

Journal Pre-proof

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PII: S1081-1206(21)00104-6

DOI: <https://doi.org/10.1016/j.anai.2021.02.006>

Reference: ANAI 3498

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 17 November 2020

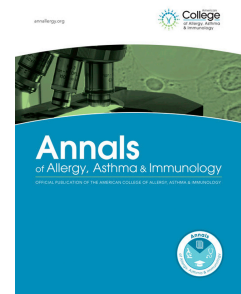
Revised Date: 5 February 2021

Accepted Date: 10 February 2021

Please cite this article as: Cianferoni A, Food Protein Induced Enterocolitis (FPIES) Epidemiology, *Annals of Allergy, Asthma and Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.02.006>.

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Food Protein Induced Enterocolitis (FPIES) Epidemiology

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Conflict of Interests

None

Funding Sources

None

Keywords

Food Protein Induced Enterocolitis Syndrome (FPIES), Epidemiology, Atopic disorder, Food Allergy

Abbreviations

FPIES (Food Protein Induced Enterocolitis Syndrome), EMR (Electronic Medical Records), OFC (Oral Food Challenges), FA (Food Allergy), AR (Allergic Rhinitis), AD (Atopic Dermatitis), IgE (Immunoglobulin Class E), Th2 (T helper class 2)

Word count

3789

Figures

None

Tables

2

20-11-0755R3

Objective Food protein induced enterocolitis (FPIES) is a syndrome with heterogeneous features (i.e., age at presentation, severity, food triggers, comorbidities) and is not as rare as initially believed. Over the last few years, the first population-based epidemiological study, few prospective birth cohort assessing FPIES prevalence, and several larger (>100 patient) studies have been published, making epidemiological estimation more reliable. In this review, we report on the available data on the epidemiology of FPIES.

Data Sources PubMed review using words FPIES, Epidemiology, and Prevalence

Study selections Review focused on population-based epidemiological study, few prospective birth cohort assessing FPIES prevalence, and several larger (>100 patient) studies

Results We identified eight population or cohort studies

Conclusion FPIES is not a rare in both children and adults and may affect as many as 900,000 people in the US alone. Most children and adult with FPIES appear to react to 1-2 foods, however they may need further diet restriction due high level of comorbidity with IgE mediated food allergies and Eosinophilic Esophagitis. Globally cow's milk, rice/oat and seafood appear to be the most common triggers

1 Introduction

Food protein induced enterocolitis (FPIES) was first formally described about 40 years ago as a syndrome characterized by prolonged vomiting and/or diarrhea with delayed onset, not associated with hives or wheezing¹. As we continue to gain knowledge of this disease, it has become clear that FPIES is a syndrome with heterogeneous features (i.e., age at presentation, severity, food triggers, comorbidities) and is not as rare as initially believed².

Pathogenetic mechanisms of and risk factors for developing FPIES remain poorly understood. While there may be a wide consensus among clinicians that FPIES is a reproducible and likely not an immunoglobulin E (IgE)-mediated food allergy, the precise mechanism is still elusive²⁻⁵.

Epidemiology, the study of how often diseases occur in different groups of people and why, helps in shaping research on the etiopathogenesis of new diseases and strategies to prevent and treat related illness⁷. However, epidemiology requires accurate measurements of disease frequency in populations and therefore the stipulation of well-defined diagnostic criteria for specific diseases⁷. One of the major limitations in studying the epidemiology of FPIES is that the International Statistical Classification of Diseases and Related Health Problems (ICD-10) established a code for the disease (K52.21) only in 2015, and the first international guidelines were published in 2017². Despite these two important steps to harmonize the criteria for diagnosis, there are still significant challenges to obtain reliable and consistent FPIES epidemiological data⁸. In this review, we report on the available data on the epidemiology of FPIES.

