Epidemiology of food protein-induced enterocolitis syndrome

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Purpose of review
To summarize the epidemiology of food protein-induced enterocolitis syndrome (FPIES).

Recent findings
FPIES is regarded as a rare non-IgE-mediated gastrointestinal allergic disorder. Older nonpopulation-based studies reported an average of 1–15 cases presenting to allergy clinics a year, but recent studies have reported figures as high as 90 cases a year. The yearly incidence of FPIES in one Australian study was one in 10,000 infants less than 2 years of age. Chronic FPIES typically presents in neonates, whereas acute FPIES is primarily a disorder of young infants. FPIES has a slight male predominance; eczema and a family history of atopy are commonly present at diagnosis; almost one in 10 infants have coexistent IgE food allergies and siblings are rarely affected. There is regional variation in common triggering foods, rates of combined cow milk and soy FPIES and multiple food group FPIES. Understanding of the epidemiology of FPIES is limited by the lack of a universally accepted definition and the publication of few prospective population-based case series.

Summary
FPIES is not as rare as once thought, but how common it is, what factors predispose to its development, and why there is regional variation needs to be addressed by future well designed population-based studies.

Keywords
enterocolitis, epidemiology, food hypersensitivity, food protein-induced enterocolitis syndrome

HISTORICAL ASPECTS
Food protein-induced enterocolitis is regarded as a rare non-IgE-mediated food allergy affecting the gastrointestinal tract. Gryboski [1] published the first case series of food protein enterocolitis to cow milk formula in neonates. Unlike cow milk proctocolitis, infants were unwell with prolonged diarrhea and vomiting after drinking cow milk formula for days to weeks. Frank or occult blood in the stools and anemia were noted in all cases, and half of the infants were failing to thrive on presentation [2,3]. Rectal biopsies showed either a slight infiltrate of lymphocytes/plasma cells or profuse polymorphonuclear cell infiltration, crypt abscess formation and mucosal injury [1].

Almost 10 years later, Powell [2,3] described the same condition following cow milk formula introduction in a smaller cohort, most of whom were neonates. Additionally, she noted some cases had abdominal distension, hypothermia, peripheral blood neutrophilia, and stools frequently contained a mixture of inflammatory cells, including lymphocytes, neutrophils and eosinophils. Both authors reported if reexposure to cow milk formula occurred after a brief period of abstinence, some infants presented acutely with profuse vomiting and diarrhea, cardiovascular collapse and neutrophilia usually 2 h after ingestion [1,3]. Powell [2,3] further recognized many infants with chronic cow milk enterocolitis also had an acute or chronic enterocolitis reaction once exposed to soy formula.

McDonald et al. [4] first coined the term food protein-induced enterocolitis (FPIE), recognizing...
Cow milk/soy protein likely triggered the reaction and that chronic exposure to the food protein was required to cause intestinal injury. Two years later the same authors reported three cases of acute egg enterocolitis in infants with cow milk/soy enterocolitis, but with no prior history of egg ingestion [5]. Some 20 years earlier, Ikola [6] had published a case of an infant with acute rice and wheat enterocolitis, following initial introduction of these foods. These early studies highlighted that acute reactions could occur without previous chronic exposure or enterocolitis and other food proteins apart from cow milk/soy could trigger acute reactions.

Sicherer et al. [7] suggested the disorder be called a syndrome, recognizing the disease was characterized by a constellation of shared clinical and laboratory features. Thus, FPIE became FPIES. Two distinct phenotypes of the disorder are recognized, acute and chronic FPIES, with the latter representative of the disorder first reported by Gryboski [1]. The differences between these two clinical phenotypes have been reviewed elsewhere [8]. To date, only cow milk/soy have been documented to cause chronic FPIES [1–9,10], whereas a range of foods has been reported to cause acute FPIES.

Epidemiological Limitations

Epidemiology is ‘the study of how often diseases occur in different groups of people and why’ [11]. Despite more than 1000 cases of FPIES being published, many epidemiological aspects of the disorder remain inadequately studied. Drawing firm conclusions from the current epidemiological data is difficult because no universal accepted definition of FPIES exists, with studies often using different criteria, mixing cases of acute/chronic FPIES [9] and subdividing acute FPIES into typical/atypical [7]; published studies are usually case reports or retrospective case series derived from specialized allergy clinics, potentially favoring the reporting of more severe, complex individuals and the majority of published literature is derived from only a handful of countries.
### Table 1. Case series examining acute and chronic food protein-induced enterocolitis syndrome

