

Food protein-induced enterocolitis syndrome in the British Isles

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2020-320924>).

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Received 9 October 2020
Accepted 11 August 2021

ABSTRACT

Background Food protein-induced enterocolitis syndrome (FPIES) is a delayed type of food allergy, most often seen in infancy. We aimed to estimate its incidence, to describe common food triggers and the patient journeys of this rare but serious condition.

Design We undertook a prospective epidemiological survey of FPIES using the British Paediatric Surveillance Unit.

Setting UK and Ireland.

Participants A survey of all paediatricians over 13 months between January 2019 and February 2020.

Main outcome measures 204 cases were reported, 98 (48%) meeting case definition, giving an incidence of 0.006% for England based on 93 cases.

Results 98 patients reported 135 trigger foods, 27% (26 of 98) had multiple food triggers. Common food triggers included cow's milk (24%, 33 of 135), fruits and vegetables (19%, 26 of 135), hen's egg (16%, 22 of 135) and fish (14%, 19 of 135). In 46% (41 of 90), the initial trigger food had been ingested three or more times before diagnosis, with a median diagnostic delay of 7.9 months (3.0, 17.3). Half (50 of 98) were admitted, yet only 5% (5 of 98) received appropriate acute treatment with ondansetron. Most cases were diagnosed by an allergy specialist (74 of 98, 76%), within a median of 7.5 (3.0, 13.3) miles from home.

Conclusion The incidence of FPIES was significantly lower than expected across the whole of the British Isles. Most reports were of cases local to specialist allergy centres, with delays in diagnosis. This suggests under-recognition of FPIES in frontline clinical setting where education of healthcare professionals is required to improve recognition, earlier diagnosis and treatment.

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a delayed type of non-IgE-mediated food allergy most often seen in infancy. Allergen exposure leads to the onset of repetitive vomiting within 4 hours of ingestion and diarrhoea may follow later.¹ FPIES is characterised by lethargy, pallor and floppiness, which may be due to hypovolaemia. It should be considered as a medical emergency, as if left untreated, it can progress to acidosis, hypotension and shock.² An acute FPIES reaction may mimic sepsis and is often misdiagnosed as such. FPIES is a clinical diagnosis with defined international consensus criteria.¹ There are no diagnostic biomarkers and this may lead to under-recognition,

What is already known on this topic?

- Global protein-induced enterocolitis syndrome (FPIES) incidence varies from 0.015% to 0.7%.
- Profuse, often repetitive vomiting from acute FPIES reactions can lead to hypovolaemic shock and metabolic acidosis.
- There are no biomarkers for FPIES, and the diagnosis relies on clinical recognition of symptoms and signs.

What this study adds?

- Incidence in England was much lower than expected at 0.006%, and cases were clustered around centres with specialist allergy services suggesting under-reporting elsewhere.
- There was a significant delay in making an FPIES diagnosis. There is a clear need to improve education among primary and secondary care.
- Initial FPIES triggers in the UK are cow's milk, fruits and vegetables, hen's egg and fish, with a quarter of cases reacting to multiple foods.

missed diagnosis, unnecessary investigation and treatment.³⁻⁴ Management includes avoidance of trigger foods and written care plans for parents to access medical services in the event of an accidental reaction due to the risk of hypovolaemia. FPIES vomiting usually responds to treatment with ondansetron.¹

FPIES has been reported throughout the developed world with an incidence between 0.015% and 0.7%.² In the UK, there had been one case series and several case reports but no prospective epidemiological studies.⁴⁻⁷ The trigger foods and patterns of cross reactivity vary between countries; in the USA, the condition is associated with multiple culprit triggers, whereas in Australia and Italy, it appears to be due to a single food in most cases.⁸⁻¹⁰ Common trigger foods include cow's milk and hen's egg, which are also implicated in immediate onset, IgE-mediated food allergies. However, soya, grains, meats and vegetables are also common precipitants of FPIES but not of IgE-related allergic reactions.

We undertook the first prospective survey of FPIES in the UK and Ireland to estimate the



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To cite: Stiefel G, Alviani C, Afzal NA, et al. *Arch Dis Child* Epub ahead of print: [please include Day Month Year]. doi:10.1136/archdischild-2020-320924