Prevalence of FPIES

In the absence of defined biomarkers or an understanding of the pathogenetic mechanism, the diagnosis of FPIES is still made based largely on non-validated clinical criteria⁹. Nowak-Węgrzyn et al. published an international consensus² in 2017, but the data collected prior were based on a variety of published diagnostic criteria that are still sometimes used in current research and clinical practice, such as those defined by Lee et al¹⁰; Powell, modified by Sicherer et al ¹¹; Miceli Sopo et al. ¹²; and Leonard and Nowak-Węgrzyn ¹³ (Table 1). While all of these criteria focus on the importance of delayed, reproducible, food-induced gastrointestinal reactions, they all vary in terms of severity of symptoms, patient age, and ancillary signs. Indeed, some criteria focus more on severe cases with life-threatening reactions, others on milder cases of acute typical gastrointestinal symptoms temporally related to food ingestion, and others include chronic symptoms and laboratory abnormalities. For example, the original Powell diagnostic criteria for FPIES focused on infants within the first 2 months of life with chronic symptoms of poor growth, leukocytosis, and diarrhea due to cow's milk or soy protein, proven by repeat challenges ¹. Sicherer et al. expanded the criteria to allow the inclusion of older children with acute symptoms triggered by milk, soy, and solid foods, even if they had detectable IgE to the causative food ¹¹. Recently, more diagnostic criteria have been published that include milder symptoms (e.g., vomiting 1–6 hours after food ingestion as a sole symptom) and no need for hematologic findings ^{11,14-18}. Finally FPIES doesn't present only with acute symptoms, but there is an increased recognition of syndrome presenting with less acute symptoms and a more chronic course: chronic FPIES. chronic FPIES is considered limited to early infancy and its true

prevalence is largely unknown. Some studies show that FPIES symptoms in the first month of life are more often chronic in nature, with diarrhea and failure to thrive as the major symptoms, as opposed to older children presenting with acute FPIES if formula was suspended during the chronic phase formula^{1,19}.

Chronic FPIES is described largely in formula-fed infants, a practice more common in Western countries, and may be underestimated as alternative formulas are readily available in developed nations. Therefore the diagnosis may never be made, as the switch to hypo-allergenic formulas may happen as soon as symptoms start and before all the characteristics typical chronic FPIES develop^{1,19}. Recently however, a well-documented case of multiple food (egg, salmon, beef) chronic FPIES with clinical characteristics similar to the one described in infants, was reported in an 20 year old young adult and confirmed with double blind placebo controlled challenge, suggesting that ~~because of~~ the current definition of chronic FPIES may not be conducive to diagnose this entity in older children and adults, contributing to its underdiagnosis²⁰.

Given the limitation in FPIES diagnostic criteria and lack of reliable biomarkers, extrapolating epidemiological data and geographic differences from case series obtained using varying diagnostic criteria may lead to false assumptions of significant geographic differences in incidence rates, phenotypes, trigger foods, and natural history of the disease that are instead due to varying diagnostic criteria used to describe different aspects of a broader clinical syndrome by clinicians in different geographic areas⁹.

Until recently, published case reports or case series from single academic centers involving limited numbers of patients were the only resources available to estimate FPIES prevalence, with severe limitations in the extrapolation of findings to the general population. Indeed, a heavy reliance on small, single-center studies is associated with a high risk of selection bias, clustering effects, and disease related to small sample sizes. Over the last few years, few larger (>100 patient) studies few prospective birth cohort assessing FPIES prevalence and the first population-based epidemiological survey have been published, making epidemiological estimation more reliable^{15,21-23}.

The FPIES cumulative incidence rates estimated using studies without selection bias such as single center birth cohorts from Israel, Spain, and the US or through a national survey of physician in Australia are between 0.15–0.7%^{21,24,25}. FPIES prevalence reported in such studies is in the same range of the 0.28% one reported in the US population based survey, which confirm that FPIES may not be a rare disease after all (Figure 1).

Katz et al. prospectively studied a birth cohort of 13,400 children at a single hospital in Israel for milk-induced FPIES and found a cumulative incidence of 0.34% (44 patients) over a 2 year period²¹. Diagnostic criteria for cow's milk-induced FPIES include age less than 9 months, delayed recurrent vomiting, and lethargy after exposure to trigger food in the absence of other IgE-mediated symptoms, such as rash, urticaria, and respiratory symptoms. In addition, a positive challenge response to milk resulted in gastrointestinal symptoms, removal of milk from the diet resulted in the resolution of those symptoms, or both.

