



# Epidemiology of non-IgE-mediated food allergies: what can we learn from that?

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## Purpose of review

To underline the main characteristics of the non-Immunoglobulin E (IgE)-mediated food allergies (food protein-induced allergic proctocolitis food protein-induced enteropathy and food protein-induced enterocolitis syndrome), which are common diseases in primary care and in allergy and gastroenterology specialty practices evaluating children.

## Recent findings

Non-IgE-mediated food allergies comprise a spectrum of diseases with peculiar features affecting infants and young children. The most prominent features of these diseases are symptoms that affect mainly the gastrointestinal tract.

## Summary

It is of paramount importance to provide the clinicians with the tools for non-IgE-mediated food allergy recognition in clinical practice to avoid the misdiagnosis with unnecessary laboratory tests and detrimental treatments.

## Keywords

food protein-induced allergic proctocolitis, food protein-induced enterocolitis syndrome, food protein-induced enteropathy, non-IgE-mediated food allergy

## INTRODUCTION

The non-IgE-mediated food allergies include three different diseases: food protein-induced enterocolitis syndrome (FPIES) food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enteropathy (FPE) [1].

These three entities present with different symptoms and grades of severity based on the diverse gastrointestinal tract affected by each one [2<sup>\*\*\*</sup>]. These diseases are listed here in order of increasing severity: FPIAP affects the distal colon causing blood-streaked stools in thriving infants; FPE affects the small intestine and presents with chronic non-bloody diarrhea resulting in malabsorption symptoms such as steatorrhea, anemia, and hypoalbuminemia until failure to thrive (FTT); finally, FPIES may affect the entire gastrointestinal system and is characterized by repetitive emesis, which can cause metabolic acidosis and hypovolemic shock [2<sup>\*\*\*</sup>].

The non-IgE mediated food allergies share several common features but have different characteristics that distinguish them from each other.

The aim of this review is to underline the main characteristics of the non-IgE mediated food

allergies to provide the clinicians with the tools for their recognition in daily clinical practice to avoid misdiagnoses with unnecessary laboratory tests and detrimental treatments.

## FOOD PROTEIN-INDUCED ALLERGIC PROCTOCOLITIS

Among the non-IgE mediated food allergies, FPIAP is surely the most common, although the exact prevalence is not known. An Israeli birth cohort study found the overall prevalence of FPIAP to be 0.16% [3].

Conversely, a prospective observational study conducted in the USA found that the cumulative incidence in healthy newborns with pediatrician-diagnosed FPIAP and established evidence of

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## KEY POINTS

- Non-IgE mediated food allergies share several common features but also have different characteristics that distinguish them from each other.
- The most prominent features of non-IgE mediated food allergies are gastrointestinal symptoms.
- There is a gradient of symptom severity of non-IgE mediated food allergies: FPIAP represents the milder one, whereas FPIES represents the more severe expression of this spectrum.
- FPIAP remains a benign and self-resolving common cause of rectal bleeding in infants, whereas FPIES appears to be on the rise, and FPE seems to be decreasing in incidence.
- It is of paramount importance that the clinicians know in detail the distinctive clinical manifestations of these diseases to avoid misdiagnosis and unnecessary elimination diets.

gastrointestinal bleeding was 17% [4<sup>22</sup>]. The overdiagnosis of FPIAP in the latter study may be due to a lack of confirmatory OFC after a period of observing a culprit-food elimination diet.

FPIAP has been found to be the major cause (up to 60% of cases) of visible rectal bleeding in infants [5,6].

FPIAP represents the milder end of the non-IgE-mediated food allergy spectrum [2<sup>22</sup>]. It typically occurs in otherwise healthy, thriving infants who have visibly blood-streaked stools with mucus [7–9].

FPIAP generally presents within days from birth and up to 6 months of age, although it has also been described in older children [7,9,10].

Symptoms usually develop gradually over time, although sometimes they can occur acutely (<12 h) after the introduction of the trigger food [11].

In breast-fed infants with FPIAP, the most common trigger foods are cow's milk (CM) and soy, although other causative foods such as egg, corn, meat, fish, apple, carrot, wheat, and sesame in the maternal diet have also been described [12].

Although the exact pathogenesis of FPIAP is unknown, it is believed to be the result of the immune response to protein allergens ingested by the mother, which passed through the breast milk to the infant [11].

In formula-fed infants, FPIAP is generally caused by CM and soy; furthermore, extensively hydrolyzed formulas have been described as the cause of FPIAP in up to 10% of infants [11].

Recently, Sopo *et al.* have proposed a management algorithm in which the decision to pursue an

elimination diet is based on the duration of hemochezia (less or higher than 1 month) [13<sup>23</sup>].

It is of paramount importance to reintroduce the suspected culprit food at home after 4–8 weeks of its elimination from a diet to confirm the diagnosis [7]: the resolution of symptoms is noted within a few days from the start of the elimination diet, and the symptoms' prompt recurrence appears once the culprit food is re-introduced [7,11,14,15].

A skin prick test (SPT) and serum food-specific IgE (s-IgE) applied to the culprit food are typically negative [16], even though atopic diseases affect up to 40–50% of patients with FPIAP [4<sup>22</sup>] whereas a positive family history of atopy is present in up to 60% of infants [17].

## FOOD PROTEIN-INDUCED ENTEROPATHY

FPE is a rare syndrome with an unknown prevalence; however, the incidence seems to be decreasing over time [14,18]. This trend is probably due to the increase in breastfeeding practice since FPE is frequently reported in formula-fed infants [15] and cases involving the use of lower-protein-content adapted formulas [18].