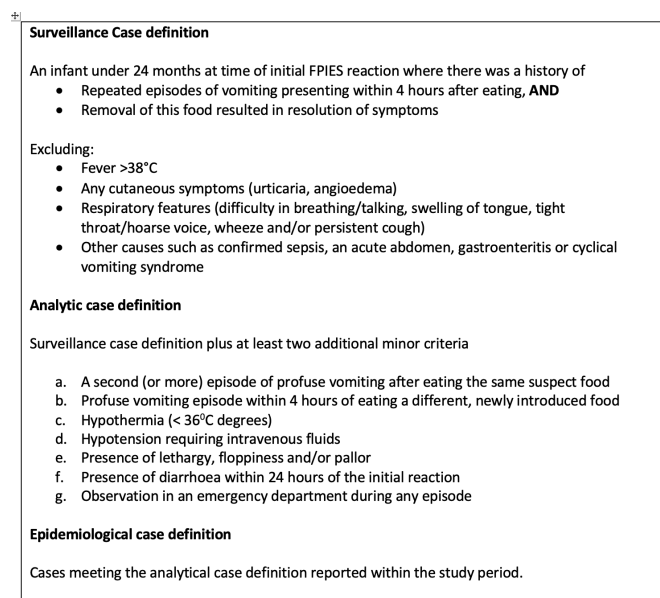


Figure 1 Surveillance, analytical and epidemiological case definitions used. FPIES, food protein-induced enterocolitis syndrome.

incidence, and describe presenting features, management and patient access to medical services.

METHODS

We used standard British Paediatric Surveillance Unit (BPSU) surveillance methodology over 13 months from January 2019 to February 2020.¹¹ Briefly, 3500 consultant paediatricians received a monthly electronic card (e-card) and reported cases fitting the surveillance case definition seen in the last month. There was a 90.6% return rate on e-cards during the study period. Reporting clinicians completed an electronic clinical questionnaire, providing data on demographics, atopic background, FPIES food triggers, clinical presentation, treatments, investigations and management of these patients (online supplemental material).

We applied an analytical case definition to reported cases (figure 1), based on the Australian paediatric surveillance study, and very similar to the international consensus guideline.¹¹⁰ Our epidemiological analysis was limited to those cases diagnosed in the study period.

To improve case ascertainment, we advertised the study through national stakeholders including patient groups FPIES UK and Allergy UK, and professional societies such as the British Society of Paediatric Gastroenterology, Hepatology and Nutrition, Association of Paediatric Emergency Medicine, and the Paediatric Allergy Group membership of the British Society of Allergy and Clinical Immunology. We also contacted regional children's allergy clinics midway and at the end of surveillance to encourage reporting from centres where several new cases of FPIES may be seen each month.

Statistical analysis was performed with Stata, V.15 (StataCorp, College Station, USA). Central tendencies are described as medians (Q1, Q3) with comparisons using the Mann-Whitney U test. Proportions were compared using χ^2 tests except where categories <10 where the Fisher's exact test was employed.

RESULTS

A total of 204 cases were reported during the study period (figure 2). A total of 98 cases met the final epidemiological

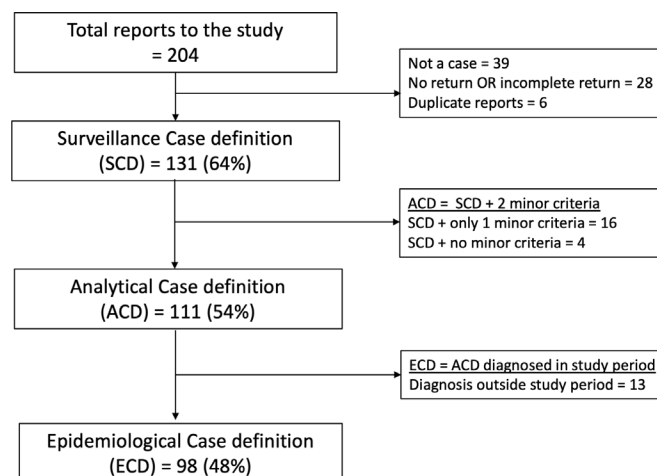


Figure 2 Reported cases' flow diagram.

case definition and were included in the subsequent analysis; 94.8% (93 of 98) were residents in England. Only five cases were reported from the other participating countries. Based on available live birth data between July 2017 and August 2019, incidence of reported FPIES for children less than 24 months in England was 0.006% (0.6 per 10 000 live births per year).

Case demographics

The median age at first reaction was 6.0 (3.0, 8.0) months. Ninety-eight patients reported 135 trigger foods, 27% (26 of 98) had multiple food triggers (table 1). Of the 26 patients who reacted to multiple foods, 18 (18%) reacted to two foods, 6 (6%) to three foods and 1 (1%) each to four and five foods. Fifty-three per cent (52 of 98) were male, but multiple food trigger FPIES cases were more likely to be female (15 of 26, 65%) versus single trigger (29 of 72, 40%; $p=0.03$) (online supplemental table 1). All cases of multiple food-triggered FPIES reacted before 9 months compared with 53 of 72 (74%) of single-food trigger FPIES ($p<0.05$).