In a cohort of about 1000 infants followed for 18 months from a single hospital in Spain (PREVALE study), the prevalence of FPIES was estimated to be 0.7% vs. 2.37% for IgE-mediated food allergy²⁶. The eight patients with FPIES had a mean age of 7.62 months and the majority were breastfed. By definition they presented with acute vomiting within or diarrhea/failure to thrive related to a specific food, but the most frequent symptoms were vomiting and lethargy 1–4 hours of ingestion of culprit food. In 75% of cases, diagnosis was not immediately made and the patients had repetitive vomiting after eating the same trigger food, suggesting that FPIES is not always suspected initially²⁶.

In Australia FPIES incidence was estimated to be around 15.4/100,000/year (0.15% among Australians) following a national survey (2012–2014) undertaken by 1400 pediatricians participating in the Australian Pediatric Surveillance Unit. This study was based on monthly notification of new cases of acute FPIES in infants less than 24 months of age, meeting the criteria of Sicherer et al. (Table 1). The median ages of first episode and diagnosis were 5 and 70 months, respectively²⁷.

Similarly, using a primary care electronic medical record cohort of about 160,000 children in the US, Ruffner et al. identified 214 patients with FPIES using the criteria of Nowak et al. (Table 1), for a prevalence of 0.14%. Interestingly, the authors found the peak age of FPIES diagnosis to be 6 months, followed by a period of relatively steady low incidence, with an average yearly incidence of 0.008% after age 3. Therefore, only a handful of children older than 3 years presented with FPIES²⁷. This could be important information to design future cohort studies.

A Japanese retrospective survey of the prevalence of “neonatal milk allergy” of any kind resulted in a rate of 0.21% among 69,796 neonates hospitalized in a 1 year period; even if the vast majority of cases were not IgE-mediated, FPIES and other enteropathies were included in the calculation^{28,29}.

Nowak et al. in the first population survey estimated that FPIES affects overall 0.28% (0.24–0.33%) of Americans, corresponding to over 900,000 people (based on the 2016 US Census). This estimate is based on a cross-sectional, population-based survey administered between October 2015 and September 2016 to a sample of 53,575 US households^{30,31,32}. In the survey, parents answered questions about FPIES regarding 38,408 children, reporting a total of 261 children with FPIES, for an estimated prevalence 0.51%, confirming previous US and international estimates. For the first time, in this survey, 0.22% of the adult respondents in a nationally representative sample of 40,443 adults self-reported FPIES³². In the study, the outcome measure of interest was lifetime prevalence of physician-diagnosed FPIES, so no specific diagnostic published criteria were used. Participants were asked, “Have you/has your child ever been diagnosed by a physician with food protein-induced enterocolitis syndrome (FPIES)? Note, this is a very specific and rare allergic condition.” Questions about the presence of other chronic atopic comorbidities were also asked³³. Despite the limitations of the approach, the authors believed that it limited the possibility of selection bias by using specific diagnostic criteria that clinicians in the territory may not be familiar with. The data reported in Nowak et al³³ are in line with those reported in studies that used published criteria to define FPIES, therefore the survey is likely a realistic estimate of the prevalence of FPIES in the US. Differently from birth cohort it has the advantage

to collect data on FPIES prevalence in older children and adults, helping to gain knowledge of natural history and comorbidity of FPIES.

Some of the described studies started to report information on chronic FPIES, helping to better understand this still poorly defined FPIES manifestation.

In a Spanish cohort, 15% of case with FPIES were chronic and caused only by cow's milk and no multi-food FPIES was seen ³⁴.

Similarly, about 22% of FPIES cases in the US Electronic Medical Record (EMR) cohort presented with chronic symptoms. In that study, children with chronic FPIES were diagnosed between 1 and 4 months of age, most commonly presenting with only one food allergy, either milk (59.2%) or soy (8.2%); the remaining 32.6% of patients were allergic to both milk and soy ²⁷.