| References | Data on all food triggers | Study design | Definition | Country | No. | Duration (years) | Center | Male (%) | Eczema (%) | FHx atopy (%) | IgE FA (%)<sup>a</sup> |
|------------|---------------------------|--------------|------------|---------|-----|-----------------|--------|-----------|------------|----------------|-----------------|
| Ruffner et al. [30<sup>a</sup>]<sup>1</sup> | Yes | Retrospective | Their own | USA | 462 | 5 | One hospital | 60 | 34 | – | – |
| Frith et al. [25] | Yes | Prospective | Their own | Australia | 90 | 1 | Australia wide | 48 | 46 | 53 | 14 |
| Garcia and Jimenez Diaz [26] | Yes | Retrospective | Sicherer et al. [7] [PC] | Spain | 16 | 12 | Unknown | 63 | – | – | – |
| Jarvinen-Seppo et al. [27] | Yes | Retrospective | Sicherer et al. [7] | USA | 76 | 8 | Single allergy clinic | – | – | – | – |
| Sopo et al. [31<sup>a</sup>]<sup>2</sup> | Yes | Retrospective | Their own/Powell [34] | Italy | 66 | 7 | Three allergy clinic | 61 | 9 | 20 | 2 |
| Mehr et al. [29] | Yes | Retrospective | Sicherer et al. [7] | Australia | 35 | 16 | Single allergy clinic | 57 | 51 | – | 11 |
| Fogg et al. [24] | Yes | Prospective | Sicherer et al. [7] | USA | 19 | 1.5 | Single allergy clinic | 53 | 11 | – | – |
| Nowak-Wegrzyn et al. [9]<sup>b</sup> | Yes | Retrospective | Sicherer et al. [7] | USA | 44 | 5 | Two allergy clinic | 59 | 34 | 77 | – |
| Sicherer et al. [7] | Yes | Retrospective | Their own | USA | 20 | 6 | Single allergy clinic | 44 | 31<sup>c</sup> | 56<sup>c</sup> | 15 |
| Katz et al. [28]<sup>**</sup> | CM only | Prospective | Sicherer et al. [7] | Israel | 44 | 2 | One hospital | 52 | 7 [PC] | – | – |
| Nomura et al. [10]<sup>b</sup> | CM only | Retrospective | Powell [34] | Japan | 30 | 3 | Japanese database | 50 | – | – | – |
| Hwang et al. [33] | CM/soy only | Prospective | Powell [34] | Korea | 23 | 4 | One hospital | 70 | 0 | – | – |
| Fukui et al. [32]<sup>b</sup> | CM/soy/wheat/rice | Not stated | Powell [34] | Japan | 10 | 4 | One hospital | – | 10 | – | – |
| Chung et al. [19] | Not stated | Prospective | Sicherer et al. [7] | Korea | 28 | – | One hospital | – | – | – | – |
| Levy and Danon [22] | Solid food only | Retrospective | Their own | Israel | 6 | 6 | One hospital | 67 | – | – | – |
| Burks et al. [23] | CM/soy | Prospective | Their own | USA | 22 | 1.5 | One hospital | – | – | – | – |
| McDonald et al. [5]<sup>b</sup> | CM/soy | Prospective | Powell [34] | USA | 10 | – | One hospital | – | – | – | – |
| Powell [3]<sup>b</sup> | CM/soy | Retrospective | Their own | USA | 9 | – | One hospital | – | – | – | – |
| Gryboski [1]<sup>b</sup> | CM | Retrospective | None set | USA | 21 | 16 | One hospital | 90 | 14 | 62 | – |

CM, cow milk; FHx, family history; –, not available; PC, personal communication with corresponding author.

<sup>a</sup>IgE FA = IgE-mediated food allergy (that is positive ssIgE and IgE-mediated clinical reaction to a separate food protein not causing FPIES).

<sup>b</sup>In these series, chronic FPIES or a combination of cases of acute/chronic FPIES was reported.

<sup>c</sup>Data only available for infants with typical FPIES (n = 16).
A prospective, population-based case series on FPIES in Australia is being conducted through a national rare disease register: the Australian Paediatric Surveillance Unit (APSU). Australian general and subspecialist pediatricians (e.g. allergists, gastroenterologists, others) report new cases of FPIES on a monthly basis. Preliminary information from the first 12 months of the study (January–December 2012) is available in abstract form [25]. The incidence of FPIES to all food triggers was one in 10,000 infants less than 2 years of age, which closely corresponds to the Australian reported incidence of eosinophilic esophagitis in children of 0.9 per 10,000 [36]. Although approximately 1400 pediatricians report on a monthly basis to the APSU, this incidence is likely to be an underestimate. Not all pediatricians report to the APSU; reporting of cases is voluntary and some cases may never be referred to a pediatrician or may remain undiagnosed.