Under-recognition and under-reporting of cases

There were several factors that suggest the under-recognition and under-reporting of cases. The number of reactions to the primary trigger was available for 90 cases; in 46% (41 of 90), the primary trigger food had been ingested three or more times before the diagnosis was made. The median age at diagnosis was 10.1 (7.2, 17.6) months, leading to a median diagnostic delay from first reaction of 7.9 (3.0, 17.3) months. Diagnostic delay was greater for multiple-trigger FPIES (12.2 months (6.3, 19.7)) compared with single-trigger FPIES (5.9 months (2.2, 16.8), $p=0.024$). In 77 of 98 (79%) cases, the initial diagnosis was made by a healthcare professional with allergy-specific expertise (table 1) with a median distance from home to the diagnosing hospital was 7.5 miles (3.8, 13.3). However, when comparing cases diagnosed by a clinician with allergy expertise versus generalists, no difference was seen in diagnostic delay, distance travelled for diagnosis or the Index of Multiple Deprivation quintile based on home postcode.

Food triggers

Cow's milk was the most frequent trigger overall, causing 24% (33 of 135) of reactions (table 2). Fruits and vegetables (19%, 26 of 135) were the second most frequent trigger group, followed by hen's egg (16%, 22 of 135) and fish (14%,

Table 1 Patient demographic characteristics

Demographic (N)	Total	Single trigger	Multiple trigger
N	98	72 (73.5%)	26 (26.5%)
Male (N=98)	52 (53.1%)	43 (59.7%)	9 (34.6%)
Ethnicity (N=85)			
White British	59 (69.4)	42 (64.6)	17 (85.0)
White other	11 (12.9)	10 (15.4)	1 (5.0)
Asian	9 (10.6)	8 (12.3)	1 (5.0)
Other	6 (7.1)	5 (7.7)	1 (5.0)
Country of residence (N=98)			
England	93 (94.9)	68 (94.4)	25 (96.1)
Northern Ireland	2 (2.0)	2 (2.8)	–
Other	3 (3.1)	2 (2.8)	1 (3.9)
Diagnosing clinician (N=98)			
Paediatric allergist	44 (44.9)	34 (47.2)	10 (38.5)
General paediatricians with special interest in allergy	26 (26.5)	19 (26.4)	7 (26.9)
General paediatrician	14 (14.3)	10 (13.9)	4 (15.4)
Allergy-associated HCP	7 (7.2)	4 (5.6)	3 (11.5)
Other paediatric specialist	3 (3.1)	1 (1.4)	2 (7.7)
Parent	2 (2.0)	2 (2.8)	–
GP	1 (1.1)	1 (1.4)	–
Age first reaction (N=93)			
Less than 9 months	73 (78.5)	48 (70.6)	25 (100)
9 or more months	20 (21.5)	20 (29.4)	–
Family history of atopy (N=80)	53 (66.3)	40 (66.7)	13 (65.0)
Personal history of atopy (N=87)			
Any	50 (57.5)	40 (61.5)	10 (45.5)
Eczema	44 (45.0)	35 (48.6)	9 (36.0)
Food allergy	32 (33.7)	22 (31.0)	10 (41.7)
IgE	9 (10.3)	8 (11.1)	1 (4.1)
Non-IgE	15 (17.2)	11 (15.3)	4 (15.3)
Indeterminate	8 (9.2)	3 (4.3)	5 (19.2)
Rhinitis	4 (4.3)	3 (4.3)	1 (4.1)
Caesarean delivery (N=75)	23 (30.7)	21 (35.6)	2 (12.5)
Term gestation (N=89) (>37/40)	82 (92.1)	62 (92.5)	20 (90.9)
Breastfeeding duration (N=75)			
Never breast fed	10 (13.3)	6 (10.5)	4 (22.2)
<4 months	20 (26.7)	17 (29.8)	3 (16.7)
4–6 months	22 (29.3)	16 (28.1)	6 (33.3)
7–12 months	17 (22.7)	13 (22.8)	4 (22.2)
>12 months	6 (8.0)	5 (8.8)	1 (5.6)

Patient number (percentage).

GP, general practitioner; HCP, healthcare professional.

