

Food protein–induced enterocolitis syndrome in Australia: A population-based study, 2012–2014

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Background: Food protein–induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal allergic disorder. Large population-based FPIES studies are lacking. **Objective:** We sought to determine the incidence and clinical characteristics of FPIES in Australian infants.

Methods: An Australia-wide survey (2012–2014) was undertaken through the Australian Paediatric Surveillance Unit, with monthly notification of new cases of acute FPIES in infants aged less than 24 months by 1400 participating pediatricians.

Results: Two hundred thirty infants with FPIES were identified. The incidence of FPIES in Australian infants (<24 months) was 15.4/100,000/y. Median age of first episode, diagnosis, and notification were 5, 7, and 10 months, respectively. There was no sex predilection. Seven percent of infants had siblings with a history of FPIES, and 5% reacted during exclusive breast-feeding. Sixty-eight had a single food trigger (20% had 2 and 12% had ≥3 food triggers). The most common FPIES triggers were rice (45%), cow's milk (33%), and egg (12%). Fifty-one percent of infants reacted on their first known exposure. Infants with FPIES to multiple versus single food groups were younger at the initial episode (4.6 vs 5.8 months [mean], $P = .001$) and more frequently had FPIES to fruits, vegetables, or both (66% vs 21%, $P < .0001$). Infants exclusively breast-fed for more than 4 months had a trend toward lower rates of FPIES to multiple food groups (23% vs 36%, $P = .06$). Sixty-four percent of infants with FPIES to multiple foods, which included cow's milk, had

coassociated FPIES to solid foods. Forty-two percent of infants with FPIES to fish reacted to other food groups.

Conclusions: FPIES is not rare, with an estimated incidence of 15.4/100,000/y. Rice is the most common food trigger in Australia. Factors associated with FPIES to multiple foods included early-onset disease and FPIES to fruits, vegetables, or both. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: Food protein–induced enterocolitis syndrome, infants, epidemiology, incidence, allergy

Food protein–induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergic disorder that occurs predominantly in infants and young children. Previous studies of FPIES have been largely based on retrospective case cohorts and highly selected populations from tertiary allergy clinics. These have suggested FPIES is a rare disorder, but its true incidence is unknown.

FPIES is triggered by ingestion of newly introduced food proteins. A previous Australian study identified grains as the most common allergenic trigger¹ compared with US,² Israel,³ and United Kingdom⁴ cohorts in which FPIES to cow's milk predominates. Data from tertiary cohorts in the United States^{2,5} have suggested that FPIES often involves reactions to multiple foods and to foods that cluster within similar taxonomically related groups,^{6,7} but characteristics that predispose to FPIES and FPIES to multiple foods are unclear.

We sought to determine the incidence of acute FPIES in the Australian population, the clinical and demographic characteristics of infants presenting with FPIES, and whether food triggers were clustered by taxonomic relationships and to identify risk factors associated with FPIES to multiple foods.

METHODS

Patient identification

Acute FPIES cases (according to standardized case definition, see below) were reported between January 2012 and May 2014 by using the Australian Paediatric Surveillance Unit (APSU) process.⁸ Monthly report cards listing conditions under surveillance were e-mailed to approximately 1400 pediatricians (subspecialists and general pediatricians) who indicated whether they had seen a patient with acute FPIES in the preceding month. On report, clinicians completed a deidentified questionnaire (see [Item E1](#) in this article's Online Repository at www.jacionline.org) with detailed demographic, diagnostic, and clinical data. Participants who had no cases to report that month were asked to respond "nothing to report." Follow-up with reporting clinicians was undertaken to confirm case definitions, missing data, or both per the study protocol (see [Item E2](#) in this article's Online Repository at www.jacionline.org). Details of subsequent FPIES during the study period to a new food in study participants were also collected (see [Item E3](#) in this article's Online Repository at www.jacionline.org). It is estimated that the 1400 pediatricians involved in APSU reporting represent approximately half of all registered pediatricians in Australia, including all subspecialties, and those not in active clinical practice.

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Abbreviations used

APSU: Australian Paediatric Surveillance Unit

FPIES: Food protein–induced enterocolitis syndrome

IQR: Interquartile range

OFC: Oral food challenge

SPT: Skin prick test

Case selection

Because it was not possible to verify the acute FPIES diagnosis based on an observed food challenge, a 2-step process was applied to potential cases before inclusion in the study (Fig 1).

The APSU case definition for reporting clinicians was as follows: any child less than 24 months of age during their first reaction, seen within the last month (not previously reported to the APSU), and meeting the following modified criteria of Sicherer et al⁹:

- (1) repeated episodes of vomiting typically presenting within 4 hours after ingestion of a food protein that has been recently introduced into the diet without any other cause identified for the episode of vomiting AND
- (2) absence of fever ($>38^{\circ}\text{C}$) and any cutaneous (urticaria, hives, and/or angioedema) and respiratory (difficulty in breathing/talking, swelling of tongue, tight throat/hoarse voice, wheeze and/or persistent cough) clinical features at the time of reaction AND
- (3) removal of the offending food protein from the diet resulting in symptom resolution.

For inclusion in the study, investigators verified the APSU reporting criteria and also required at least 2 additional minor criteria as follows:

- (1) a second (or more) episode of profuse vomiting after eating the same suspect food;
- (2) a profuse vomiting episode within 4 hours of eating a different and newly introduced food;
- (3) hypothermia ($<36^{\circ}\text{C}$);
- (4) hypotension requiring intravenous fluids;
- (5) presence of lethargy, floppiness, and/or pallor;
- (6) presence of diarrhea within 24 hours of the initial reaction; and
- (7) observation in an emergency department during any episode.

We applied these more stringent secondary clinical criteria because vomiting alone is a common pediatric presentation with a wide diagnostic differential, and it was not possible to confirm submitted cases based on an oral food challenge (OFC). We excluded any cases of diarrhea alone because of the potential of including cases of food intolerance or other non-IgE-mediated gastrointestinal tract allergy (eg, allergic proctocolitis) and because cases of FPIES with diarrhea alone appear to be rare apart from neonatal cohorts from Japan. Use of additional minor diagnostic criteria is in line with recent international consensus guidelines on FPIES.¹⁰

Data recording and analysis

Individual trigger foods were recorded. Foods were grouped according to the following classification for analysis: grain, cow's milk, soy, egg, fish, meat (chicken, beef, lamb, and pork), vegetable, fruit, and other. Infants with multiple-trigger FPIES were defined as 2 or more individual food groups reported to cause separate FPIES reactions. Where reports fulfilled case definition but some data fields were missing, all possible available data were included in the analysis.

