously but were avoided as a precaution. OFCs were undertaken in the Mount Sinai Clinical Research Unit according to the guidelines of Powell,[19] as modified by Sicherer and colleagues.[2,4] A peripheral intravenous line was placed before the OFC. Subjects were given from 0.06 g up to 0.6 g of food protein per kilogram of body weight (usually 0.3 g of protein/kg body weight; maximum, 3 g of protein) in 3 equal doses over a 45-minute period and remained under observation for 4 to 8 hours after the ingestion of the challenge food. In the case of grains with low protein content, such as rice and oat, an age-appropriate food portion was served. We used modified Powell criteria to determine the positivity of an OFC result: (1) emesis, diarrhea, or both and (2) increase in peripheral polymorphonuclear leukocyte count of 3500 cells/mm^3 or greater. The OFC result was considered positive if both criteria were met, equivocal if 1 criterion was met, and negative if both were negative.[19] If symptoms of a reaction developed, subjects were treated and kept under observation for approximately 6 hours. A CBC with differential was obtained immediately before the OFC and before discharge (ie, at 6 hours if the OFC result was positive). The treatment was administered at the attending physician's discretion and included intravenous normal saline bolus, intravenous corticosteroids, or both. In the subjects who had specific IgE to the incriminated food during follow-up, the OFC protocol was adapted by administering incrementally increasing doses of the food protein every 15 minutes, as per the protocol for IgE-mediated food allergy.[21]

Statistical analysis

Analyses were performed with SAS/STAT Version 9.2 software (SAS Institute, Cary, NC). Comparisons of risk factors and between-group data for continuous variables were assessed with a *t* test for independent variables or a Mann-Whitney *U* test. A *P* value of less than .05 was considered significant. Cumulative survival curves were drawn by using the Kaplan-Meier method to investigate the natural course of FPIES.

RESULTS

Subjects' characteristics

Subjects' characteristics and the offending foods are summarized in Table I and Fig 1. One hundred sixty subjects were enrolled. Eighty-six 86 (54%) were male, and the median age at diagnosis was 15 months (25% to 75% interquartile range [IQR], 9-24 months). Among those 160 patients, 82 (51%) were enrolled prospectively, and 78 were identified through the retrospective chart review. Thirteen (8%) subject received a diagnosis after 5 years of age; 5 of them had FPIES to fish or shellfish with late onset. Six subjects with FPIES to milk and 2 with FPIES to soy or egg were given diagnoses after 5 years of age, although symptoms appeared earlier in life (median age of 9 months; IQR, 8-12 months). Forty-eight (30%) children had at least 1 positive OFC result confirming the diagnosis of FPIES; the other 112 (70%) subjects presented with a history of typical symptoms after ingestion of the food less than 12 months before the initial visit, and a confirmatory OFC was not performed.[2] The median delay between first reaction and diagnosis was 7 months (range, 0-143 months).

The majority of subjects had an allergic background, and 39% were sensitized to another food(s) (ie, detectable specific IgE, positive SPT response, or both). Thirty-nine (24%) subjects with FPIES had positive specific IgE to the FPIES food, and 82% of those children had FPIES to milk, soy, or both. Comparison of characteristics of children with milk FPIES and a positive specific IgE to milk with those with milk FPIES but who were not sensitized to milk is shown in Table II. None of the children with IgE sensitization to milk resolved their milk allergy while in the study. Among those who had no IgE sensitization to milk, the median age of milk FPIES resolution was 61 months ($P = .003$, Fig 2). Detailed information regarding the individual subject's course of IgE positivity is presented in Table E1 in this article's Online Repository at www.jacionline.org.

Causative foods

Cow's milk and soy were the most commonly reported individual foods (n = 70 [44%] and n = 66 [41%], respectively), followed by grains (n = 70 [44%], including rice [n = 36], oat [n = 26], barley [n = 6], and wheat [n = 2]; Fig 1). The majority of subjects reacted to 1 food (n = 104 [65%]), 42 (26%) children reacted to 2 foods, and 14 (9%) children reacted to 3 or more foods (median, 3 foods, range, 3-10 foods). Comparison between

TABLE I. Characteristics of subjects with FPIES

No. of patients	160
Sex, no. (%)	
Male	86 (54)
Female	74 (46)
Age at diagnosis (mo)	
Median	15
IQR*	9-24
Age at most recent follow-up (mo)	
Median	45
IQR*	23; 82
Diagnosis, no. (%)	
Confirmed by positive OFC result	48 (30)
Based on positive clinical history	112 (70)
Incriminated food, no. (%)	
Milk only	35 (22)
Soy only	36 (22)
Both milk and soy	21 (23†)
Milk and/or soy and solid food(s)	18 (11†)
Solid food(s) only	50 (31)
FPIES reaction to: no. (%)	
1 Food	104 (65)
>1 Food	56 (35)
ED for the initial reaction, no. (%)	
Milk and/or soy FPIES	49 (31)
Solid food FPIES	21 (13)
Specific IgE positivity, no. (%)‡	
To the FPIES food	39 (24)
To other foods	63 (39)
Additional allergic conditions, no. (%)	
Atopic dermatitis	91 (57)
Allergic rhinitis	60 (38)
Asthma	40 (25)
Birth history	
Cesarean section	46 (29)
Vaginal delivery	114 (71)
Positive family history, no. (%)	
Allergic disease	123 (77)
Food allergy	55 (34)
FPIES	10 (6)

*25% to 75% interquartile range.
†Representing the proportion of children with FPIES to both milk and soy among children with milk or soy FPIES.
‡IgE positivity defined as a positive SPT response (mean wheal ≥3 mm) or detectable serum food-specific IgE (>0.35 kU_A/L). Diagnosis of FPIES was based on modified Powell clinical criteria (see text).[2,19]

single- and multiple-food FPIES is presented in Table E2 in this article's Online Repository at www.jacionline.org. Twenty-six (16%) children reacted to both cow's milk and soy, of whom 5 (19%) reacted also to a solid food. Among the 46 subjects with FPIES to oat, rice, or both, 35% had concomitant FPIES to oat and rice. Most of the children reacting to more than 3 foods reacted to milk, soy, or both and a solid food(s) (n = 9 [64%], Table III). More than half of the subjects with solid food FPIES reacted to 2 or more foods.