19 of 135). Rice and soya-triggered FPIES accounted for only 4.4% (6 of 135) and 5.2% (7 of 135), respectively. The most common initial food trigger was cow's milk (33%, 32 of 98), followed by fish (15%, 14 of 98) and hen's egg (14%, 14 of 98; online supplemental tables 1 and 2). There were only two cases (2%) where the initial trigger was soya. In the 32 cases where milk was the initial trigger, only 2 cases claimed soya was a subsequent trigger. There were no cases reported in

Table 2 Food triggers from all reported reactions

	Total reported reactions, n (%)
Total reported reactions	135
Dairy	33 (24.4)
Milk	31 (23.0)
Baked milk	2 (1.4)
Eggs	22 (16.3)
Eggs	20 (14.8)
Baked egg	5 (3.7)
Soya	7 (5.2)
Fish	19 (14.1)
Meat	11 (8.1)
Chicken	6 (4.4)
Beef	2 (1.5)
Other meats*	3 (2.2)
Grains	15 (11.1)
Oat	7 (5.2)
Rice	6 (4.4)
Wheat	3 (2.2)
Fruits and vegetables	26 (19.3)
Banana	8 (5.9)
Avocado	5 (3.7)
Sweet potato	5 (3.7)
Potato	2 (1.5)
Other fruit or vegetable†	6 (4.4)
Peanut and tree nuts	4 (3.0)
Coconut seed	3 (2.2)

The table describes the number of reactions where this food was implicated as a trigger (n (%)). For reactions triggered by a compound meal, all potential food triggers were included. For example, a reaction caused by a mixed dish of rice and chicken, both rice AND chicken are recorded here as triggers.

*Other meats included pork, turkey and lamb.

†Other fruits and vegetables included strawberry, mango, prune, broccoli, butternut squash and legumes.

exclusively breastfed infants before the introduction of solid foods.

Presenting features

Vomiting comprised part of the surveillance case definition, so was present in all cases. Where data were available, the most common secondary presenting features included lethargy or floppiness (84 of 93, 90%), pallor (73 of 87, 84%) or loose stool (44 of 85, 52%) (table 3). Hypothermia (4 of 49, 8.2%), hypotension (3 of 71, 4.2%) and bloody stool (3 of 85, 3.5%) were the least frequently reported presenting features.

Initial management

Half of cases (50 of 98, 51%) were admitted or observed during at least one of their FPIES reactions (table 3). Management involved oral rehydration solution (39 of 98, 40%), intravenous fluids (25 of 98, 25%) and intravenous antibiotics (13 of 98, 13.0%). Four patients were admitted to the paediatric intensive care unit and one patient was treated with intramuscular epinephrine (first-line treatment for anaphylaxis, not for FPIES). Only 5% (5 of 98) received ondansetron as treatment. No patients were treated with steroids or underwent an unnecessary surgical procedure.

Dietary management

At the time of diagnosis, 46% (41 of 98) of patients were already excluding at least one food from their diet. This proportion was higher for the multiple-food trigger group

Table 3 Clinical presenting features, initial management and further management on discharge of FPIES cases

Presenting features	Total (N=98)	Single trigger (N=72)	Multiple trigger (N=26)
Vomiting	98 (100)	72 (100)	26 (100)
Diarrhoea	44/86 (51.2)	30/64 (46.9)	14/22 (63.6)
Bloody stool	3/85 (3.5)	2/62 (3.2)	1/23 (4.3)
Pallor	73/87 (83.9)	58/64 (90.6)	15/23 (71.4)
Lethargy/floppiness	84/93 (90.3)	67/71 (94.4)	17/22 (77.3)
Hypotension	3/71 (4.2)	0/51 (0)	3/20 (15.0)
Hypothermia	4/49 (8.2)	2/38 (5.3)	2/11 (18.2)
Observed or admitted	50 (51.0)	36 (50.0)	14 (53.9)
Paediatric intensive care admission	4 (4.1)	2 (2.8)	2 (7.7)
Oral rehydration solution	39 (39.8)	29 (40.3)	10 (38.5)
Intravenous fluids	24 (24.5)	19 (26.4)	5 (19.2)
Ondansetron	5 (5.1)	2 (2.8)	3 (11.5)
Intravenous antibiotics	13 (13.3)	9 (12.5)	4 (15.4)
Intramuscular epinephrine	1 (1.0)	1 (1.4)	–
Abdominal ultrasound scan	4 (4.1)	3 (4.2)	1 (3.9)
Barium study	2 (2.0)	2 (2.8)	–
Other investigations*	13 (13.3)	6 (8.3)	7 (26.9)
Discharged with epinephrine autoinjector	3 (3.1)	1 (1.4)	2 (7.7)
Discharged with action plan	65/95 (68.4)	51/72 (71.0)	15/23 (57.7)
Given open access	30 (30.6)	19 (26.4)	11 (42.3)
Had follow-up arranged	93 (94.9)	69 (95.8)	24 (92.3)
Referred onwards	89 (90.8)	66 (91.7)	23 (88.5)
Paediatric allergist	54 (55.1)	39 (54.2)	15 (57.7)
General paediatrician with allergy interest	31 (31.6)	24 (33.3)	7 (26.9)
General paediatrics	4 (4.1)	3 (4.2)	1 (3.9)
Other†	3 (3.1)	1 (1.4)	1 (3.9)
Dietitian involved	63 (64.3)	46 (63.9)	17 (65.4)
Food challenge performed	7 (7.1)	5 (6.9)	2 (7.7)

The denominator is stated where there are missing data.