Statistics

Continuous data were described as means (SDs) or medians (interquartile range [IQRs]). The Mann-Whitney *U* test was used for comparisons between

skewed variables. Associations between categorical variables were analyzed by using χ^2 analysis. Pairwise comparisons between food groups within patients were assessed by using the McNemar test, where individual food trigger pairs were examined for evidence of any imbalance between members of the pair. In infants who reacted to one member (food) of the pair but not the other, these tested whether there was evidence that one of the foods was more likely to cause a reaction than the other. These tests were performed both in infants who were known to have been exposed to both members of the pair and also irrespective of exposure status. Correlations between pairs of food groups were described by using phi coefficients (numerically equal to Pearson correlations) and plotted on a grid. There was no adjustment made for multiple statistical comparisons. All analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC). The incidence rate per 100,000 births/y was calculated as the number of reported cases over the sum of the reported population of infants 0 to 24 months of age for the year ending June 2013 (midpoint of study period) according to Australian Bureau of Statistics population data (<http://www.abs.gov.au/AUSSTATS/abs@.nsf>).

Ethics

The study was approved by the Human Research Ethics Committee at the Sydney Children's Hospital network (11/CHW/9).

RESULTS
Incidence

Two hundred thirty infants aged less than 24 months with acute FPIES who met the final inclusion criteria were identified over the 29-month period, with a new-case incidence of 15.4/100,000/y. One hundred sixty-nine (73%) were reported to the APSU by pediatric allergists/immunologists, 55 (24%) by general pediatricians, and 6 by other physicians. By state of residence at the time of report, infants were from New South Wales ($n = 86$), Victoria ($n = 51$), Queensland ($n = 40$), South Australia ($n = 24$), and Western Australia ($n = 28$), with no reports from the Australian Capital Territory, Tasmania, or the Northern Territory. The regions with no reports represent less than 5% of all reporting pediatricians. The state-based incidence ranged between 13 and 24/100,000/y.

Demographics

Demographics of the cohort are presented in Table I. The median age at notification to the APSU was 10 months (IQR, 7–14 months). There was no sex predilection. One hundred thirteen (49%) infants were reported to have a current history of an allergic disorder, with 33 having 2 or more disorders. Peanut, cow's milk, and/or egg were the most common IgE-mediated food allergies reported ($n = 23$; 3 had had a prior clinical reaction, 12 were avoiding the food based on a positive skin prick test [SPT] response [size was not recorded], and in 8 cases no further information was provided). Infants with FPIES and eczema were more likely to have an IgE-mediated food allergy (28 [30%] of 94; 2 had data missing) compared with those without eczema (9 [7%] of 133; 1 had data missing; $P < .0001$).

Feeding history

Duration of exclusive breast-feeding was available in 210 of 230 infants (Table I). Eleven (5%) infants had FPIES reactions while exclusively breast-feeding. Of these infants, 8 had cow's milk as their reported first trigger food (2 had grains and 1 had chicken). Seven were reported to subsequently have FPIES to

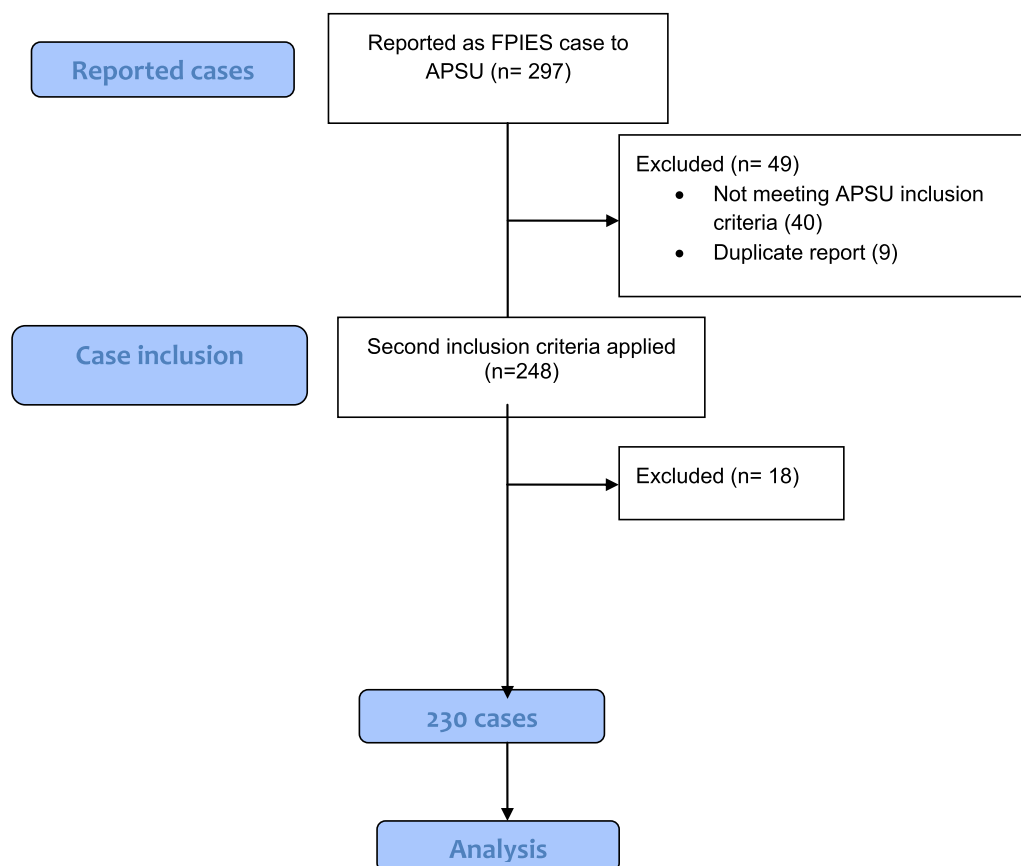


FIG 1. Flow chart illustrating case ascertainment and screening with secondary inclusion criteria applied after APSU case definition was met and duplicated cases were discarded.

more than 1 food trigger (but not necessarily through breast milk). These triggers were not able to be verified by food challenge. Timing of first solid-food introduction was available in 215 of 230 infants. Of these 215 infants, solids were introduced in 7 (3%) infants at less than 4 months of age, 185 (86%) by 4 to 6 months of age, 9 (4%) by 7 to 12 months of age, and 1 by greater than 12 months of age, and 13 (6%) had no solids introduced at the time of the report. The type of solid first introduced was recorded in 190 of 230 infants. Rice (152 [80%]) was the most common first solid, followed by vegetables (26 [14%]) and fruits (10 [5%]). The type of first weaning food was not associated with an increased risk of FPIES to cow's milk or rice ($P = .71$). The median time of formula introduction for those infants with and without FPIES to cow's milk was 3.1 and 3.8 months, respectively ($P = .97$); however, there were some missing data from infants without FPIES to cow's milk for this variable.

Family history

One hundred twelve infants had at least 1 sibling, and 8 (7%) of those had siblings who were reported to have had a history of FPIES (no further information was recorded). Thus if the incidence rate of FPIES is 15.4/100,000/y, this would mean a sibling risk would be marginally increased to 16.4/100,000/y.