Epidemiology of food triggers

Cow's milk is the most common cause of FPIES all over the world. Typically the cow's milk FPIES happens the first time it is introduced into the diet, between 2 and 7 months ^{8,11,17,18,21,23,34,35} (Figure 2).

The fact that cow's milk is the most common FPIES trigger in the US, was demonstrated in two series of respectively 150 in 462 FPIES cases identified through a ~~retrospective~~ retrospective chart review, in which cow's milk accounted for 44% ³⁶ and 67% ¹⁵. Almost identical data were reported from Italy in a food challenge series (43%) ³⁷ and retrospective reviews (67%). Also in Spain, milk was the most common food in birth cohort studies (50%) and in retrospective cases (36.7%) ¹⁷. Cow's milk is not only the

most common cause but frequently appears to cause severe reactions, with a significant proportion of patients not outgrowing their sensitivity by school age^{36,38}. In the US Wang et al. found that 28% of patients outgrew FPIES by 2 years, 53% by 3 years, 65% by 4 years, and 72% by 5 years³⁸. Caubet et al., in an American cohort, found that patients with specific IgE to milk (atypical FPIES) didn't outgrow their FPIES, whereas those who did not develop IgE for milk (typical FPIES) outgrew their sensitivity at a mean age of 5.1 years³⁶. In Australia and in a tertiary level referral center in the US, cow's milk appeared to be the most common food after grains, with 33% and 36% of cases^{39,40}. In Israel, Japan, and Korea, only data on FPIES triggered by milk or soy are available though^{21,41-43}, therefore is hard to know if most common compared to other food.

Even if pathogenesis is unknown the fact that most children are diagnosed in infancy or early childhood and tend to outgrow point to the fact that FPIES may be due to a food allergic reaction linked to immune factor present early on in life. Milk may just happen to be the first food introduced in most countries and therefore could be associated with more cases. The increased severity may be due to the fact that infants are exposed to higher doses immediately as opposed to first few introductions of solid foods.

Soy (alone or in combination) is reported to be a trigger in ~25–50% of children in large US case series, occurring after milk in 30–40% of cases^{15,36}. South Korea reports similar incidence⁴². However soy is an uncommon trigger outside the US and Asian countries, and ~~once again~~ feeding practices such as the common use of soy formulas

could explain this phenomenon ¹⁷. An additional explanation could be that children outgrow their soy allergy early. In a group of South Korean infants diagnosed with cow's milk FPIES in the first 2 months of life, a food challenge at 6 months of age confirmed cow's milk allergy in 63% and soy allergy in 25%⁴². Rates of tolerance to cow's milk and soy were 41.7% and 90.9% at 8 months and 63.6% and 91.7% at 10 months, respectively. Patients outgrew soy triggered FPIES at age 14 months ⁴².

In other countries and parts of the US, solid foods are among the most common triggers along with cow's milk ^{8,16,18,34,44}. Grains, especially rice, are the most common cause of FPIES in Australia (45%) ³⁹. In the US, rice was the most common solid food found in retrospective cases (16–39%) ^{4,15,38,39}. Rice is a much rarer trigger in Spain and Italy, with no cases reported in a Spanish birth cohort. Rice was instead cause of 4–10% cases in Italian retrospective cohorts^{17,26,34,37,39}. Of note, regardless of the country of origin, one-third of children who react to rice react to oats as well, whereas rarely they react to wheat or quinoa ^{15,18,23,39}.

Seafood is a common cause of solid food FPIES in Italy (12%) and Spain (34.2%), but a less common trigger in the US and Australia ^{17,34,44,45}. In an Italian retrospective review on fish-triggered FPIES, sole and cod were the most commonly implicated, with 81% of FPIES triggered exclusively by either a single (65%) or multiple fish (35%) ⁴⁶. Shellfish is a common food triggers in Mediterranean countries as well as in adults (Figure 2)⁴².

The data on solid food are limited to just six children in Israel, two children in Korea, and no children in Japan ^{21,41-43}. Therefore more studies are needed from these countries to understand prevalence and characteristics of solid food FPIES.