We compared 50 children with solid food FPIES with 92 children with milk FPIES, soy FPIES, or both observed over the same time period (Table IV). The median age at the onset of solid food FPIES was significantly greater ($P = .001$) and exclusive breast-feeding was significantly longer lasting ($P = .0001$) compared with the milk FPIES, soy FPIES, or both group. Three subjects had chronic FPIES while being exclusively breast-fed. One hundred four (65%) of 160 subjects in our study were fed a hypoallergenic formula. Among 104 subjects fed a hypoallergenic formula, 64 (61.5%) were fed an extensively hydrolyzed casein-based formula (Nutramigen [Mead Johnson, Glenview, Ill] or Alimentum [Abbott Nutrition, Columbus, Ohio]), and 40 (38.5%) were fed an amino acid–based formula. Children with milk FPIES, soy FPIES, or both were exposed to an infant formula significantly earlier than children with solid FPIES ($P < .001$). Fifty-seven (62%) of 92 infants who had FPIES to milk, soy, or milk and soy were exposed to only milk, soy, or both milk and soy formulas, respectively, in the first few weeks of life. The majority (47/75 [63%]) of subjects with milk FPIES, soy FPIES, or both of those for whom early feeding history was available, reported chronic symptoms (diarrhea, colitis, reflux, and/or failure to thrive) in early infancy, occurring shortly after the introduction of milk-based formula, soy-based formula, or both. Removal of milk, soy, or both from the diet resolved chronic symptoms, but subsequently, these subjects had acute episodes with typical FPIES symptoms after ingestion of milk, soy, or both (mean age, 7 months; range, 0.03-60 months). Among the 26 subjects with FPIES to both milk and soy, the majority (61.5%) had symptoms to both foods within a period of less than 2 months. Nine subjects had FPIES to soy several months after onset of FPIES to milk (median, 6 months; IQR, 2.6-6.5 months).

OFCs and outcomes

Subjects' characteristics and symptoms observed during the OFC are presented in Table V. One hundred eighty standardized OFCs were performed in the Mount Sinai Clinical Research Unit to 15 different foods in 82 subjects. Seventy-four challenge results were positive in 47 subjects; 106 (59%) were negative, indicating tolerance to the incriminated food (see Table E3 in this article's Online Repository at www.jacionline.org). One hundred thirty-four (75%) challenges were performed in subjects with a prior history of FPIES reaction to the index food; 46 (25%) challenges were performed to foods that had been avoided as a precaution. Prior reactions to incriminated foods were reported in 93% of subjects with positive OFC results and in 60% of subjects with negative OFC results ($P < .001$). The challenge foods resulted in a positive OFC result in 58% of OFCs for milk (total number of OFCs, n = 72), 45% for soy (n = 44), 21% for grains (n = 48), 20% for egg (n = 5), and 33% for beef (n = 3) and in none of the challenges for chicken (n = 3), fish (n = 1), sweet potatoes (n = 1), apple (n = 1), pear (n = 1), and banana (n = 1). There were no significant differences regarding OFC outcome by food.

The majority of severe reactions associated with hypotension occurred after an OFC to milk or soy (12/14 [86%]); 2 occurred after ingestion of oat and wheat (see Table E4 in this article's Online Repository at www.jacionline.org). The severity of the reaction during an OFC did not correlate with the reported severity of the initial reaction to the incriminated food. Fifteen (20%) subjects with a positive OFC result reported having ingested a small quantity of the incriminated food without reaction. In the majority (83%) of the OFCs, the symptoms started 120 minutes or more after the first dose (maximum of 370 minutes); in the remainder (17%) of the OFCs, symptoms started as soon as 35 minutes after the first dose. Among those children with an onset of symptoms sooner than 120 minutes after food ingestion, 40% had detectable food-specific IgE levels. The median time from the onset of symptoms to complete recovery was 50 minutes (IQR, 13-95). Because

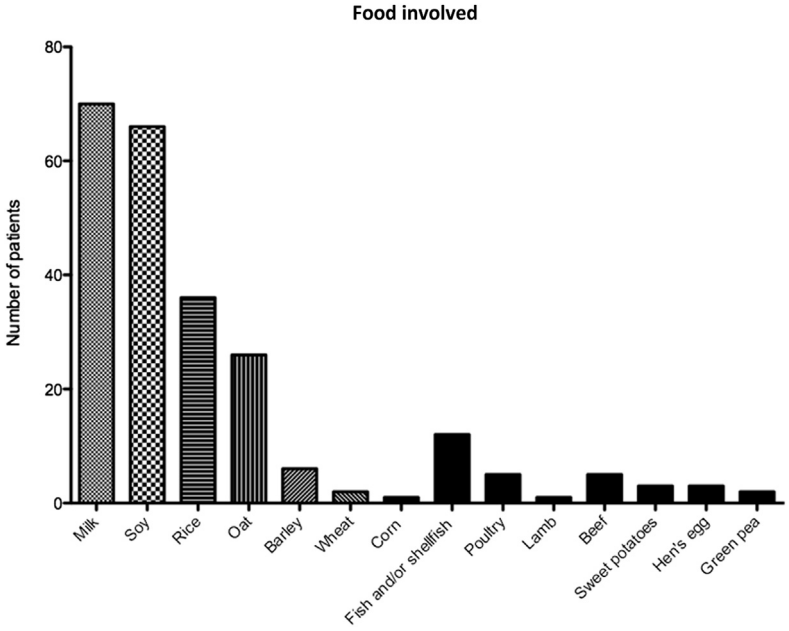

FIG 1. FPIES food triggers.