A family history in a first-degree relative of allergic disease (asthma, eczema, allergic rhinitis, or IgE-mediated food

allergy) was common, present in 57% of children, and reported in 97 (42%) mothers, 71 (31%) fathers, and 43 siblings (38% of those with siblings). A family history of allergic disease was more likely in infants who had a sibling with FPIES compared with those without FPIES (8/8 [100%] vs 64/104 [62%], $P = .03$).

FPIES episode characteristics

Because some infants were reported to have reacted to more than 1 food, there were 350 FPIES triggers to a total of 40 different foods in 230 infants.

Time to diagnosis. The median age at the first episode was 5.0 months (IQR, 4-6 months), and age at diagnosis was 7 months (IQR, 5.5-11 months). The median delay in diagnosis was 1.5 months (IQR, 0.5-4.5 months; Table I). Infants often presented with multiple episodes before a correct diagnosis was made (Table II). Of those presenting to a health professional after their first FPIES reaction, in 57 (25%) a correct diagnosis was made after their first reaction, in 99 (44%) a correct diagnosis was made after 2 reactions, and in 68 (30%) a correct diagnosis was made after 3 or more reactions.

Number of exposures before first known FPIES reaction. Of the 350 first FPIES reactions to individual food triggers, the number of times the food had been ingested before a reaction was recorded in 311 cases. One hundred fifty-eight (51%) infants reacted on their first known exposure, 45 (14%)

TABLE I. Cohort characteristics

Diagnosis	Median (IQR)	
Age at first episode (mo)	5.0 (4-6)	
Age at first diagnosis (mo)	7.0 (5.5-11)	
Delay in diagnosis (mo)	1.5 (0.5-4.5)	
Characteristics	No. (n = 230)	Percentage
Male	110	48
Female	119	52
Any allergic disorder	113	49
Eczema	96	42
IgE-mediated food allergy	37	16
Asthma	8	3
Allergic rhinitis	6	3
Eosinophilic esophagitis	1	<1
Family history of atopy	130	57
Sibling with FPIES	8/112*	7
Born in Australia	225/228	99
Term infant (>36 wk)	66/89†	
Mode of delivery		
Vaginal	61/79†	
Cesarean section	18/79†	
Exclusive breast-feeding		
<4 mo	64/210	28
4-6 mo	136/210	59
>6 mo	9/210	4
One trigger food	156	68
Two trigger foods	46	20
Three trigger foods	15	7
Four or more trigger foods	13	6
Symptoms on reaction		
Vomiting	230	100
Pallor	179	78
Lethargy	172	75
Floppiness	162	70
Diarrhea	81	35
Hypotension	36	16
Hypothermia	23	10
Bloody diarrhea	13	6
Attended emergency department	132	57
with FPIES reaction		
Abdominal ultrasound	19	16
Intravenous antibiotics	9	6
Surgical consultation	10	7
Barium swallow	8	6
Advised to avoid causative food only‡	138/223	62

*Of those with siblings.

†Significant missing data.

‡Not foods in the same or different food group.

reacted after 1 previous tolerant exposure, 33 (11%) reacted after 2 tolerant exposures, and 75 (24%) reacted after 3 or more tolerant exposures (Table II). Of infants who reacted to fish, fewer had a history of tolerant exposures compared with other infants who reacted to other food groups ($P = .026$).

Symptoms. The median onset of symptoms was 2 hours after ingestion (IQR, 1.5-2.5 hours) and was consistent across all food trigger types (Table II). Presenting clinical features in children during any episode of FPIES are summarized in Table I. Profuse vomiting was present in all per the case definition, followed by pallor (78%), lethargy (75%), floppiness (70%), diarrhea (35%; 6% with bloody diarrhea), hypotension (16%), and hypothermia (10%).

Trigger food or foods causing FPIES

Individual food triggers. The most common individual food trigger in infants was rice (45%), followed by cow's milk (33%), egg (12%), oats (9%), and chicken (8%; Table II). One hundred fifty-six (68%) of 230 infants had only 1 identified trigger food at the time of data collection. Of the remainder, 46 (20%) had 2 triggers, 15 (7%) had 3 triggers, 8 (3%) had 4 triggers, and 5 (3%) were reported to have 5 or more triggers (Table I).

Triggers by food group. By food group, grains were the most common food triggers (52%), followed by cow's milk (33%), egg (12%), meats (10%), fruits (10%), vegetables (8%), soy (7%), fish (5%), and others (3%). Seventy-three percent ($n = 168$) of infants had reacted to 1 food group, and 27% (62) reacted to 2 or more food groups.

Exposure to modified forms of trigger foods. Four of 5 infants with FPIES to egg and reported exposure to baked egg reacted to baked egg. Twelve children with FPIES to cow's milk reported exposure to baked milk, and all were tolerant.

Allergen sensitization to food triggers. An SPT to 224 of 350 individual food triggers was performed in 152 infants. The SPT response was less than 3 mm to the triggering food in 211 (94%) instances, 3 to 4 mm in 7 instances, and 5 mm or more in 6 instances. Of those infants with SPT results, those with FPIES to egg were more likely to have a SPT responses of 3 mm or greater (28%) compared with all others (3%, $P < .0001$). An SPT response of 3 mm or greater to the trigger food was reported in 7 of 25 infants with FPIES to egg, 4 of 49 infants with FPIES to cow's milk (4/49 [8%]), and 1 of 78 infants with FPIES to grains. Serum specific IgE measurement to the food trigger was performed in 2 instances, and results were negative in both cases.

Factors associated with FPIES to multiple food groups

Infants with FPIES to multiple food groups were younger at the initial FPIES episode than those with FPIES to a single food group (median, 5.0 vs 5.5 months; OR for multiple triggers 0.84 per month, 95% CI [0.74-0.95], $P = .0049$). This remained significant when adjusted for age at survey completion to allow for the potential that those with FPIES to a single food might not have had time to react to another food trigger.

The proportion of infants with FPIES to multiple foods who were exclusively breast-fed for less than 4 months was higher than those with FPIES to single food groups (11% vs 20%, $P = .06$). A higher proportion of infants with FPIES to fruits, vegetables, or both had FPIES to multiple food groups when compared with other food groups (66% vs 21%, $P < .0001$).

There were no differences in infants who had FPIES to multiple food triggers versus those with FPIES to single food triggers with respect to sex, mode of delivery, personal or family history of allergy, history of siblings with FPIES, age of solid-food introduction, or sensitization (SPT) to the food trigger.

Associations between food trigger groups

We examined food group associations using 2 methods, phi coefficients and the McNemar test, which view the data in different ways. By using phi coefficients and examining the whole data set simultaneously, weak associations were observed for the combinations of cow's milk-soy, egg-nut, fish-meat, and fruit-vegetable FPIES triggers (Fig 2).