*Other investigations included urine, blood, viral and cerebrospinal fluid (CSF) cultures, electroencephalogram (EEG), electrocardiogram (ECG), surgical review and CT/MRI.

†Other referrals were to paediatric gastroenterology and neonatal clinics. Number of cases (percentage).

FPIES, food protein-induced enterocolitis syndrome.

(73%, 16 of 26) compared with the single trigger group (38%, 25 of 72) (online supplemental table 3). Following diagnosis, trigger food exclusion was advised to all patients, and additional foods were excluded in 18% (18 of 98) (online supplemental table 4). The most common additional dietary exclusion in cow's milk triggered FPIES was soya, excluded in 11 of 32 (34%) (online supplemental table 3). In 32 cow's milk-triggered FPIES, 22% (7 of 32) of infants received an extensively hydrolysed formula, 34% (11 of 32) an amino acid formula and 19% (6 of 32) were breast fed, while in 22% (7 of 32), dietary management was not known. At the time of diagnosis, 46 of 98 (47%) were still in part breast fed, and of these 31 of 46 (67%) had maternal dietary exclusion.

Further management

Follow-up was arranged in 95% (93 of 98) of cases with 55% (54 of 98) referred to a regional paediatric allergist and 65% (63 of 98) had a dietitian involved (table 3). An FPIES action plan was provided at discharge in 68% (65 of 98) of cases, 31% (30 of 98) had direct open access to acute paediatric services arranged. Three cases were discharged with an epinephrine autoinjector suggesting possible diagnostic confusion.

DISCUSSION

This is the first prospective epidemiological study of FPIES in the UK and Ireland. We estimated an incidence of 0.006% for England alone but this is likely to be an underestimate due to under-recognition by healthcare professionals. We were unable to calculate incidence in other participating countries as only five other cases were reported. Cow's milk, fruits and vegetables, hen's egg and fish were the most common specific trigger foods and about a quarter of infants had more than one trigger. There was a significant delay in making an FPIES diagnosis with many infants experiencing three or more FPIES reactions before a healthcare professional confirmed the diagnosis. Most reported were diagnosed clustered around local specialist centres.

Our incidence is much lower than reported elsewhere in the world.¹ The UK-based EAT Study cohort described an incidence of 0.23% of FPIES, with 3 cases in 1303 infants.^{12 13} Although we used the same analytical case definition as the Australian surveillance study to allow for international comparison, we found only half their rate of cases.¹⁰ This may be due in part to differences in patient access to paediatricians between the two countries, which is more limited in the UK. Many potential cases may have presented to primary care alone, as half the cases identified did not present to an emergency department. Under-recognition may be particularly true for milk-triggered FPIES, as milder cases may be mistaken for non-IgE milk allergy, for which guidelines encourage management in primary care.¹⁴ Accurate BPSU reporting is reliant on contact with senior secondary care staff, reported outside of the acute setting. Many of the milder cases may not have been seen by a consultant paediatrician and slipped through the surveillance net. Most infants had suffered several reactions before the diagnosis was made with a significant lead time to diagnosis. For a disease presenting in infancy during weaning, unnecessary diagnostic delay is not acceptable, and compares poorly with the short lead times reported by Australian surveillance.¹⁰ In the future, surveillance should also include allied health professionals and general practitioners, as milder cases are likely to present and be managed under their supervision.

FPIES food triggers are similar to those reported in other countries but describe a pattern unique to the UK.⁷ As in other studies, cow's milk, which is the main staple food for young infants, remains the most common trigger. There were very few soya-triggered cases compared with the USA and France, and significantly fewer cases of rice FPIES than seen in the Australian study.^{8 10 15} Unlike US reports, milk soy cross reactivity was uncommon, so it may be possible to use soya as an acceptable formula choice for UK children with FPIES over the age of 6 months. Tolerability of soya was not explicitly examined in the survey, however there was a significant delay in the FPIES diagnosis, making it likely that the infants would have been exposed to many additional foods including soya. FPIES reactions occur to common weaning foods and will vary by the country of residence, and may also be related to genetic factors.² This will impact on clinical practice, for instance, international consensus guidance suggests avocado is a 'safe food', yet we and others report this as a more common trigger.^{1 16} Advice on the introduction of complimentary foods should be tailored to local patterns of food triggers.

We have undertaken a survey of FPIES in the UK and Ireland and found evidence of delayed diagnosis leading to multiple allergic reactions and under-recognition with clusters of cases around centres with specialist interest. In the absence of a biomarker for diagnosis, improvement of recognition and education among frontline clinicians in primary and secondary care

and prompt referral of cases to specialist services will help to improve outcomes for patients and families.