TABLE II. Comparison of subjects with milk FPIES sensitized to milk with those not sensitized to milk

	Subjects with milk FPIES, negative specific IgE to milk	Subjects with milk FPIES, positive specific IgE to milk*
No. of patients, no. (%)	53 (76)	17 (24)
Age of onset		
Median	3.5	5
IQR†	0.5-9	3-7.5
Age of tolerance		
Median	61	NA‡
IQR†	49-173	
Atopic dermatitis, no. (%)	24 (45)	10 (59)
Asthma, no. (%)	13 (25)	5 (29)
FPIES to >2 foods, no. (%)	27 (51)	9 (53)
Duration of breast-feeding		
Median	0.3	0.5
IQR†	0-2.8	0-2.8

*The detailed clinical and laboratory characteristics of the subjects with IgE sensitization to cow's milk are presented in Table E1. The median cow's milk–specific serum IgE antibody level was 5.14 kU_A/L (range, 0.39 to >100 kU_A/L; IQR, 0.702-37.125 kU_A/L).

†25% to 75% interquartile range.

‡None of the children with positive milk-specific IgE outgrew milk FPIES during the study ($P = .003$).

of the potential risk of severe reaction, these OFCs have to be performed under medical supervision, independently of the food involved.

The absolute neutrophil count (ANC) measured before and 5 to 8 hours after the positive challenge result showed a median increase of 1850 cells/mm^3, with an average of 3228 cells/mm^3 (IQR, 825-4200 cells/mm^3). The absolute lymphocyte and basophil counts were not changed significantly after the OFC, whereas the eosinophil peripheral count was significantly decreased, with an average of −60 cell/mm^3 (range, −50 to 300 cells/mm^3; $P < .05$). There was a mild increase in the platelet count (median, 19,000/mm^3; range, −121,000 to 110,000/mm^3).

Resolution of FPIES

We followed the 160 subjects for a median of 23 months (IQR, 3-56 months). Among the 60 subjects with 3 years or more of follow-up, 34 (57%) recovered at least 1 food during the study period. Twenty-three (68%) patients had a negative OFC result that confirmed tolerance, whereas the other 11 patients reported introducing the food at home. The cumulative probability of recovery was calculated for each food and presented in Fig 2. The median age when tolerance was documented either by an OFC or by a parental report of food reintroduction at home was 4.7 years for rice, 4 years for oat, and 6.7 years for soy. The overall median age for milk tolerance was 13.8 years; the median age of milk FPIES resolution for subjects with undetectable milk-specific IgE was 5.1 years, whereas none of the subjects with detectable milk-specific IgE became tolerant to milk in the study ($P = .003$, Fig 2). Five subjects remained intolerant after 16 years of age (milk, n = 3; soy, n = 2); all had serial OFCs performed approximately every 2 years, documenting their FPIES reactions at these ages. Subjects with persistent milk FPIES after age 3 years had a higher (46%) proportion of positive specific IgE measurements to milk compared with none (0%) of the children with milk FPIES resolved by age 3 years ($P < .05$, Table VI). Among the 17 subjects with milk FPIES and detectable milk-specific IgE, 7 (41%) subjects had symptoms of IgE-mediated food allergy at follow-up (see Table E1). Two subjects had multisystem reactions suggestive of anaphylaxis. Of note, 5 subjects underwent a supervised OFC to milk confirming an IgE-mediated allergy. The remaining children were not offered the challenge because of the recent history of unintentional ingestion with reactions or because of the cow's milk–specific IgE antibody levels exceeding the 95% decision point for clinical reactivity.