Complementary feeding practices can explain some of the regional variation of food triggers in FPIES; however, in other instances, other reasons are likely to be involved, such as the criteria for selection of cases, clinical awareness, atopic comorbidities, gut microbiome, genetic factors, etc. For example, rice is introduced early in Italy, but only accounted for 4% of cases in the study of Sopo et al.¹⁷. Katz et al. exposed 40/44 infants with cow's milk FPIES to soy, but none reacted⁸. In a study in Italy, no patients with cow's milk FPIES reacted to soy¹⁷.

Cases of FPIES with more than one trigger have been noted in several countries, with varying rates: none in birth cohorts (Spain, Israel)^{21,26} and 15% (Italy)¹⁷, 16% (Spain)³⁴, 32% (Australia)⁴⁰, and 35–69% (US)^{15,36,39} of case series. In all case series, reactions to more than four foods were extremely rare. The differences in different centers may in part be related to feeding practices and selected populations (e.g., patients with more complex cases reacting to multiple foods are more likely to present to specialized allergy clinics).

Limited data on FPIES in adults are available. Those patients are defined as having evidence of a supportive medical history of typical FPIES symptoms, no evidence of IgE mediated food allergy, and resolution of symptoms with elimination of the causative food, or oral food challenge confirmation if the history is unclear⁴⁷. Shellfish appears to be the most common trigger and eggs the second most common^{47,48,49}. In all the available studies in the adults the appearance of FPIES reaction was typically delayed 1–2 hours after eating, no ICU admission was described, and it appeared to be new onset after acquired tolerance^{47,48,49}. In the studies where the atopic status of the adult

FPIES patients was reported, these patients were reported to be atopic, but skin prick test (SPT) of the triggering food was typically negative^{47 49}.

Atopic Comorbidities in FPIES

Even if FPIES is not IgE-mediated, more data have emerged showing that children with FPIES have nevertheless comorbid IgE-mediated atopy.

In the previously cited US population-based study³³, it was estimated that many atopic conditions were present in the FPIES population at a significantly higher level than the general population. Indeed, 65.3% of children with FPIES in the US had one or more current parent-reported IgE-mediated food allergies vs. 7.3% of the general population ($p < 0.001$), 32.6% had lifetime physician-diagnosed allergic rhinitis vs. 12.75% of the general population ($p < 0.001$), 25.2% had asthma vs. 12.1% of the general population ($p < 0.0001$), 8.9% had a latex allergy vs. 1% of the general population ($p < 0.001$), 5% had an insect allergy vs. 2.2% of the general population ($p = 0.007$), and 3.4% had urticaria vs. 0.5% of the general population ($p < 0.001$)³³. Eczema and drug allergy were similar in FPIES and the general population (Table 2)³³. Similar data are reported for adults (Table 2), with higher incidence of atopic dermatitis and lower incidence of food allergy. In adults, only drug allergy was not significantly increased in patients with FPIES (Table 2)³³.

Significantly higher levels of atopic comorbidities have been reported in a large primary care medical record cohort in the US, with 214 FPIES cases followed in a tertiary pediatric hospital compared to 158,296 controls²⁷. In that study, FPIES patients had significantly more atopic dermatitis (20.6% vs. 11.7%, $p < 0.001$), IgE-mediated food allergies (23.8% vs. 4%, $p < 0.001$), asthma (26.6% vs. 18.4, $p < 0.01$), and allergic

rhinitis (28.0% vs. 16.7, $p < 0.001$)²⁷. Interestingly, in FPIES the risk of developing food allergies to any food (not only their trigger food) was independent of the development of atopic dermatitis. However, based on an analysis of the data over time, FPIES did not appear to be a first step in the atopic progression. The majority of patients with FPIES and IgE-mediated food allergies were sensitized to eggs, peanuts, milk, and tree nuts, similar to what is observed in children with IgE-mediated food allergies²⁷.

Other retrospective studies from the US and Europe cited also a frequent atopic co-association, in 30–57% of cases^{34,39,46}.