TABLE II. Characteristics of FPIES reactions by food trigger

Trigger food groups	Infants with FPIES reactions*	Age at first reaction (mo), median (IQR)	Time from ingestion to reaction (h), median (IQR)†	Ingested food ≥ 2 times without symptoms before first FPIES reaction†	≥ 3 FPIES episodes before diagnosis of FPIES food†
Grain	119 (52%)	5.5 (5.0-6.0)	2 (1.5-2.0)	52/135 (39%)	24/135 (18%)
Rice	102 (45%)				
Oat	21 (9%)				
Wheat	8 (3%)				
Corn	2 (1%)				
Quinoa	1				
Mixed grains	1				
Barley	1				
Cow's milk	75 (33%)	3.0 (2.0-5.0)	2 (1.5-2.5)	27/75 (36%)	22/75 (29%)
Meat	22 (10%)	8.0 (6.0-10.0)	2 (0.5-6.0)	3/28 (11%)	7/28 (25%)
Chicken	19 (8%)				
Beef	6 (3%)				
Lamb	3 (1%)				
Egg	27 (12%)	8.0 (7.0-10.0)	2 (2-2.5)	6/27 (22%)	8/27 (30%)
Fruit	22 (10%)	6.0 (5.0-7.0)	2 (1.0-2.0)	7/25 (28%)	3/25 (12%)
Banana	9 (4%)				
Pear	6 (3%)				
Avocado	5 (2%)				
Apple	4 (2%)				
Melon	1				
Vegetable	18 (8%)	6.0 (5.0-7.0)	2 (1.0-2.5)	6/23 (26%)	4/22 (18%)
Sweet potato	7 (3%)				
Potato	5 (2%)				
Pumpkin	4 (2%)				
Carrot	2 (1%)				
Peas	2 (1%)				
Other	3				
Soy	16 (5%)	5.0 (2.5-7.0)	2 (1.0-2.5)	4/16 (25%)	6/16 (38%)
Fish	12 (5%)	12.0 (10.0-14.0)	2 (2.0-3.0)	2/15 (13%)	6/15 (40%)
Unspecified	5 (2%)				
White	4 (2%)				
Tuna	4 (2%)				
Salmon	2 (15%)				
Other	6 (3%)				
Lentil	2				
Prawn	2				
Goat's milk	1				
Peanut	1				

*Proportion of infants reported to react to this food of a total of 230 infants. Percentages do not add up to 100% because some infants have multiple triggers.

†Per individual FPIES trigger.

By means of pairwise comparison using the McNemar test with dual known exposures, those infants with FPIES to grains were likely to have a coassociated FPIES to fruits, vegetables, or both ($P < .001$). In most other instances, there was insufficient dual exposure to the foods of interest to make complete pairwise comparisons. There was a weak association between FPIES to cow's milk/soy ($P = .035$), with 28 known to have had dual exposure and no significant associations between meat/fish ($P = .059$), cow's milk/grain ($P = .066$), rice/oats ($P = .3$), egg/meat ($P = .46$), fruit/vegetable ($P = .41$), fish/shellfish ($P = 1.0$), and banana/avocado ($P = .65$). This was also true when groups were compared regardless of a history of known reported exposure (results not shown).

Associations between individual food triggers

In infants with FPIES to rice with a history of known oral exposure to other grains, 11 of 26 had concurrent FPIES to oats,

only 3 of 32 had concurrent FPIES to corn, and 2 of 40 had concurrent FPIES to wheat.

Exposure to other milks in infants with FPIES to cow's milk was examined. Of those known to be exposed, 1 of 25 infants reacted to amino acid formula, 6 of 28 infants reacted to extensively hydrolyzed formula, 7 of 10 infants reacted to partially hydrolyzed formula, 5 of 5 infants reacted to lactose-free cow's milk, and 8 of 17 infants reacted to soy.

Thirty-three of 75 infants with FPIES to cow's milk reported FPIES reactions to at least 1 other food group, including 22 to grain, 12 to soy, 6 to vegetable, 4 to fruit, 3 to meat, 2 to egg, and 1 to fish. Five of 12 infants with FPIES to fish had reported reactions to other food groups, including 4 to grains, 3 to meat, and 1 to cow's milk.

Investigations

Of the 230 infants with FPIES, 91 (40%) had never attended an emergency department for treatment of an FPIES reaction, 86

FOOD GROUP	COW MILK	SOY	EGG	NUT	FISH	MEAT	FRUIT	VEGE	GRAIN	OTHER
COW MILK	1.00									
SOY	0.25	1.00								
EGG	-0.20	-0.05	1.00							
NUT	-0.05	-0.02	0.18	1.00						
FISH	-0.12	-0.06	-0.09	-0.02	1.00					
MEAT	-0.13	0.03	-0.03	-0.02	0.12	1.00				
FRUIT	-0.10	-0.09	-0.12	-0.02	-0.08	-0.01	1.00			
VEGE	0.00	-0.02	-0.06	-0.02	-0.07	0.07	0.35	1.00		
GRAIN	-0.31	-0.08	-0.27	-0.07	-0.09	-0.10	0.05	-0.01	1.00	
OTHER	-0.06	-0.04	-0.06	-0.01	-0.04	-0.05	0.13	-0.05	-0.01	1.00

FIG 2. Phi coefficients (Pearson correlations) between FPIES trigger food groups (binary variable: 0 = no, 1 = yes) in 62 children with multiple trigger food groups. Green represents positive correlations, yellow represents no correlation, and red represents negative correlation, with darker colors representing stronger positive or negative correlation.

(37%) had attended once, 36 (16%) had attended twice, and 10 (4%) had attended at least 3 times (no data in 7 cases). Of the 132 children presenting to the emergency department on at least 1 occasion, only a small proportion had investigations performed (Table I).

Advice by reporting pediatrician

Parents of 138 infants were advised to avoid the causative trigger food only, and 85 were advised to avoid additional foods (7 had missing data). Advice to avoid causative foods only compared with additional foods was not associated with type of practitioner (allergist vs pediatrician), FPIES to multiple versus single foods, requirement for emergency department presentation, intravenous fluids, or hypothermia.

Of the 128 infants breast-feeding when the diagnosis of FPIES was made, 30 mothers were specifically advised to exclude the causative food from the maternal diet, and a further 3 were advised to avoid the causative foods and other additional foods. One hundred thirty (57%) of 230 of the infant's parents were provided with an emergency written management plan for their child's FPIES.