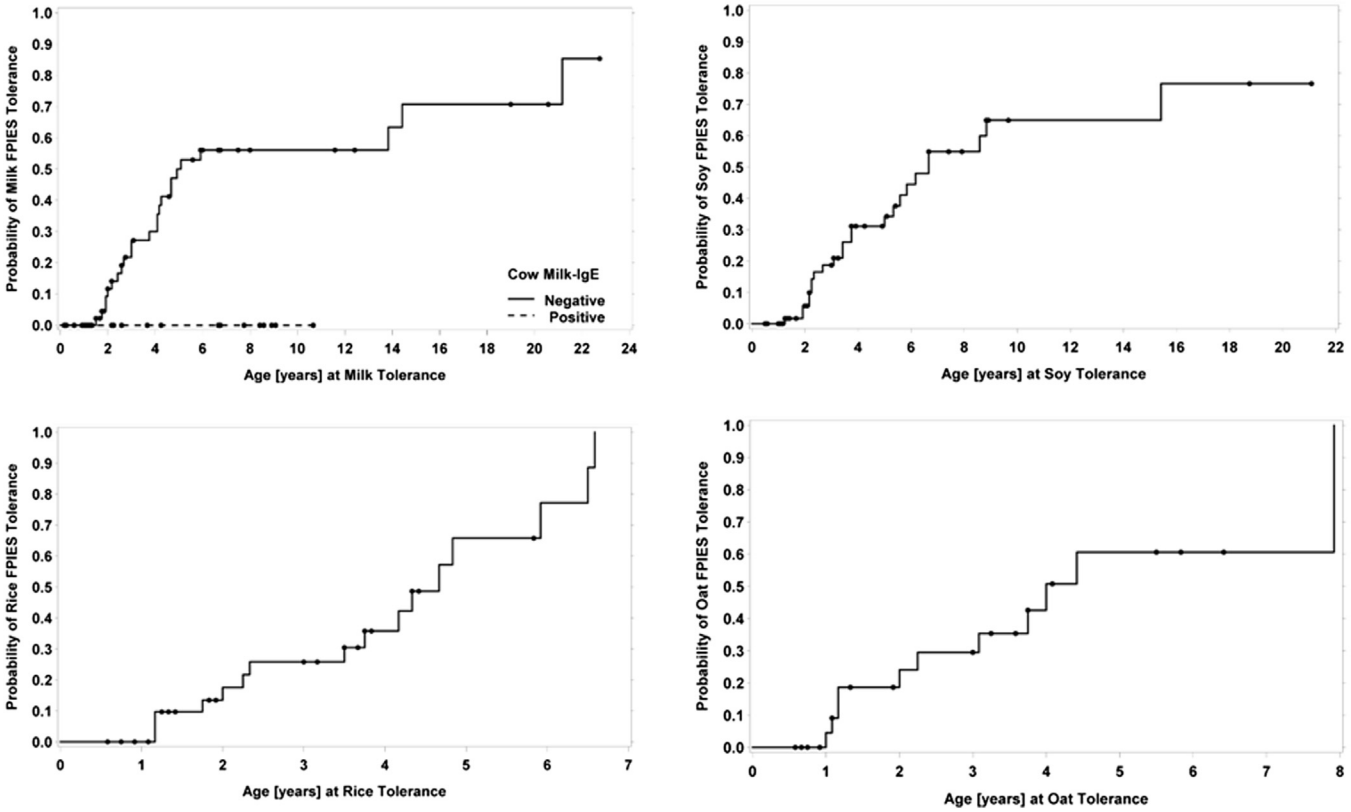

FIG 2. Kaplan-Meier survival curves for cow milk, soy, rice, and oat FPIES. Median age at tolerance for milk was 13.82 years (95% CI, 4.67 years; not established), that for soy was 6.67 years (95% CI, 5.00-15.42), that for rice was 4.67 years (95% CI, 3.5-5.92), and that for oat was 4.00 years (95% CI, 2.25-7.92).

TABLE III. Rates of concomitant FPIES to multiple foods

If FPIES to:	Milk	Soy	Solid
Milk	NA	38%	20%
Soy	37%	NA	14%
Solid*	20%	13%	44%*

NA, Not applicable.
*More than 50% of the subjects with solid FPIES reacted to 2 or more foods. Forty-four percent of subjects with FPIES to rice reacted to oat.

In addition to cow's milk, we found that 16 subjects with FPIES to soy, 3 subjects with FPIES to rice, 2 subjects with FPIES to oat, and 1 patient with FPIES to egg had specific IgE to the offending food.

DISCUSSION

We report data from a large cohort of subjects with FPIES and the largest number of OFCs performed for FPIES to date. In this cohort 24% had detectable specific IgE antibodies to the food that triggered the FPIES, and 39% had concomitant IgE sensitization to other foods; to our knowledge, this latter observation has not been reported previously. Among children with specific IgE to cow's milk, 41% changed from the milk FPIES phenotype to an IgE-mediated phenotype over time. We confirmed that the presence of specific IgE to cow's milk is a risk factor for persistence of milk FPIES beyond 3 years of age. Although IgE antibodies to the causal food are typically not detected in subjects with FPIES, there are reports in which children had detectable IgE to the causal protein either at presentation or during follow-up, which is referred to as "atypical" FPIES.[13] In our study 24% of subjects had positive specific IgE measurements to the FPIES-induced food(s). It has been suggested that acute FPIES reactions are associated with T_H2 skewing of the T-cell cytokine profile.[22] One can speculate that a T_H2-skewed lymphocyte response might predispose to developing specific IgE to food, which can eventually lead to a classic IgE-mediated reaction, as we have documented during the study in 41% of subjects with positive milk-specific IgE levels. Of note, Onesimo et al[23] described 2 cases of atypical FPIES that turned into IgE-mediated gastrointestinal anaphylaxis.

The inflammation in the intestinal tract caused by FPIES might enhance the penetrability of food proteins and their presentation to the immune system. Sicherer et al[2] suggested that the presence of specific IgE to the involved antigen in subjects with FPIES, which is usually negative, predicted a prolonged sensitivity to the antigen. We found that none of the children with positive milk-specific IgE outgrew milk FPIES during the study. Although this observation is likely confounded by the delayed attempts at introduction because of the awareness of the role of specific IgE in prolonged FPIES, it is nevertheless intriguing and worth further investigation. Because subjects initially presenting with or later having food-specific IgE antibodies might be at risk for more persistent FPIES and/or progression to an IgE-mediated food allergy phenotype (observed in approximately 33% in this study), SPTs, measurement of serum food-specific IgE levels, or both in the initial and follow-up evaluations is useful. In children with positive specific IgE levels, it is particularly important to adapt the OFC protocol and carry out the OFC under conditions

TABLE IV. Comparison between milk FPIES, soy FPIES, or both and solid food(s) FPIES