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Acknowledgements We would like to thank Richard Lynn and Jacob Avis from the British Paediatric Surveillance Unit for their help and advice throughout this study, the admin team at the Leicester Royal Infirmary, in particular, Farkhanda Mohiyuddin, and Mattia Giovinnini from the Evelina. We also wish to acknowledge the support of the patient support groups, in particular, Carla Jones from Allergy UK and Louise Littler from FPIES UK.

Contributors GS and CA contributed equally to this paper. GS and ME-L designed and executed the study as lead investigators. GS undertook data collection and liaison with reporters. CA undertook analysis of the data and wrote the paper with GS and ME-L. All other authors made substantial contributions to the design of the study, interpretation of data and in the drafting and critical revision of the paper. All authors gave final approval of the version published.

Funding The study was supported by an award from the Midlands Asthma and Allergy Research Association, Leicester, UK.

Competing interests NAA reports regional study leave support from Nutricia and Mead Johnson, and personal fees from Reckitt Benckiser, during the conduct of the study. ME-L reports personal fees from Danone Nutricia, Mead Johnson, Novartis, DBV technologies and Nestle, outside the submitted work; and he is chair of BSACI Registry for Immunotherapy (BRIT) that receives unrestricted grant funding from ALK Abello, Stallergenes Greer and Allergy Therapeutics. JH reports grants and personal fees from Aimmune Therapeutics, grants from DBV Technologies and Johnson & Johnson, outside the submitted work. He is president of Irish Association of Allergy and Immunology and co-chair of Irish Food Allergy Network, which receive unrestricted financial support for educational activities from pharmaceutical and infant formula companies. LJM reports lecture, travel and accommodation fees from Danone Nutricia, Mead Johnson and Regeneron; is on advisory board of Danone Nutricia and Novartis Principle; and chief investigator for commercial clinical trials for Danone Nutricia and Regeneron. GS reports personal fees from Nutricia and personal fees from DBV technologies, outside the submitted work.

Patient consent for publication Not required.

Ethics approval The study was approved by the London Stanmore Research Ethics Committee (IRAS 237585); separate approval was required from the Confidentiality Advisory Group for collection of identifiers in England and Wales under Section 251, NHS Act (2006) (18/CAG/0113) and from the NHS Scotland Public Benefit and Privacy Panel (1819-0123).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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**Case notification form - Strictly Confidential****BPSU Number**
Version 2.1**Food Protein Induced Enterocolitis Syndrome****Reporting Instructions:**

Please complete questions on tabs A through H

This should take about 20-30 minutes of your time and you will need access to their medical notes

Case Definition:

- An infant under 24 months at time of initial FPIES reaction where there was a history of
- Repeated episodes of vomiting presenting within 4 hours after eating **AND**
- Removal of this food resulted in resolution of symptoms

Excluding:

- Fever >38°C
- Any cutaneous symptoms (urticaria, angioedema)
- Respiratory features (difficulty in breathing/talking, swelling of tongue, tight throat/hoarse voice, wheeze and/or persistent cough)
- Other causes such as confirmed sepsis, an acute abdomen, gastroenteritis or cyclical vomiting syndrome

Section A: Reporter details

This page of the case notification form will be stored separately from the rest of the questionnaire and personal identifying information for the case will be used only for linkage of records.

A1	Date of questionnaire completion	
A2	Consultant responsible for case	
A3	<i>Name of reporter if other</i>	
A4	Hospital	
A5	Hospital postcode	
A6	Telephone number	
A7	Email	
A8	Speciality of consultant	
A9	<i>Other speciality</i>	

Section B: Case Details

This page of the case notification form will be stored separately from the rest of the questionnaire and personal identifying information for the case will be used only for linkage of records.

B1	NHS / CHI Number	
B2	Partial home postcode	
B3	Sex	
B4	Date of birth	
B5	Ethnicity	
B5i	<i>Ethnicity other</i>	
B6	Country of residence	
B6i	<i>Other country</i>	

If you chose an "any other" ethnicity (in the orange) enter further details in the orange box

If resident in England look up the Index of Multiple Deprivation (IMD) score based on their the FULL home postcode from <https://tools.npeu.ox.ac.uk/imd/>

O2	IMD score	
O3	IMD quintile	

Code	Ethnicity - enter code in question B5
	White
1	English / Welsh / Scottish / Northern Irish / British
2	Irish
3	Gypsy or Irish Traveller
4	Any other White background
	Mixed/ Multiple Ethnic Groups
5	White and Black Caribbean
6	White and Black African
7	White and Asian
8	Any other Mixed / Multiple ethnic background
	Asian / Asian British / Asian Irish
9	Indian
10	Pakistani
11	Bangladeshi
12	Chinese
13	Any other Asian background
	Black / African / Caribbean / Black British / Black Irish
14	African
15	Caribbean
16	Any other Black / African / Caribbean background
	Other ethnic group
17	Arab
18	Any other ethnic group

Section C Presentation and clinical features

C1	Age of initial presentation in months		months
C2	Date of diagnosis of FPIES		
C3	Have alternative diagnoses been excluded?		
C4	Has exclusion of the food resolved symptoms		
C5	Has the patient had a further episode of profuse vomiting after eating the same suspected food?		