DISCUSSION

The true population incidence of FPIES is unknown. The study by Katz et al³ is the only other current study that has reported an incidence of FPIES. This Israeli single-center large birth cohort only examined FPIES to cow's milk and reported a 2-year cumulative incidence of 0.34%. The relative proportion of FPIES compared with other allergic diseases presenting at tertiary allergy clinics has been estimated at approximately 1%.^{5,6,11} No large-scale whole-country study has been published to date. We report an Australian population-based incidence of acute FPIES in infants less than 24 months of age of 15.4/100,000/y. This estimate is consistent across most states in Australia, ranging from 13 to 24 cases per 100,000/y, except in low-population states and territories in which no reports were made. The strengths of our current population-based study include its population coverage and the use of a more restrictive FPIES case definition, given that vomiting is a common pediatric condition and that it was not possible based on our study design to challenge patients to confirm the diagnosis of FPIES. The use of a system of major

and minor criteria is in line with moves to tighten the clinical criteria used to diagnose FPIES.^{7,10} It is likely that the APSU methodology is subject to underreporting, and the true incidence is likely to be higher. Underreporting is likely to be due to a combination of infants presenting to primary care practitioners rather than pediatricians/allergists (particularly with less severe presentations), voluntary reporting, incomplete coverage of all practicing pediatricians/allergists within the APSU surveillance system, and parents self-managing without any health care professional involvement. Underreporting of less severe FPIES in our study is suggested by the high cumulative prevalence of FPIES to cow's milk observed in Israel³ and considerably higher than the overall FPIES incidence we report in our survey. It is likely that infants with less severe FPIES might have not come to specialist attention in the APSU cohort but would have been included in the Israeli single-center birth cohort.

Previous case cohort studies, almost exclusively from tertiary allergy units, have reported on clinical characteristics of FPIES, including common types of trigger food, the spectrum and timing of clinical symptoms, and possible associated or risk factors for FPIES (summarized in Leonard and Nowak-Węgrzyn⁷). Despite differing case definitions and inclusion criteria for FPIES between these studies and with our current study, some useful comparisons and observations can be made.

A striking difference is the regional variation in which foods commonly cause FPIES. We again report rice as the most common cause of FPIES in Australian infants,^{12,13} with 45% of infants reacting to rice. This is in contrast to data from the United States,^{2,5} the United Kingdom,⁴ Italy,¹¹ and Spain,¹⁴ where FPIES to cow's milk predominates. In these cohorts FPIES to rice accounts for 4% to 23% of all triggers. The low reported rate of FPIES to rice in the United Kingdom (4% of all triggers) is surprising,⁴ given similar infant feeding practices between Australia and the United Kingdom, with the common use of rice cereal as a first weaning food in both countries.¹⁵ The reported US rates of FPIES to rice (19% to 23%) are approximately half the Australian rate.⁵ The reasons for these variations are unclear, and in our cohort the introduction of rice or cow's milk as the first weaning food was not an associated risk factor for the development of FPIES to either of these food triggers.

We found that FPIES to soy is now uncommon in Australia (at 7% of infants) compared with US reports of 41%² and previous Australian cohort-based reports of 34% (1992-2007)¹² and 13%

(2008–2012),¹³ perhaps reflecting decreasing use of soy formula over time in Australia¹⁶ relative to the United States, where the use of soy formula remains more common.¹⁷ Five percent of infants in our study were reported to react to an allergen while exclusively breast-feeding. Although we cannot prove on the basis of our questionnaire that these cases definitely were triggered by food proteins in breast milk, it does highlight that FPIES through breast milk exposure can occur,^{11,18,19} and food proteins in breast milk appear more likely to trigger non-IgE-mediated food reactions than IgE-mediated food reactions. Despite only 5% of cases occurring during exclusive breast-feeding, almost a quarter of breast-feeding mothers at the time of the report were advised to avoid the trigger allergen in their own diets.

Approximately two thirds of infants in our cohort had a single food trigger identified as causing their FPIES, and 73% reacted to a single food group. These rates are generally in keeping with some US² and United Kingdom⁴ reports but generally lower than those previously reported for Australia (66% to 84%), Italy (85%), Spain (94%), and other US cohorts.⁵ We were particularly interested in identifying any risk factors or predictors for FPIES to multiple foods compared with FPIES to a single food. Younger age at first FPIES episode and reactions to fruits/vegetables were highly associated with having FPIES to multiple foods compared with FPIES to a single food. There was a suggestion that a shorter period of exclusive breast-feeding (of <4 months) was associated with FPIES to multiple foods. Others have examined duration of breast-feeding in cohorts with FPIES, finding similar (US)⁵ and higher (Italy)¹¹ rates than those of the general population, but none have specifically examined breast-feeding duration as a potential risk for FPIES to multiple foods. Given the potential ramifications of this association, this requires further exploration and replication in future population-based studies.

We looked for evidence of FPIES-triggering foods clustering together because such information would be useful to inform further challenge-based studies and assist with avoidance advice and OFCs. Previously, FPIES to cow's milk/soy^{2,5} and rice/oats¹ have been reported as potential coassociations. Because of the cross-sectional nature of the study and the inability to expose all infants with FPIES to all relevant possible triggers, it is possible we have underestimated these associations. Despite these limitations, we found strong interactions between FPIES to grains and fruits/vegetables. The relatively low reported exposure to soy milk in infants with cow's milk FPIES hampered the capacity to fully interrogate this potential pairing; however, principal component analysis suggested associations between the fruit/vegetable, soy/cow's milk, egg/nuts, and fish/meat groups. On this basis, infants presenting with FPIES to fruits or vegetables with no prior history of exposure to grains might be considered at risk for FPIES to grains and candidates for an OFC.

Some previous reports have suggested that it is unusual for infants to be reactive to both a solid food and cow's milk^{3,20}; however, of 33 infants with FPIES to cow's milk and at least 1 other identified food trigger, we found that 22 had a grain trigger and others had FPIES reported to fruit, vegetables, meat, egg, and fish. FPIES to fish has been considered to occur in isolation or only associated with other seafood^{21,22}; however, 42% of infants with FPIES to fish in this cohort had reports of reactions to other food groups, including grains, meats, and cow's milk.

There have been a few case reports of children with FPIES to egg and cow's milk tolerating heat-modified foods.²³ We found infants with FPIES to cow's milk appeared more likely to be

tolerant to baked product than infants with FPIES to egg. However, we had no further information as to what baked goods these children were tolerating, and such data need to be interpreted with caution given the low numbers reported to have been exposed to baked allergens.

Our study found the median time of onset of symptoms (2 hours), type and frequency of symptoms, and age at presentation depending on the type of trigger to be in line generally with previous reports (summarized in Leonard and Nowak-Węgrzyn⁷).^{1-3,5,11} Just over half of the infants reacted on the first known oral exposure, suggesting that sensitization can occur through other routes, such as epicutaneously or through breast milk, as with IgE-mediated food allergy. However, we did note, for the first time, that there were less tolerant exposures before first FPIES reactions to fish than to other food triggers. A family and personal history of atopy was common in infants with FPIES, as previously reported.^{2,11} The presence of eczema in those with FPIES increased the risk of coexistent pediatrician-reported IgE-mediated food allergy. The risk of FPIES was significantly increased in those with a sibling with FPIES, which is consistent with previous reports.² There was less reported delay in FPIES diagnosis (median delay, 1.5 months) than noted previously in Australia elsewhere (summarized in Leonard and Nowak-Węgrzyn⁷). This might be due to increasing awareness, particularly given the large number of pediatricians involved in the APSU who received study protocols and information about newly listed conditions, including FPIES, at the commencement of surveillance.⁸ Just over half of the parents of infants with FPIES were provided with written management plans to guide responses to further episodes.