Food involved	M/S	Solid food(s) only	M/S and solid food(s)	*P* value*
No. of patients (%)	92 (58)	50 (31)	18 (11)	
Age at diagnosis (mo)				
Median	15	13	12.5	.9
IQR†	9-24	9-33	7-21.3	
Age at onset of FPIES (mo)				
Median	5	7	4	.0007
IQR†	2-10	6-12	2-6	
Sex, no. (%)				
Male	54 (59)	26 (52)	6 (33)	.45
Female	38 (41)	24 (48)	12 (67)	
Diagnosis based on: no. (%)				
Positive history	59 (64)	45 (90)	8 (44)	.005
Positive OFC result	33 (36)	5 (10)	10 (56)	
Reaction to: no. (%)				
1 Food	71 (77)	33 (66)	0 (0)	.99
>1 Food	21 (23)	17 (34)	18 (100)	
Age at formula introduction (mo)				
Median	0.03	1.5	0.2	.0002
IQR†	0.03-1.5	0.05-9.5	0.03-1.3	
Age at solid food introduction (mo)				
Median	5.3	6.0	5	.17
IQR†	4-6	5-6	3.3-6	
Duration of exclusive breast-feeding (mo)				
Median	0.03	3.8	0.4	.0001
IQR†	0.0-2.1	0.1-6	0-4.3	
Past history, no. (%)				
Cesarean section	30 (33)	12 (24)	4 (22)	.27
Eczema	50 (54)	29 (58)	12 (67)	.58
Rhinitis	38 (41)	16 (32)	6 (33)	.32
Asthma	22 (24)	12 (24)	6 (33)	.94
Positive family history, no. (%)				
FPIES	10 (11)	0 (0)	0 (0)	.1
Food allergy	36 (39)	14 (28)	5 (28)	.2
Atopy	70 (76)	39 (78)	5 (28)	.5

M/S, Cow's milk, soy, or both.
**P* value for comparison between solid food FPIES and cow's milk/soy FPIES. The 18 patients having concomitant FPIES to solid food and FPIES to milk, soy, or both were excluded from this analysis.
†25% to 75% interquartile range.

TABLE V. Characteristics of OFCs in subjects with FPIES

Food involved (no.)	Milk (n = 72), soy (n = 44), grains* (n = 48), others† (n = 16)
No. of positive OFC results/no. of total OFCs (%)	74/180 (41)
No. of patients	82
Age at OFC (y)	
Median	2.8
IQR‡§	2-5
Sex, no. (%)	
Male	41 (50)
Female	41 (50)
Symptoms during the positive OFC, no. (%)	
Vomiting	70 (96)
Abdominal pain	59 (80)
Hypotension	14 (19)
Diarrhea	5 (7)
Altered state of consciousness/lethargy	5 (7)
Timing of the reaction in positive OFC (min [range])	
From the first dose	150 (35-370)
From the last dose	120 (5-320)
To complete recovery	50 (0-460)
Treatment of positive OFC, no. (%)	
Intravenous normal saline bolus	70 (96)
Intravenous corticosteroids	69 (94)
None	3 (4)
Hospitalization	0 (0)
No. of reactions before OFC	
Median	2
Range	0-multiple
Timing from the most recent reaction (mo)	
Median	13
IQR‡	7-53

There were no statistically significant differences between the characteristics of the OFCs to milk, soy, grains, and other foods.
*Grains include oat (n = 14), rice (n = 13), corn (n = 3), wheat (n = 10), and barley (n = 8).
†Other foods include egg (n = 5), beef (n = 3), chicken (n = 3), fish (n = 1), apple (n = 1), pear (n = 1), sweet potatoes (n = 1), and banana (n = 1).
‡25% to 75% interquartile range.
§Range: 0.8-30.3.

in which an anaphylactic reaction can be properly treated. Another previously unrecognized finding is the relatively high (39%) prevalence of IgE sensitization to foods and clinical expression of IgE-mediated food allergy (30% of the children with IgE sensitization) among children with FPIES. This finding emphasizes the utility of allergy testing for the most common food allergens before introduction into the diet of children with FPIES.

In our clinical practice an initial diagnosis of FPIES is based on clinical criteria.[19] OFCs are performed to assess whether tolerance to the offending food has developed. Because of the risk of a severe reaction (particularly hypotension), the foods that have caused FPIES reactions in the past should be introduced under medical supervision, regardless of the food involved. Negative OFC results in subjects with infantile FPIES reduce a parent's inconvenience and the social isolation resulting from strict dietary management. There is debate as to when follow-up OFCs are appropriate. In this study 160 subjects with FPIES were followed for a median 23 months. Sixty-four (40%) subjects achieved tolerance to at least 1 food. According to the results of the Kaplan-Meier curves, cumulative tolerance probability was 50% at 6 years of age. However, resolution of FPIES appears to be population dependent, particularly for cow's milk and soy.[4,5,14,23] Although we found that cow's milk FPIES resolved in 20% by 3 years of age, a Korean cohort showed more than 60% resolution by 10 months of age and an Israeli birth cohort showed 90% resolution by 30 months.[4,5,14,24] Similarly, we found that 20% of cases of soy FPIES resolved by 3 years of age, whereas in the Korean cohort more than 90% of children showed resolution of soy FPIES by 10 months of age.[24] These differences are likely explained by the higher proportion of subjects with detectable food-specific IgE levels and atopic dermatitis among the subjects who were referred to a major allergy center and the differences in methodology compared with the Israeli and Korean studies.[14,24] The data for resolution of solid food FPIES are scarce. In our studies resolution by 5 years of age occurred in 65.5% of children reactive to grains, whereas resolution of FPIES to meat and fish/shellfish took more time (50% and 0% at 5 years of age, respectively). Forty-six OFCs were performed to assess tolerance to foods