C6 *Were any of the following features present during the primary SUSPECTED FPIES episode?*

A	Repeated vomiting within 4 hours of consumption	
B	Diarrhoea within 24 hours of consumption	
C	Bloody diarrhoea within 24 hours of consumption	
D	Recorded hypotension	
E	Patient requiring intravenous fluid	
F	Pallor	
G	Floppiness	
H	Lethargy	
I	Skin (e.g urticaria, angioedema)	
J	Respiratory (e.g stridor, wheeze)	
K	Child attended emergency walk in centre or A&E	

C7	On the primary suspected FPIES episode what was the patient's temperature?	
C8	Who made the diagnosis of FPIES?	
C8A	State other HCP / specialist	

Section C

Presentation and clinical features

Primary FPIES episode

C9A

These questions relate to the primary FPIES trigger food(s) that lead to the initial diagnosis being made. In some cases it may be impossible to identify a single allergen, for instance a child reacting to rice pudding both milk and rice may be suspected.

Please record ALL allergens that were implicated in this reaction.

- ☐ Milk
- ☐ Baked Milk
- ☐ Soya
- ☐ Egg
- ☐ Baked Egg
- ☐ Fish
- ☐ Chicken
- ☐ Beef
- ☐ Other Meat
- Please state other meat
- ☐ Rice
- ☐ Corn
- ☐ Wheat
- ☐ Oats
- ☐ Other Grain
- Please state other grain
- ☐ Fruit or Vegetable
- Please state fruit or vegetable(s)
- ☐ Other food
- Please state other food
- ☐ Triger not known

C9B	Age of initial reaction to these foods		months
C9C	Number of FPIES reactions before diagnosis was made?		Make a note of the number of presentations to emergency services here
C9D	Has food ever been ingested without FPIES reaction?		
C9E	Average time from ingestion of food trigger to FPIES reaction		
C9F	Were allergy tests positive to these food triggers?		
C10	Has the child experienced subsequent FPIES reactions to other foods?		

If answer to C10 is Yes, complete the second and third presentation Tabs (labelled CII second, and CII third) then move on to section D Medical History

Section D: Family History/Past Medical History

D1

Family history of an allergic disorder in a parent or sibling?

D2

Does any sibling have a diagnosis of FPIES (or a previous diagnosis now outgrown)?

D3

Does the index child have any other allergic disorder?
If yes please specify:

D3A

Eczema

D3B

Wheeze / Asthma

D3C

Allergic Rhinitis

D3D

Food Allergy

D3E

Please state other food allergy

D4

Duration of exclusive breast feeding?

months

D5

Age when solids first introduced:

months

D6

At the time of diagnosis of FPIES was the child already excluding any food allergens?

D6A

Specific food(s) excluded

D7

At the time of diagnosis was the child exclusively breast feeding?

D8

Mode of delivery

D9

Gestation

D10

	Describe allergic disease	
Mother		D10M
Father		D10F
Sibling(s)		D10S

Section E: Feeding advice following diagnosis

E1	Following diagnosis, which food(s) were avoided in the child’s diet	Causative foods Causative & additional foods
E1A	<i>Leave blank</i>	
E2	Following diagnosis, were any food(s) excluded from the maternal diet if still breastfed?	
E2A	<i>Leave blank</i>	
E3	If an infant formula was required which formula was tolerated	
E4	Was feeding advice provided by a dietician?	

Once completed please move to next tab

Section F: Investigations

F1	Did the child require observation in walk in centre / A&E / child assessment unit or require a hospital admission for any FPIES reaction?	
F2	<i>Ignore and move on to F3</i> Number of PICU admissions	
F3	<i>Were any of the following interventions/investigations performed during ANY FPIES episode prior to diagnosis?</i>	
F3A	Abdominal Ultrasound	
F3B	Abdominal barium study	
F3C	Gas enema	
F3D	CT or MRI scan	
F3E	EEG	
F3F	Surgical consultation	
F3G	Operation, please specify	
F3H	Other procedure of investigation. Please specify	

F4

Were any of the following results of investigations found during ANY FPIES episode prior to diagnosis?