The APSU has been used to investigate and report on the incidence of many pediatric diseases over the last 20 years in Australia²⁴⁻²⁶ and meets Centers for Disease Control and Prevention criteria for disease surveillance systems.⁸ Weaknesses of the APSU methodology include that not every practicing pediatrician in Australia received or returned a report card, not all infants with FPIES are seen by a pediatrician or allergist, and cases can be missed. It is estimated that approximately half of Australian pediatricians in active clinical practice participate in the APSU. The cross-sectional nature of the data means that duration of the illness and natural history of disease cannot be examined. The strengths are that it captures a relatively representative sample of the population rather than just those infants who attend a tertiary allergy clinic, which can skew FPIES reports by disease severity, relative economic prosperity, or proximity to tertiary services. During the study period, the APSU had an average response rate/month of 90% from approximately 1400 pediatricians.²⁴

In summary, in our Australian population-wide cohort, we found that FPIES is not rare, has no sex predilection, and most commonly occurs as a response to a single food and single food group. The associations we have found require replication in a prospective cohort in which exposure to all potential FPIES food triggers is undertaken. Currently, we would suggest that infants at high risk of FPIES to multiple foods include those who present early with FPIES to fruits, vegetables, or both. Supervised challenges might be useful before introduction when the food associations we observed are strongest.

We thank all the pediatricians who participated in the current study by reporting infants with FPIES through the APSU system and the staff of the APSU. We thank Iandra Consulting Services for assistance with the MS Access database.

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Food Protein Induced Enterocolitis Syndrome (FPIES)**Australian Paediatric Surveillance Unit**

Please contact *Dr Sam Mehr* sam.mehr@health.nsw.gov.au; or APSU ; apsu@chw.edu.au if you have any questions about this form. Please keep a record of the child's unit number in your APSU folder

Instructions: Please answer each question by ticking the appropriate box or writing your response in the space provided.

DK=Don't Know; NA=Not Applicable; NVD = normal vaginal delivery; C/S = caesarian section

REPORTING CLINICIANS DETAILS

1. APSU Dr Code/Name: / _____
2. Are you a: ☐ Paediatrician ☐ Adult physician
3. Your Specialty: ☐ Allergist/Immunologist ☐ Gastroenterologist ☐ General Paediatrician ☐ Other (specify) _____
4. Month/Year of Report: / 5. Date questionnaire completed: / /

PATIENT DETAILS

6. First 2 letters of first name: 7. First 2 letters of surname: 8. Date of Birth: / /
9. Delivery details: ☐ NVD ☐ C/S ☐ DK 10. Term/preterm: ☐ Term (≥ 37 wks) ☐ Pre-term (< 37 wks) ☐ DK
11. Sex: ☐ M ☐ F 12. Postcode family: 13. Country of Birth: _____ ☐ DK

If this patient is primarily cared for by another physician who you believe will report the case and could provide additional details, please write the other physician's name in the space below then complete the questionnaire details above this line and return to APSU. If no other report is received for this child we will contact you for further information requested in the remainder of the questionnaire.

The primary clinician caring for this child is: **Name:** _____

Hospital: _____

12. Does the child have siblings? Yes ☐ No ☐ DK ☐ 12a. If yes, have any sibling(s) had FPIES? Yes ☐ No ☐ DK ☐

13. Family history of an allergic disorder (eczema, asthma, allergic rhinitis or immediate IgE food allergy) in any of the following:

Mother: Yes ☐ No ☐ DK ☐

Father: Yes ☐ No ☐ DK ☐

Siblings: Yes ☐ No ☐ DK ☐ NA ☐

FEEDING HISTORY

14. Duration of exclusive breast-feeding before the first episode? < 4 m ☐ 4-6m ☐ 7-12m ☐ > 12 m ☐ Never breast fed ☐ DK ☐
15. Did any FPIES episode occur when the child was exclusively breastfed? Yes ☐ No ☐ DK ☐ NA ☐
16. Age when solids were first introduced: < 4 m ☐ 4-6m ☐ 7-12m ☐ > 12 m ☐ Solids not yet introduced ☐ DK ☐
17. First solid food introduced: Rice cereal ☐ Vegetable ☐ Fruit ☐ Meat ☐ Other ☐ (specify) _____
- No solids introduced and child currently exclusively breast fed ☐ or exclusively bottle fed ☐ or combined breast/bottle fed ☐

MEDICAL HISTORY

18. Does the child have any other allergic disorder? Yes ☐ No ☐ DK ☐

18a. If YES, please specify:

Eczema: Y ☐ N ☐ DK ☐ Asthma: Y ☐ N ☐ DK ☐ Allergic rhinitis: Y ☐ N ☐ DK ☐ Eosinophilic oesophagitis: Y ☐ N ☐ DK ☐

Immediate IgE mediated food allergy: Y ☐ N ☐ DK ☐ If IgE food allergy which food(s) (specify if SPT alone and/or had clinical reaction) _____

19. Was the child prescribed an adrenaline injector for an immediate IgE food allergy? Y ☐ N ☐ DK ☐ N/A ☐

AGE PRESENTATION, CLINICAL FEATURES, AND TRIGGERS OF FPIES REACTIONS

20. Age at initial FPIES episode (in months): _____ 21. Age at diagnosis of FPIES (in months): _____

22. Were any of the following clinical features present during ANY FPIES episodes?

Vomiting ☐ Diarrhoea ☐ Bloody Diarrhoea ☐ Pallor ☐ Floppiness ☐ Lethargy ☐

Hypothermia ($< 36^{\circ}\text{C}$) ☐ Hypotension requiring IV fluids ☐

23. Please complete the table below

Food triggers of FPIES (specify)	Age (months) of initial reaction to food trigger	Number of FPIES episodes before diagnosis of FPIES made	Number of times knowingly ingested food trigger without initially having an FPIES reaction	Average time from ingestion of food trigger to FPIES reaction (hrs)	Skin prick test (SPT) result of food trigger**	RAST result of food trigger ***
		0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
		0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
		0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
		0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
		0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐

* If child has had 2 or more episodes, please average the estimated time to reaction ** if SPT is 6x5 then mean result = 5.5 mm; *** quantitative result with units preferred, qualitative result accepted (e.g. negative, low positive, etc.)