IgE-mediated food allergies are reported in varying percentages in case series: 0% in Korea, 10% in Italy⁴⁶, 15.7% in Spain³⁴, 16% in Australia⁴⁰, 18% in Israel²¹, and 5–39% in the US^{36,39}.

While varying percentages of atopic dermatitis, allergic rhinitis, and asthma are reported in case series in different countries (Table 2), the ages of reported cases may influence the level of comorbidities more than true geographical differences. For example, Korea and Israel often report early neonatal onset of FPIES, an uncommon age for IgE-mediated disease to manifest^{21,42}. In Italy, Sopo et al. reported atopic dermatitis in 30% of FPIES cases triggered by fish, with mean age at onset of 14 months, and only 9% in a cohort with cow's milk as the major culprit and mean age at onset of 5.7 months^{17,46}. Similarly, in the general US population, atopic dermatitis was not increased in children, but it was in adults³³.

Eosinophilic esophagitis (EoE), another food allergy that is not IgE-mediated, has been reported to be associated with FPIES according to the previously cited US population

study^{33, 50}. In that study, 19% of children and 13% of adults with EoE were reported to have a history of FPIES vs. 0.48% and 0.19% of the general population⁵⁰. In an Australian case series, EoE was reported as a comorbidity in 0.5% of FPIES patients, and in Australia the incidence of EoE in pediatrics is reported to be 0.01%⁵¹. More studies need to be done to confirm this association.

Risk factors for developing FPIES

There are no firm data to support an association between prenatal or perinatal maternal/paternal risk factors and the development of FPIES. In the Israeli prospective birth cohort, an association was noted with spontaneous delivery (a smaller proportion developed FPIES) and Jewish religion (a greater proportion developed FPIES), but no association was noted between the development of FPIES and gestational age, maternal age, number of siblings, maternal dairy consumption, or age at introduction of cow's milk²¹. In Japan, birth weight of <1 kg was associated with a higher rate of neonatal milk allergy (though not all neonatal milk allergy was FPIES in this series), and Nomura et al. noted an association with lower birth weight and a less severe FPIES cluster^{28,41}. The US, Italian, and Australian cohorts did not assess pre-natal or post-natal risk factors^{11,15-18}.

In the Australian study it was noticed that babies breastfed less than 4 months tended to have more multiple food FPIES than those with longer exclusive breastfeeding. Otherwise, no differences between those two groups was noticed 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 food triggers⁴⁰.

Family history of FPIES appears to be present in some families, as reported in a population study where 13 families (4.9%) reported multiple children with FPIES; five children (1.9%) had a parent (in all cases a father) with FPIES³³. To date there have been only three published cases of siblings with FPIES, and all three were twins (one set of identical and two sets of fraternal), although a family history of atopy appears to be common in those with FPIES (15–70%)^{39,46}.

It is not clear if instead sex predispose to FPIES development. While it appears to be a slight predominance of males affected across several culturally and geographically distinct populations, not all studies find a significant difference among sex^{27,33,39,47}. For example a male predominance was reported in a US electronic medical cohort study in the FPIES group compared with the overall cohort (64% vs. 51%, $p < 0.001$)²⁷. However the US study on general population found no differences in different sex in FPIES patients of any age group³³.

The majority of FPIES case series published so are from Western countries and predominantly of Caucasian race⁸, suggesting that ethnicity and race may also play a role in predisposition to FPIES. In a US general population survey, the majority of children and adults with FPIES were white but it was not different than in the healthy population surveyed³³. On the other hand, in the US EMR cohort, Ruffner et al. found a predominance of white patients in the FPIES group compared with the overall cohort (77% vs. 50%, $p < 0.001$ for both). In the same study, they found that FPIES was less common in the black population (9% FPIES vs. 32% overall) and in those with non-private insurance (16% vs. 33%, $p < 0.001$)²⁷.

Finally, research from Japan suggested that different FPIES phenotypes may exist based on race or ethnicity. A group of 46 infants with a high prevalence of IgE to milk (47%) was defined as having a specific phenotype of FPIES distinct from the Western phenotype, characterized by early onset of vomiting (100%), bloody stools (47%), and some FPIES features ²².