TABLE VI. Comparison of children with FPIES to milk that resolved by age 3 years and those with persistent milk FPIES

	Resolved by age 3 y	Persistent after age 3 y	No follow-up after age 3 y	*P* value*
No. of patients (%)	11 (16)	37 (53)	22 (31)	
Age (mo [at resolution])				
Median	26	80	19	.01
IQR†	23-32	56-119	13-26	
Sex, no. (%)				
Female	5 (45)	19 (51)	13 (59)	.75
Male	6 (55)	18 (49)	9 (41)	
Age at first symptoms (mo)				
Median	0.8	2	3	.34
IQR†	0.2-6	0.5-6	0.5-5	
History of early exposure to milk, no. (%)	7 (64)	29 (78)	18 (82)	.43
Diagnosis, no. (%)				
Confirmed by an OFC	1 (9)	26 (70)	6 (27)	.0001
Based on positive history	10 (91)	11 (30)	16 (73)	
Detectable milk-specific IgE, no. (%)				
Positive serum IgE or SPT responses	0 (0)	11 (30)	6 (27)	.04
FPIES to other foods, no. (%)				
Soy	5 (45)	14 (38)	8 (36)	.80
Grains	2 (18)	4 (11)	3 (14)	.53
Beef	0 (0)	2 (5)	4 (18)	.75
History, no. (%)				
IgE-mediated allergy to other foods	3 (27)	12 (32)	7 (32)	.60
AD	6 (55)	18 (49)	10 (46)	.51
Asthma	5 (45)	9 (24)	4 (18)	.15

AD, Atopic dermatitis.
*Comparison of FPIES resolved by age 3 years and subject with persistent FPIES after age 3 years.
†25% to 75% interquartile range.

avoided for precaution; results of 11% of these OFC were positive, highlighting the importance of reintroducing these foods under medical supervision.

Several studies examined the relative prevalence of causative foods in subjects with FPIES.[5,6,8,14,25] In our series milk and soy were the single most common foods inducing FPIES, followed by rice, which is similar to a report from another large US center.[6] In contrast, in Australia, Israel, and Italy soy is not frequently reported. The majority reacted to a single food, whereas approximately one third reacted to multiple foods (n = 56 [35%]). The majority of the subjects with milk FPIES, soy FPIES, or both had chronic symptoms (diarrhea, colitis, reflux, and/or failure to thrive) in early infancy, occurring shortly after the introduction of milk-based formula, soy-based formula, or both. Chronic symptoms resolved on avoidance of milk/soy, but subsequent acute episodes with typical FPIES symptoms occurred after ingestion of milk/soy. These data are in line with the concept of acute-on-chronic FPIES previously described in infants.[2] Although higher rates (up to 60%) of concomitant FPIES to both milk and soy have been reported, in our series the risk of soy FPIES in a child with milk FPIES was 38%, and the risk of milk FPIES in a child with soy FPIES was 37%. Given the above and the recent studies documenting low rates of soy FPIES in infants with milk FPIES,[6,8,14] soy formula might represent an acceptable alternative in subjects with milk FPIES, although supervised introduction is prudent. However, in subjects with FPIES to milk or soy within the first 1 month of life, it is prudent to delay soy or milk introduction until age 12 months.[26] For these patients, exclusive breast-feeding should be encouraged. Alternatively, either a casein hydrolysate–based formula or an amino acid formula are recommended. These formulas lead to resolution of symptoms in all our subjects with milk FPIES, soy FPIES, or both. The mean age at onset of solid food FPIES tends to be older than that of milk FPIES, soy FPIES, or both, reflecting the usual sequence of food introduction, whereas the age of first solid food introduction was not different. Our data regarding the prevalence of reactions to foods from similar food groups are likely confounded by the fact that after the onset of FPIES to 1 food, subsequent introduction of other foods was usually delayed. Nevertheless, infants with solid food FPIES were likely to react to other foods: 52% reacted to more than 1 food protein, and 26% reacted to milk, soy, or both. In those with cereal-induced FPIES, sensitivity to other cereal grains was evident in nearly half of the patients. In particular, we found that 44% of subjects with FPIES to rice reacted to oat, likely reflecting introduction of these foods usually at the same age. On the basis of these results, infants with cereal FPIES appear particularly vulnerable and might benefit from delayed introduction of grains beyond the first year of life. It remains to be determined whether delayed introduction of other foods with high protein content, such as legumes and poultry, is indicated. This might avoid sensitization/reactions to other foods during a possible period of developmental susceptibility. However, confirming previous reports,[12] onset after early infancy can occur with some foods, such as fish or shellfish (n = 11; median age, 30; range, 5-415).