FOODS INTRODUCED INTO DIET OF CHILD

Please specify whether any of these foods/milk/formulas have been introduced

Grains	Introduced?	Age introduced (months)	If introduced, FPIES reaction?
Rice	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Wheat	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Oat	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Rye	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Barley	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Corn	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Formulas/milk			
No formula and continue breast feeding	Y ☐ N ☐ DK ☐		
Lactose free cow formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Soy formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Cow milk formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Partial hydrolysed formula (e.g NAN-HA, etc)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Extensive hydrolysed formula (e.g. Alfare, Pepti-J, etc)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Amino acid formula (e.g Elecare, Neocate)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Other solid foods			
Whole egg (egg white alone , or egg white + yolk)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Baked egg products (e.g biscuit, cake, muffin)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Baked milk products (e.g. biscuit, cake, muffin)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Legumes (e.g. beans, lentils, peas)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Sweet potato	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Fish	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Shellfish	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Poultry	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Banana	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Avocado	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐

FEEDING ADVICE FOLLOWING DIAGNOSIS

24. Following diagnosis, which food(s) were recommended for exclusion or avoidance in the child's diet?

Causative food(s) only ☐ Other food(s) ☐ (please specify): _____

25. Following diagnosis, were any food(s) excluded from the maternal diet if still breastfed?

Causative food(s) ☐ Other food(s) ☐ (please specify): _____**EMERGENCY DEPARTMENT (ED) VISITS AND INVESTIGATIONS**

26. How many times did the child present to an emergency department with symptoms typical of FPIES prior to diagnosis?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 5+ ☐ DK ☐27. Were any following interventions/investigations performed during any FPIES episode prior to diagnosis? Y ☐ N ☐ DK ☐ NA ☐Abdominal U/S ☐ Barium study ☐ CT scan ☐ MRI scan ☐ EEG ☐ ECG ☐ IV antibiotics ☐
Gas enema ☐ Surgical consultation ☐ Operation ☐ (specify type) _____ Other ☐ (specify): _____28. Were any of the following identified during an episode of FPIES? Y ☐ N ☐ DK ☐ NA ☐Leukocytosis: Y ☐ N ☐ DK ☐ Neutrophilia: Y ☐ N ☐ DK ☐ Thrombocytosis: Y ☐ N ☐ DK ☐Metabolic acidosis: Y ☐ N ☐ DK ☐ Hypoglycaemia: Y ☐ N ☐ DK ☐**MANAGEMENT**29. Was an adrenaline injector provided for future emergency FPIES management? Y ☐ N ☐ DK ☐30. Was a written emergency plan given in case of future FPIES reactions? Y ☐ N ☐ DK ☐31. Did the child have a challenge to the causative food trigger(s) to support the diagnosis of FPIES? Y ☐ N ☐ DK ☐ If yes, how?☐ Increasing incremental amounts (e.g given every 15-20 minutes) until a meal size portion consumed☐ As a meal size portion of food given as a single, once off dose☐ Other (please specify): _____ DK ☐

Thank you for your help with this research project. Please return this questionnaire to the APSU in the reply-paid envelope or Fax . Australian

Paediatric Surveillance Unit, Kid's Research Institute, Locked Bag 4001, Westmead NSW 2145 The Australian Paediatric Surveillance Unit is a unit of the Royal Australasian College of Physicians (Paediatrics and Child Health Division) and is funded by the NHMRC (Enabling Grant No. 402784); the Australian Government Department of Health and Ageing; and Sydney Medical School, University of Sydney. This study has been approved by a Human Research Ethics Committee properly constituted under NHMRC guidelines.

Food Protein Induced Enterocolitis Syndrome (FPIES)

Background

FPIES is a paediatric non-immunoglobulin E mediated allergic disorder triggered by ingestion of certain food protein(s). The majority of children present with their first FPIES episode when less than 12 months of age. The diagnosis of FPIES remains a clinical one, with children presenting typically 2-4 hours after ingestion of a food protein recently introduced into the diet, with profuse vomiting and some subsequently develop diarrhea^{1,2}. Some children present in a moribund state, with pallor, floppiness, reduced body temperature, hypovolemic shock and/or metabolic acidosis¹⁻³.

Delays in diagnosis are frequent, since common FPIES food triggers such as rice are considered to be hypoallergenic, and presenting clinical features can mimic more common paediatric conditions, such as sepsis and surgical abdominal emergencies^{2,3}. Consequently children often have multiple episodes, additional investigations and prolonged hospital admissions before a diagnosis of FPIES is made²⁻⁴. The prognosis for FPIES is good and most attain tolerance to the food trigger by three years of age². Early and accurate diagnosis is important to enable appropriate dietary advice and prevention of recurrences, emergency management plans in case of future reactions and a food challenge to be arranged, typically at 3-4 years of age, to ascertain tolerance.

The prevalence of FPIES in Australian children is unclear. To date the majority of studies published have examined cases presenting to individual tertiary Paediatric hospitals or specialised Allergy outpatient clinics and have been retrospective in design²⁻⁵.

The prospective collection of information on FPIES reactions in the paediatric setting will enable the estimation of the incidence of FPIES, and facilitate a better understanding of the demographic and clinical features, causative foods and common associated food sensitivities, and current management practices of clinicians caring for children with FPIES. Such a study would also draw the attention of the paediatric and broader community to this allergic condition, enabling the development of educational material for clinicians and parents, and formulation of clinical practice guidelines.

Study Objectives

- Estimate the incidence of FPIES in Australian children
- Describe the demographic features of children with FPIES
- Determine the causative food trigger(s) and common co-sensitisations
- Describe clinical and laboratory features of FPIES reactions
- Describe the current diagnostic and management practices of children presenting with FPIES.

Case Definition and reporting instructions

Please report any child ≤ 24 months of age whom you have seen within the last month and have not previously reported to the APSU, meeting the following case definition criteria:

1. Repeated episodes of vomiting typically presenting within 4 hours after ingestion of a food protein that has been recently introduced into the diet without any other cause identified for the episode of vomiting **AND**
2. Absence of fever (>38°C), any cutaneous (urticaria, hives, and/or angioedema) and respiratory clinical features (difficulty in breathing/talking, swelling of tongue, tight throat/hoarse voice, wheeze and/or persistent cough) at the time of reaction **AND**
3. Removal of the offending food protein from the diet resulted in resolution of symptoms

Follow-up instructions

A questionnaire requesting de-identified details about the patient and aspects of the diagnosis will be sent to clinicians who notify a case of FPIES via email, post or may be downloaded from the APSU website (www.apsu.org.au)

Please return the completed questionnaire to the APSU by post or fax as instructed on the questionnaire.