An international classification of diseases code for FPIES will be introduced in 2015. This will assist in the study of FPIES presentations to hospitals. However, almost half of cases of FPIES do not attend a hospital and misdiagnosis of FPIES is frequent in emergency departments [29]. Miscoding of cases will invariably occur. Nevertheless, the code will give future studies the ability to link population-based data with emergency presentations to improve case ascertainment.

### Gender and Age of Onset
Most case series report only a slight male predominance (50–60%; Table 1). FPIES reactions to the offending food protein in breast milk are rare [10,37,38], suggesting direct oral ingestion of larger quantities of food proteins are required to cause a reaction in the majority of individuals. The age of onset of FPIES, therefore, appears to be influenced by when food proteins are directly introduced into an infant’s diet.

Chronic FPIES is essentially a disorder of newborns following the introduction and repeated exposure to cow milk or soy protein formulas. The median age of onset of chronic cow milk enterocolitis reported by Powell [3] and Gryobksi [1] was 1 week (range 4 days–3 weeks) to 4 weeks (range 3 days–4 months), respectively.

Acute FPIES often presents in infants between 4 and 6 months of age, and in approximately 75% of cases reactions occur after their first or second known ingestion of the causative food [29]. This 4–6-month window of peak presentations corresponds to the age when solids are most commonly

### Table 2. Onset of food protein-induced enterocolitis syndrome in months.

| Study                        | All triggers | Cow milk and soy | Solids | Individual solids |
|------------------------------|--------------|------------------|--------|------------------|
| Ruffner et al. [30*] (USA)   | –            | 7 (0.7)          | 12.1 (1.1) | Rice 7.4 (5.1)     |
|                              |              |                  |        | Oats 9.3 (6.2)     |
|                              |              |                  |        | Egg 11.3 (9.6)     |
|                              |              |                  |        | Wheat 11.9 (9.5)    |
|                              |              |                  |        | Chicken 17.6 (12.3) |
| Nowak-Wegrzyn et al. [9] (USA)| –            | 1 (2 days–12 months)* | 5.5 (3–7 months) | –                |
| Frith et al. [25] (Australia; unpublished data) | 6.2 (3.4) | 3.8 (2.6) | 7.5 (3.3) | Rice 6.3 (3.3) |
|                              |              |                  |        | Chicken 6.7 (1.3)  |
|                              |              |                  |        | Oats 7.1 (1.4)     |
|                              |              |                  |        | Wheat 7.5 (0.7)    |
|                              |              |                  |        | Fruits 7.8 (3.0)   |
|                              |              |                  |        | Vegetables 9 (2.8) |
|                              |              |                  |        | Egg 8.4 (2.1)      |
| Mehr et al. [29] (Australia) | 5.6 (2.7)    | 4.9 (2.6)        | 6.1 (1.7) | Rice 5.2 (0.8)*    |
|                              |              |                  |        | Oat 5.7 (1)        |
| Sopo et al. [31*] (Italy)    | 5.7 (5.1)    | 3.5 (2.4)*       | 10.6 (6.7) | –                 |

* Data presented from studies in which age of onset recorded and triggers included to cow milk, soy and solid foods. Data presented as either mean onset of age (standard deviation) or median onset of age (age range).
* Data for other solid foods not presented as <3 cases per solid food.
* Data for other solid foods not presented as <3 cases per solid food.
* Figure relates to cow milk FPIES only. The authors included three children with soy FPIES with other foods.
introduced [39]. Not surprisingly, those with cow milk and soy FPIES present earlier than those with solid food FPIES (Table 2), given such formulas are introduced earlier than solids. Infants with acute FPIES to rice/oats present at a younger age compared with those with FPIES to wheat, fish or egg (Table 2). This again likely reflects feeding practices, with rice cereals being among the commonest weaning foods in westernized countries, such as Australia and the USA, whereas foods such as wheat, fish and eggs tend to be introduced later [40–42]. Based on recent data, chicken FPIES occurred earlier in an Australian study compared with a large USA case series (Table 2). Chicken is recommended in Australian feeding guidelines to be tried as one of the first solid foods [43], whereas in one USA study [40], only 28% of infants had eaten chicken by 6 months of age.