Subjects with milk/soy FPIES were breast-fed for significantly shorter periods than subjects reacting to solids. This suggests that an early exposure to formula predisposes to milk/soy FPIES (Table IV). Milk/soy FPIES in exclusively breast-fed infants is extremely rare, suggesting an important protective role of breast-feeding.[27,28] In our cohort no patient had acute FPIES while being exclusively breast-fed; however, 3 (2%) infants had chronic FPIES symptoms to milk in the maternal diet. Breast milk might provide protection (eg, IgA antibodies and partially processed food proteins) or the threshold dose of allergen might not be reached in breast milk to trigger a full acute FPIES phenotype.[29]

Diagnosis of FPIES is fraught with difficulties. A delayed diagnosis is common and might be due to the lack of definitive diagnostic tests and the unusual nature of symptoms that lack the "classic allergic" skin and respiratory involvement. Low index of suspicion in case of grains and vegetables that are widely considered to be hypoallergenic might also contribute to the delay in diagnosis. FPIES diagnosis is based on the characteristic history and/or an in-hospital OFC performed with full resuscitation facilities at hand, particularly for rapid intravascular volume repletion. Diagnostic criteria have been proposed for milk FPIES[19] and have not been validated in all types of FPIES. Our data suggest that these criteria could be modified to improve recognition of this potentially severe disease and not include an age limit for either age of onset or age for OFC. The vast majority of the subjects experienced repetitive vomiting (96%) and abdominal pain (80%), but diarrhea was observed in only 7% during the food challenge. These results are similar to other descriptions of acute FPIES-related reactions in which diarrhea were not as prevalent, which is in contrast to chronically exposed children.[5,8,29] Other symptoms included hypotension (19%) and lethargy (7%). Regarding laboratory tests, the Powell criteria for a positive OFC include an increase in the ANC of greater than 3500

cells/mm^3.[2,19] Although an increase in ANCs was observed in the vast majority of subjects with a positive OFC result, the mean increase was less than 3500 cells/mm^3 (ie, 3228 cells/mm^3). In addition, our data are likely confounded by treatment with intravenous steroids, which increases the peripheral blood neutrophil count. Considering OFCs were done within a minimum of 12 months of the most recent reaction to the offending food and thus excluded the subjects with the most severe phenotype, revising the criteria to decrease the required ANC increase as a major criterion could be considered. Of note, an isolated ANC shift without associated symptoms is not sufficient to consider the OFC result positive according to the Powell criteria and should not lead to avoidance of the food. Hypotension that was observed in our population could be added as a minor criterion. Although the limitations of our study include a mixed prospective and retrospective method of patient ascertainment, single-center experience, limited follow-up, and absence of OFC in a subgroup of patients, our observations raise clinically important questions and warrant validation by other investigators.

In conclusion, FPIES is an underrecognized non–IgE-mediated food allergy that most commonly affects infants and is usually caused by cow's milk, soy, rice, and oat. Early recognition of the symptoms of FPIES and removal of the offending food are imperative to prevent misdiagnosis and mismanagement of symptoms that might mimic viral illness or sepsis and lead to failure to thrive when food is chronically present in the diet. Our data suggest that introduction of milk formula, soy formula, or both within the first weeks of life is an important risk factor for the development of FPIES to milk, soy, or both. The diagnosis of FPIES is based on clinical criteria that should not include an age restriction because FPIES can occur at any age. Although a physician-supervised OFC remains the gold standard for diagnosis of FPIES, diagnostic criteria for a positive OFC result might need to be modified to remove diarrhea and stool studies as major positive criteria because diarrhea is relatively uncommon during an OFC in older children. Close follow-up is required to determine when foods might be added back into the diet. Although solid food FPIES resolves in most subjects by 5 years of age, subjects with milk and soy FPIES, as well as those with detectable food-specific IgE, might have a more protracted course. Further studies are needed to determine the pathophysiology and biomarkers of FPIES, as well as the features of natural history that are unique for specific foods.

We thank Erin Moshier, MS, for expert statistical analysis.

Clinical implications: FPIES typically resolves by age 6 years, but milk FPIES, especially with detectable food-specific IgE, can have a protracted course and eventually transition to acute reactions/anaphylaxis.

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TABLE E1. Characteristics of subjects with milk FPIES and detectable milk-specific IgE

Age at initial FPIES reaction* to milk (mo)	Initial† milk-specific IgE (kU_A/L); age	Initial† milk SPT (mm) at diagnosis; age	Follow-up (mo)	IgE-mediated clinical milk allergy; age	Milk-specific IgE (kU_A/L) at follow-up; age	Milk SPT (mm) at follow-up; age	Atopic diseases	FPIES to other food(s)
6	12; 12 mo	Positive; 17 mo	64	Sneezing and cough, hives; 21 mo	33.2; 36 mo	Not done	A, AD, AR, beef, lamb IgE allergy	Soy
6	<0.35; 12 mo	0/0; 18 mo	83	After 25% of OFC serving: nasal congestion, emesis, Benadryl, Solu-Medrol, ranitidine, epinephrine; 84 mo	0.73; 81 mo	4/26; 60 mo	AD	No
8	Not done	0/0; 16 mo	91	Acute throat symptoms, hives; 48 mo	0.95; 11 y	16/28; 11 y	A, AR, AD	No
<12	1.08; 36 mo	0/0; 9 mo	72	Acute urticaria; 62 mo	>100; 5 y, 25; 7 y	Not done	Egg IgE allergy	No
12	6.01; 48 mo	7/24; 72 mo	56	Skin rash to contact with milk and immediate (30 min after food ingestion) abdominal pain; 60 mo	12.3; 8 y	4/12; 8 y	AD, AR, pork IgE allergy, penicillin allergy	No
3	Not available	Not available	35	Immediate emesis and skin rash; 5 mo	Not done	9/17; 32 mo	AR	Rice, oat
3	26.8; 48 mo		50	Wheezing, emesis; 30 mo	9.7; 60 mo	22/40; 72 mo	AD, AR, peanut IgE allergy	Soy
4	Increased; 8 mo	Large; 8 mo	0	No	5.14; 11 mo	Not done	No	Soy
0.5	0.93; 11 mo	Not done	30	No	0.51; 48 mo	0/0; 48 mo	AD, A; positive sIgE to peanut, cashew, pistachio, egg white	Soy
6	<0.35; 18 mo	0/0; 18 mo	86	No	Not done	6/24	AD	No
7	0/0; 7 mo	Not done	20	No	0.91; 28 mo	0/0; 23 mo	No	No
4	<0.35 to milk and casein; 13 mo	7/20; 17 mo	14	No	Not done	0/0; 32 mo	AD	No
0.03	7.97; 60 mo	12/32; 60 mo	42	No	48.9; 84 mo	Not done	A, AR, AD; positive sIgE to egg, soybean, peanut, sesame	Soy
4	2.95; 12.5 mo	Not done	0	No	0.62; 27 mo	0/0; 27 mo	AD	Soy
1	Casein 0.55; 7 mo	8/30; 11 mo	5	No	Not done	Not done	AD; positive sIgE to peanut, egg, and soy	No
12‡	<0.35; 10 mo	0/0; 10 mo	4	No	73.7; 16 mo	0/0; 16 mo	Positive sIgE to barley, beef, chickpea, egg, wheat	Salmon, broccoli, spinach, chicken
5	Not done	0/0	77	No	0.39; 10 mo	0/0 at multiple time points	A, AR, AD	Soy