Investigator contact details (*Principal investigator and contact person)

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Associate Prof Richard Loh (Head of Immunology, Pathwest, Children's and Adolescents' Health Services, Princess Margaret Hospital, Perth & Clinical Associate Professor, University of Western Australia, Perth)

Associate Prof Peter Smith (Associate Professor in Clinical Medicine, Bond University, Robina, Queensland and Griffith University, Southport, Queensland)

Associate Prof Mimi Tang (Group Leader, Allergy and Immune disorders, MCRI Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Victoria University of Melbourne Department of Paediatrics)

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Associate Prof Yvonne Zurynski (Deputy Director, Australian Paediatric Surveillance Unit)

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1. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol* 2005;115:149-56.
2. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics* 2009;123:e459-64.
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NEW FPIES FOOD TRIGGER(S) IN A PREVIOUSLY REPORTED CASE

Food Protein Induced Enterocolitis Syndrome (FPIES)

Australian Paediatric Surveillance Unit

Please contact *Dr Sam Mehr* ; sam.mehr@health.nsw.gov.au; or APSU ; apsu@chw.edu.au if you have any questions about this form. Please keep a record of the child's unit number in your APSU folder

Instructions: Please answer each question by ticking the appropriate box or writing your response in the space provided.

DK=Don't Know; NA=Not Applicable

REPORTING CLINICIANS DETAILS

1. APSU Dr Code/Name: / _____
2. Are you a: ☐ Paediatrician ☐ Adult physician
3. Your Specialty: ☐ Allergist/Immunologist ☐ Gastroenterologist ☐ General Paediatrician ☐ Other (specify) _____
4. Month/Year of Report: / 5. Date questionnaire completed: / /

PATIENT DETAILS

6. First 2 letters of first name: 7. First 2 letters of surname: 8. Date of Birth: / /
9. Sex: ☐ M ☐ F 10. Postcode of family:

If this patient is primarily cared for by another physician who you believe will report the case and could provide additional details, please write the other physician's name in the space below then complete the questionnaire details above this line and return to APSU. If no other report is received for this child we will contact you for further information requested in the remainder of the questionnaire.

The primary clinician caring for this child is: **Name:** _____

Hospital: _____

MEDICAL HISTORY

11. Has the child developed any new allergic disorder(s) since the last notification? Yes ☐ No ☐ DK ☐
- 11a. If YES, please specify:
 Eczema: Y ☐ N ☐ DK ☐ Asthma: Y ☐ N ☐ DK ☐ Allergic rhinitis: Y ☐ N ☐ DK ☐ Eosinophilic oesophagitis: Y ☐ N ☐ DK ☐
 Immediate IgE mediated food allergy: Y ☐ N ☐ DK ☐ Other: Y ☐ N ☐ DK ☐ (specify) _____
- 11b. If yes to IgE mediated food allergies, was an adrenaline injector prescribed? Y ☐ N ☐ DK ☐ NA ☐

AGE PRESENTATION, CLINICAL FEATURES, AND TRIGGERS OF NEW FPIES TRIGGER(S)

12. Please specify the new FPIES food trigger(s), age (mos) when first episode to new trigger(s) occurred, number FPIES episodes to the new trigger(s), number times had new food trigger(s) without reaction, average time from ingestion to reaction, and skin prick test/radioallergosorbent test (RAST) result of new food trigger(s).

New food triggers of FPIES (specify trigger(s))	Age (in months) when first episode occurred to new trigger(s)	Number FPIES episodes to date to this new trigger(s)	Number of times knowingly ingested food trigger(s) without initially having an FPIES reaction	Average time from ingestion of food trigger (s) to FPIES reaction (hrs)*	Skin prick test (SPT) result of food trigger(s)**	RAST result of food trigger(s) ***
_____	_____	1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
_____	_____	1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
_____	_____	1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
_____	_____	1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐
_____	_____	1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ DK ☐	_____ DK ☐	_____ DK ☐	_____ DK ☐

* If child has had 2 or more episodes, please average the estimated time to reaction ** if SPT is 6x5 then mean result = 5.5 mm; *** quantitative result with units preferred, qualitative result accepted (e.g. negative, low positive, etc.)

13. Did FPIES reaction to new food trigger(s), occur whilst child was exclusively breast fed? Yes ☐ No ☐ DK ☐

14. Since the new FPIES food trigger(s) have any of these foods/milk/formulas been introduced into the child's diet?

Grains	Introduced	Age introduced (months)	If introduced, FPIES reaction
Rice	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Wheat	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Oat	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Rye	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Barely	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Corn	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Formulas/milk			
No formula and continue breast feeding	Y ☐ N ☐ DK ☐		
Lactose free cow formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Formulas/milk	Introduced	Age introduced (months)	If introduced, FPIES reaction
Soy formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Cow milk formula/milk	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Partial hydrolysed formula (e.g NAN-HA)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Extensive hydrolysed formula (e.g. Alfare, Pepti-J)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Amino acid formula (e.g Elecare, Neocate)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Other solid foods			
Egg	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Baked egg (e.g biscuit, cake, muffin)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Legumes (e.g. beans, lentils, peas)	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Sweet potato	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Fish	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Shellfish	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Poultry	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Banana	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐
Avocado	Y ☐ N ☐ DK ☐	DK ☐	Y ☐ N ☐ DK ☐

FEEDING ADVICE FOLLOWING NEW FPIES TRIGGER(S)

15. Following diagnosis of the new FPIES food trigger(s), which food(s) were recommended for exclusion in the child's diet?

Causative food(s) only (i.e new food trigger and previous reported food triggers causing FPIES) ☐

Other food(s) ☐ (please specify): _____

16. Following diagnosis, were any food(s) excluded from the maternal diet if still breastfed?

Causative food(s) (i.e. new food trigger and previous reported food triggers causing FPIES) ☐

Other food(s) ☐ (please specify): _____

EMERGENCY DEPARTMENT (ED) VISITS AND INVESTIGATIONS FOR NEW FPIES TRIGGER(S)

17. Were any of the following identified following FPIES by the new food trigger(s) ? Y ☐ N ☐ DK ☐

Leukocytosis: Y ☐ N ☐ DK ☐ Neutrophilia: Y ☐ N ☐ DK ☐ Thrombocytosis: Y ☐ N ☐ DK ☐

Metabolic acidosis: Y ☐ N ☐ DK ☐ Hypoglycaemia: Y ☐ N ☐ DK ☐

MANAGEMENT OF NEW FPIES TRIGGER(S)

18. Did the child have a challenge to the new food trigger(s) to support the diagnosis of FPIES to the trigger(s) ? Y ☐ N ☐ DK ☐

If yes, how were the food portions given? (please select ONE of the options below)

☐ Increasing incremental amounts (e.g given every 15-20 minutes) until a meal size portion consumed

☐ As a meal size portion of food given as a single, once off dose

☐ Other (please specify): _____ DK ☐

**Thank you for your help with this research project. Please return this questionnaire to the APSU in the reply-paid envelope or Fax.
 . Australian Paediatric Surveillance Unit, Kid's Research Institute, Locked Bag 4001, Westmead NSW 2145**

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