Although FPIES is recognized primarily as a pediatric condition, a case of adult-onset FPIES has been reported to molluscs [44]. It is likely other cases of adult-onset FPIES exist, but have not been reported.

**ATOPY**

FPIES is pathophysiologically a non-IgE-mediated disorder, but atopic disease and a family history of atopy are frequently present (Table 1). Eczema is the most common atopic disorder at diagnosis. Rates of eczema and family history of atopy vary between studies, with higher rates often reported in studies from the USA and Australia compared with those from Israel and Italy (Table 1). Asthma, allergic rhinitis and eosinophilic esophagitis are less frequent, most likely reflecting the later onset of these conditions [29,30*].

Coexistent IgE-mediated food allergies have also been reported in some series (2–15% cases; Table 1). Unlike the phenomenon described by Sicherer et al. [7], in which infants with atypical FPIES have IgE sensitization to the triggering food, in these cases infants have FPIES to one food (e.g. rice) but IgE sensitization and a history of immediate IgE reaction to a separate food (e.g. cow milk) [29]. This combination of non-IgE gut allergy and

![Figure 1](https://www.co-allergy.com/V14N3/Figure1.png)

**FIGURE 1.** Causative triggers of food protein-induced enterocolitis syndrome in infants (%). Data derived from case series from the USA [7,9,24,27,30*], Australia [25,29] and Italy/Spain [31*]. Only case series examining acute FPIES reactions to all foods included. Cases from Italy (n = 66) and Spain (n = 16) combined. Some children had FPIES to more than one food trigger. Rice was the commonest grain trigger (Australia 44%, USA 19% and Italy/Spain 4%), followed by oats (Australia 7%, USA 16% and Italy/Spain 0%).
IgE-mediated food allergy has also been recognized in children with eosinophilic esophagitis [45].

SIBLINGS
There have only been three reports of siblings with FPIES. All were twins (two sets of fraternal and one identical twins) [9,46]. In all cases, the twins reacted to the same food protein (soy in one set, cow milk in the other two). There are no reports of parents of affected infants having had childhood or adult-onset FPIES. This is in contrast to eosinophilic esophagitis, in which there is a strong familial association in both parents and siblings [47,48].

RISK FACTORS
Katz et al. [28**] reported those with cow milk FPIES were more likely to be delivered by cesarean section (C/S; relative risk 2, \( P = 0.0023 \)) than those born by vaginal delivery. The same authors reported Jewish mothers were more likely to have babies with FPIES than non-Jewish mothers; however, Jewish mothers were also more likely to have a C/S (personal communication, Katz). Delivery by C/S can disrupt microbiota composition, and such flora has been associated with eczema predisposition [49]. These findings by Katz et al. [28**] need to be confirmed by others, and stool microbiota studies in infants with FPIES are required. We speculate that intestinal microbiota colonization, modified by factors such as birth mode and feeding practices, may be important in promoting FPIES development. No other risk factors for FPIES have been studied or described, particularly other life-style changes associated with an altered gut microbiota milieu, such as antibiotic use or birth order.

TRIGGERS
Like IgE-mediated food allergy, the bulk of reactions in FPIES are caused by a restricted number of foods. The majority of FPIES reactions are caused by cow milk, soy, rice/oats and egg [7,9,24,25,29,30*,31^]. Cow milk and grains are among the commonest causes of acute FPIES; however, geographic differences exist (Fig. 1). Cow milk is the most frequent cause of FPIES in series from the USA [7,9,24,27,30^] and Italy/Spain [26,31^]. Soy is a common trigger in the USA but uncommon in Australia [25,29], Israel [28**] and Italy/Spain [26,31^] (Fig. 1). Combined soy and cow milk FPIES (Table 3) and FPIES to multiple food triggers (Fig. 2) are much more commonly reported in the USA than other countries.

Grains (and, in particular, rice) are the most common solid food triggers in both the USA