Conclusion

In the last year there have been significant advances in understanding the epidemiological characteristics of the FPIES population. Using data from cohorts and general populations, it now appears that FPIES has a prevalence between 0.01 and 0.7% in most Western countries, with about one million affected in the US alone. Caucasian males may be more at risk, but more data are needed. Family history of food allergy may be a risk factor to develop FPIES, even if more studies are needed to confirm this finding. The most common triggers of FPIES around the world are cow's milk, rice/oats, fish, soy, and eggs, with some variations based on geographic areas. Children with FPIES appear to be more at risk of many atopic diseases, including IgE and possibly non-IgE food allergies. Hopefully these data will help to direct the research to understand the pathogenesis of this disease.

333 **Table 1.** Most common criteria of food protein induced enterocolitis (FPIES).

Reference	Major Criteria	Minor Criteria	Diagnosis
Lee et al. ¹⁰	Repetitive vomiting 0.5–4 hours after eating suspected food(s)	Second (or more) episode of repetitive vomiting 0.5–4 hours after eating same suspected food Repetitive vomiting episode 0.5–4 hours after eating a different food Associated floppiness, pallor, and/or diarrhea (within 24 hours) during at least 1 episode Need for emergency department visit and/or intravenous fluid therapy during at least 1 reaction	Major and 2 minor
Nowak-Węgrzyn et al. (International Consensus) ²	Vomiting in the 1–4 hour period after eating suspected food and absence of classic IgE-mediated allergic skin or respiratory symptoms	Second (or more) episode of repetitive vomiting after eating same suspected food Repetitive vomiting episode 1–4 hours after eating a different food Extreme lethargy with any suspected reaction Marked pallor with any suspected reaction Need for emergency department visit with any suspected reaction Need for intravenous fluid support with any suspected reaction Diarrhea within 24 hours (usually 5–10 hours) Hypotension Hypothermia	
Powel criteria modified by Sicherer et al. ¹¹	Younger than 9 months of age at initial presentation Exposure to culprit food elicits repetitive vomiting, diarrhea,	A standardized oral food challenge or isolated re-exposure elicits typical symptoms	

	or both within 4 hours without any other cause Symptoms limited to gastrointestinal tract Avoidance of offending protein results in symptom resolution		
Miceli Sopo et al. ¹²	Younger than 2 years of age at first presentation Exposure to culprit food elicits repetitive and significant vomiting, pallor, hyporeactivity, and lethargy within 2 to 4 hours Absence of symptoms that suggest IgE-mediated reaction Avoidance of offending protein in the diet results in symptom resolution Re-exposure or oral food challenge elicits typical symptoms within 2 to 4 hours; 2 typical episodes are needed for definitive diagnosis Diarrhea may be present, much less frequently and later; symptoms last a few hours, usually less than 6 hours		
Leonard and Nowak-Węgrzyn ¹³	Younger than 9 months of age at initial diagnosis Repeated exposure to culprit food elicits gastrointestinal symptoms without alternative cause Absence of symptoms suggesting IgE-mediated reaction Removal of culprit food results in symptom resolution Re-exposure or oral food challenge elicits typical symptoms within 4 hours		

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337 **Table 2.** Atopic comorbidities in FPIES patients.

Country	IgE-mediated food allergy	Atopic dermatitis	Allergic rhinitis	Asthma
Australia ⁴⁰	16%	42%	3%	3%
Italy ^{17,46}	10%	9-19%	NA	NA
Israel ²¹	18%	NA	NA	NA
Korea ⁴²	0%	NA	NA	NA
Spain ^{26,34}	2.3–15.7%	NA	NA	Na
US children ³³	65%	9.2%	32.6%	25.2%
US adults ³³	42.5%	22.3%	31.1%	37.4%
US Philadelphia, PA ^{15,27}	19–23.8%	20.6–34%	28%	17– 26.6%
US New York City, NY ³⁶	39%	57%	38%	25%
US Houston, TX ³⁹	5%	46%	19%	7%

338 NA=Not available

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Figure 1: Estimated Prevalence of FPIES

Figure 2: Most common foods that cause FPIES