Serum food-specific IgE antibody levels were measured with the CAP System FEIA (Thermo Fisher, Portage, Mich); the lower limit of detection was 0.35 kU_A/L, and the upper limit of detection was 100 kU_A/L. SPTs were done as described by Leonard and Nowak-Wegrzyn.[13] The median cow's milk–specific serum IgE antibody level was 5.14 kU_A/L (range, 0.39->100 kU_A/L; IQR, 0.702-37.125 kU_A/L). None of the children with positive milk-specific IgE levels outgrew milk FPIES during the study. Five subjects underwent supervised oral milk challenges with reactions: 3 of them had 2 positive challenges, 2 had 1 positive challenge, and 1 had 3 positive challenges, 2 with classic FPIES symptoms and the most recent challenge with hives. The remaining children were not offered the challenge because of a recent history of unintentional ingestion with reactions or because of cow's milk–specific IgE antibody levels exceeding the 95% decision point for clinical reactivity.

AD, Atopic dermatitis; *AR*, allergic rhinitis; *A*, asthma; *sIgE*, specific IgE.

*All of these 17 patients have a history of classic FPIES reactions to milk.

†Earliest available test results of SPT and/or milk-specific IgE.

‡This patient had reactions to broccoli, rice, chicken, and spinach at 8 months of age.

TABLE E2. Comparison of subjects with FPIES to single and multiple foods

No. of food(s) involved	FPIES to 1 food (n = 104)	FPIES to 2 foods (n = 42)	FPIES to ≥3 foods (n = 14)
Age at diagnosis (mo)			
Median	16	13	11
IQR*	9-28	8-24	8-16
Age at onset (mo)			
Median	7	5	4
IQR*	4-12	0.7	3-6
Detectable sIgE to the food causing FPIES, no. (%)	26 (25)	11 (26)	2 (14)
Detectable sIgE to other food(s), no. (%)	47 (45)	12 (29)	4 (3)
Positive familial history for atopic disease, no. (%)	80 (77)	30 (71)	13 (93)
Positive familial history for FPIES, no. (%)	6 (6)	3 (7)	0 (0)

There were no statistically significant differences between those with single-food and those with multiple-food FPIES.
*25% to 75% interquartile range.

TABLE E3. Comparison of failed and passed OFCs

	Failed OFC	Passed OFC	*P* value
No. of challenges performed, no. (%)	74 (41)	106 (59)	
Prior reactions to the challenge food, no. (%)	69 (93)	65 (61)	.0001
No. of patients challenged*	47 (57)	54 (66)	
Age (y)			
Median	3.5	2.3	.001
IQR†	2.3-8.7	1.8-4.3	
Sex, no. (%)			
Male	25 (53)	26 (48)	.1
Female	22 (47)	28 (52)	
Incriminated food, no. (%)			
Milk	42 (57)	30 (28)	.1
Soy	20 (27)	24 (23)	.1
Grains‡	10 (13)	38 (36)	
Others§	2 (3)	14 (13)	
Time from the last FPIES reaction (mo)			
Median	27	23	.3
IQR†	20-45	20-45	

*Of note, some patients underwent multiple OFCs to the same or different foods; some patients had both positive and negative OFC results.
†25% to 75% interquartile range.
‡Grains include oat, rice, wheat, and corn.
§Other foods include egg, chicken, beef, apple, and pear.

TABLE E4. Comparison of patients who had documented hypotension during the OFCs with children who did not have hypotension

	Severe reaction during OFC (n = 14)	Nonsevere reaction during OFC (n = 60)
Age (mo)		
Median	54.5	40.4
IQR*	18-96	28-105
Sex, no. (%)		
Male	8 (57)	33 (55)
Female	6 (43)	27 (45)
Food, no. (%)		
Milk	9 (64)	33 (55)
Soy	3 (21)	17 (28)
Grains (oat or wheat)	2 (14)	8 (13)
Other (beef or egg)	0 (0)	2 (3)
Positive history of hospitalization because of FPIES no. (%)	6 (43)	23 (38)
Detectable sIgE to the food causing FPIES, no. (%)	3 (21)	17 (28)
Detectable sIgE to other food(s), no. (%)	1 (7)	12 (20)

There were no statistically significant differences between the characteristics of the subjects with a severe reaction and those with a mild reaction.
*25% to 75% interquartile range.