F4A

Leucocytosis

Leave blank

x10(9)/L

F4B

Neutrophilia

Leave blank

x10(9)/L

F4C

Thrombocytosis

Leave blank

x10(12)/L

F4D

Metabolic Acidosis

Leave blank

F4E

Hypoglycaemia

Leave blank

mmol/L

F4F

Methaemoglobinaemia

Leave blank

F4G

Leave blank

F4H

Leave blank

g/dL

Section G: Emergency Management

How was the child managed during these emergency department/ emergency walk in centres / hospital admissions?

G1 Please tick all interventions that were used at least once

- ☐ Oral Rehydration
- ☐ Intravenous fluid
- ☐ Corticosteroids
- ☐ Ondansetron
- ☐ Anaphylaxis management as IM adrenaline
- ☐ IV antibiotics

G2

Was an adrenaline autoinjector provided for future emergency FPIES management?

G3

Was a written emergency action plan given in case of future FPIES reactions?

G4

Did the child have a challenge to the causative food trigger(s) to support the diagnosis of FPIES?

Section H: Outcomes

H1	Was follow up arranged following a diagnosis of FPIES?	
H2	Was the child referred to clinic?	
H2A	If yes please state nature of clinic?	
H2B		
H3	Was open access to the local hospital arranged for the child?	

Thank you for taking the time to complete the Questionnaire

Return details

Return by email preferably using an NHS dot net (@nhs.net) account
If you do not have access to an NHS dot net account make sure that this spreadsheet remains password protected

Stiefel and Alviani et al (2021) Food Protein Induced Enterocolitis Syndrome (FPIES) in the British Isles

Online supplementary material

Supplementary Table 1 Primary food triggers for all cases, single and multiple trigger FPIES. Numbers of cases (not reactions) (percentage).

Primary food trigger	Total (N= 98)	Single trigger (N = 72)	Multiple trigger (N=26)
Milk	32 (32.7)	23 (31.9)	9 (34.6)
Egg	14 (14.3)	13 (18.1)	1 (3.85)
Fish	15 (15.3)	15 (20.8)	-
Fruit and vegetables	14 (14.2)	8 (11.1)	6 (23.1)
Grains	10 (10.2)	4 (5.6)	6 (23.1)
Meat	7 (7.1)	3 (4.2)	4 (15.4)
Peanut and tree nuts	4 (4.1)	4 (5.6)	-
Soya	2 (2.1)	2 (2.8)	-

Supplementary Table 2 Total reported numbers of FPIES reactions. Number of reactions (percentage)

	Total reactions reported (N=135)
Number of times food ingested before diagnosis made (n=114)	
• 1	21 (18.4)
• 2	45 (39.5)
• 3	24 (21.1)
• >3	24 (21.1)
Reproducibility of symptoms to the food trigger causing the initial reaction (n=131)	85 (64.9)
Timing of reaction from ingestion (n=113)	
• <1 hour	7 (6.2)
• 1-2 hours	77 (68.1)
• >2-4 hours	27 (23.9)
• >4 hours	2 (1.8)

Supplementary table 3 Dietary management of FPIES cases. Number (percentage)

	Total population	Single trigger	Multiple trigger
N	98	72	26
Already excluding foods at time of diagnosis	41 (45.6)	25 (37.8)	16 (72.7)
Food exclusion advised at diagnosis			
Causative foods only	80 (81.6)	61 (84.7)	19 (73.1)
Additional foods	18 (18.4)	11 (15.3)	7 (26.9)
Maternal dietary exclusion if still breastfed (N = 46)			
Causative foods only	24 (52.7)	20 (55.6)	4 (40.0)
Additional foods	7 (15.6)	4 (11.1)	3 (30.0)
No exclusion	15 (33.3)	12 (33.3)	3 (30.0)
Use of non-standard infant formulas in milk FPIES (N = 32)			
EHF	7 (21.9)	5 (21.7)	2 (22.2)
AAF	11 (34.3)	7 (30.4)	4 (44.4)
Breastfed	6 (18.8)	5 (21.7)	1 (11.1)
Soya formula	1 (3.1)	1 (4.3)	-
Don't know	7 (21.9)		

Supplementary Table 4 Excluded foods based on the main primary FPIES triggers. numbers (percentage)

Foods excluded at time of diagnosis	Milk primary trigger (32)	Egg primary trigger (14)	Fish Primary Trigger (15)
Milk	32 (100)	4 (28.5)	-
Egg	2 (6.3)	14 (100)	2 (13.3)
Fish	1 (3.1)	-	14 (93.3)
Nuts	-	1 (7.1)	2 (13.3)
Grains	2 (6.3)	-	-
Fruit/ vegetables	-	-	-
Meat	1 (3.1)	-	-
Soya	11 (34.4)	-	-
Seeds	1 (3.1)	-	-