| Table 3. Infants with cow milk food protein-induced enterocolitis syndrome also reacting to soy protein |
|---------------------------------------------|
|                | Cow milk FPIES (n) | Combined cow milk and soy FPIES (n) | Percentage of cow milk FPIES reacting to soy |
| Australia      |                  |                                  |                                            |
| Frith et al. [25] | 25               | 2                              | 10                                          |
| Mehr et al. [29] | 7                | 0                              | 0                                           |
| Israel         |                  |                                  |                                            |
| Katz et al. [28**] | 44               | 0                              | 0                                           |
| Italy/Spain    |                  |                                  |                                            |
| Garcia and Jimenez Diaz [26] | 7               | 0                              | 0                                           |
| Sopo et al. [31^]  | 44               | 0                              | 0                                           |
| Korea          |                  |                                  |                                            |
| Hwang et al. [33] | 15               | 4                              | 21                                          |
| USA            |                  |                                  |                                            |
| Ruffner et al. [30^] | 310             | 135                            | 44                                          |
| Jarvinen-Seppo et al. [27] | 44           | 20                            | 45                                          |
| Fogg et al. [24]  | 13               | 9                              | 69                                          |
| Nowak-Wegrzyn et al. [9] | 29            | 15                            | 52                                          |
| Sicherer et al. [7] | 13              | 8                              | 62                                          |
| Burks et al. [23]  | 4                | 6                              | 60                                          |
| Powell [3]      | 8                | 5                              | 63                                          |
| Grybowski [1]   | 21               | 3                              | 14                                          |

Data included from studies examining FPIES to cow milk/soy. FPIES, food protein-induced enterocolitis syndrome.
and Australia [25,29], but in Australia rice is the most common FPIES trigger overall, causing more reactions than cow milk (Fig. 1). The frequency of other solid food triggers is similar between these two countries. In contrast, fish is the commonest cause of solid food FPIES in Italy/Spain [26,31], but relatively uncommon cause in the USA [7,9,24,27,30] and Australia [25,29] (Fig. 1).

This variation in FPIES triggers between countries may in part be due to differences in the rates of breast-feeding, frequency of cow milk/soy formula use, populations included in the case series, intestinal microbiota composition and when and what food proteins are introduced into an infant’s diet. Based on 2010 data [39], Australia had higher rates of breast-feeding initiation (96%), and continuation at 6 months (60%), compared with the 2010 USA breast-feeding data [50] (75% initiation and 43% continuation at 6 months). By 3 months of age, 46% of Australian infants had received a non-human milk formula, compared with 60% in the USA. As most cow milk FPIES occurs in infants less than 3 months of age, the higher rates of cow milk FPIES in the USA compared with Australia may in part be due to the combination of shorter duration of breast-feeding and more frequent use of cow milk formulas.

Soy formulas are also much more commonly used in the USA compared with Australia and Europe. In the USA, 10% of infants at 3 months of age had been fed soy formula [51]. In contrast, only 3% of Australian infants less than 24 months had ever been exposed to soy formulas/milks [39]. Australian [52] and European [53] feeding guidelines do not recommend the use of soy formula under 6 months, whereas American guidelines make no such restrictions [54].

Grain cereals, such as rice, are common weaning foods in both the USA and Australia, and fish is uncommonly introduced into the diets of young infants [40,51], but is commonly eaten by Italian infants [55]. Rice is the commonest weaning solid food in the United Kingdom, Japan and China [42,56], but whether FPIES to rice is common and a more frequent cause than other foods has not been studied.

Differences in dietary behaviors cannot completely explain regional differences in food triggers, highlighting a role for other factors. Rice is a common weaning food in Italy [56], and yet in the retrospective case series of Sopo et al. [31], rice constituted only 4% of cases of acute FPIES. Italy has similar rates of breast-feeding and formula use as Australia [55], but the frequency of cow milk FPIES is

FIGURE 2. Infants with food protein-induced enterocolitis syndrome to single or multiple different food triggers. Data derived from case series from the USA [7,9,24,27,30], Australia [25,29] and Italy/Spain [31]. Only case series examining acute FPIES reactions to all foods included. Cases from Italy (n = 66) and Spain (n = 16) combined.
similar to the USA. Katz et al. [28] exposed 40 of the 44 infants with cow milk FPIES to soy; however, none reacted. It is likely that the combination of genetic, coexistent atopic disease, intestinal microbiota, breast-feeding and dietary practices may all be important in influencing these regional differences.

CONCLUSION

FPIES can no longer be regarded as a rare disorder. Some aspects of its epidemiology are well documented, such as its occurrence predominantly in infants, slight male predominance, lack of sibling concordance and common food triggers. However, most of these data are derived from retrospective case note studies from allergy clinics and a different picture may emerge from population-based cohorts. The best way to understand the epidemiologically of FPIES is by the establishment of well designed population-based registries/studies. International collaboration is required to establish an agreed definition of FPIES, and this will allow sharing and direct comparison of country-specific data. These steps will improve the understanding of FPIES and will provide insights that are required for those who study, advocate for and manage patients with FPIES.

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None.

Conflicts of interest

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