In FPE, the structural damage of the small intestine seems to be the result of food-specific T cell infiltration, eosinophils, and localized production of IgE, causing malabsorption [7].

The most common trigger foods are CM and soy, although other culprit solid foods include rice, egg, poultry, fish, and shellfish [18,19].

In the last decades, increasing attention has been focused on the microbiome to suggest a possible role in the pathogenesis of non-IgE mediated food allergy [20<sup>24</sup>].

In one study, it was described that *Bacteroides* and *Alistipes* (genera Bacteroidetes) and *Sarcina* (genera Firmicutes) were present significantly in CM-FPE when compared with the healthy controls [21].

In another recent study, a significantly higher presence of some members of the Clostridiales order (Coriobacteriaceae family) was found in allergic infants [22].

Another study found that Corinobacteriaceae (mainly *Collinsella* genus) were present in higher rates in infants with CM-FPE [23]. In that study, the main difference between CM-FPE infants and the healthy group was the reduction of *Bacteroides* (family Bacteroidaceae) in infants with CM-FPE after the restricted diet period.

The symptoms appear within weeks from the introduction of CM formula, usually within nine months of life, typically in the first two months [7,15].

Clinical manifestations of FPE combined with the resolution of symptoms within several weeks under an elimination diet or switching to an elemental formula are used in the diagnosis of FPE [24]. The reintroduction of the culprit food can be performed at home after 4–8 weeks of elimination diet [7]. SPT and s-IgE for the culprit food are not useful in diagnosis [16].

The prognosis is mostly favorable with a resolution by 1–2 years of age [25,26], although in some cases, the FPE may be more persistent, independently from the culprit food [27–29].

## FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

FPIES is the most severe disease of non-IgE-mediated food allergies [2<sup>°</sup>].

FPIES generally affects the whole gastrointestinal system, presenting with delayed, repetitive emesis, diarrhea, lethargy, pallor, and hypothermia up to hypovolemic shock in severe acute FPIES [30–34], whereas in chronic FPIES, the main symptoms are watery diarrhea (occasionally with mucus and/or blood) as well as intermittent but progressive vomiting and FTT. Occasionally, symptoms may progressively get worse also in chronic FPIES, leading to dehydration and metabolic acidosis [32, 35,36].

The exact FPIES prevalence and incidences are unknown for several reasons. First of all, although this entity was described for the first time in 1967 by Gryboski [37], FPIES received a specific diagnostic code (K52.2) in October 2015 by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

Second, the pathogenesis is still obscure, and no biomarkers are available for diagnosis [38<sup>°</sup>].

Moreover, although a diagnosis of FPIES is based on clinical history, the gold standard to confirm the diagnosis remains a supervised OFC, which is a time-consuming and risky procedure [39<sup>°</sup>].

Finally, the misdiagnosis of FPIES with other common pediatric illnesses like gastroenteritis or sepsis is typical [40]. For all these reasons, epidemiologic studies on FPIES are not easy to conduct.

However, FPIES should not be considered a rare disease, as previously believed [41]. Comparable cumulative incidences of CM-FPIES in children during the first 2–3 years of life has been found by two studies conducted in Israel and Spain: 0.34% and 0.35%, respectively [42,43<sup>°</sup>], although an Australian study reported an incidence of 0.015% cases per year in children younger than 2 years [44]. The lower incidence of the latter study may be because it relied on voluntary reporting by pediatricians and only acute FPIES is included. For this reason, FPIES incidences may have been underestimated.

Moreover, the latest prevalence study has estimated that 0.51% of children in the United States are reported as having FPIES [45<sup>°</sup>].

The main studies on FPIES incidences and prevalence are summarized in Table 1 [42,43<sup>°</sup>,44,45<sup>°</sup>, 46,47<sup>°</sup>,48].

It has been observed that males are affected slightly more than females [32].

Population-based studies have demonstrated some environmental risk factors associated with the development of FPIES: in particular, Katz *et al.* have found that Israeli Jewish ethnicity and births by cesarean section were associated with the development of FPIES [42]. It is hypothesized that the microbiome may have been disrupted by the cesarean section, predisposing the infant to the development of FPIES; however, more studies on stool microbiota in infants with FPIES are necessary to confirm these findings. Furthermore, it is possible that intestinal microbiota could be influenced not only by the birth mode (vaginal versus cesarean section) but also by the maternal use of antibiotics during pregnancy and by infant consumption of antibiotics.

Boyer *et al.* demonstrated that the stools of FPIES infants had significantly more Proteobacteria and

**Table 1.** Reported incidence or prevalence of food protein-induced enterocolitis syndrome in the general population

| Authors [Reference]                            | Studied population | Incidence (I) or Prevalence (P) |
|------------------------------------------------|--------------------|---------------------------------|
| Katz <i>et al.</i> [42]                        | Israeli infants    | I = 0.34% (CM-FPIES)            |
| Mehr <i>et al.</i> [44]                        | Australian infants | I = 15.4/100.000/year           |
| Alonso <i>et al.</i> [43 <sup>°</sup> ]        | Spanish infants    | I = 0.7%<br>I = 0.35 (CM-FPIES) |
| Nowak-Węgrzyn <i>et al.</i> [45 <sup>°</sup> ] | US children        | P = 0.51%                       |
| Ruffner <i>et al.</i> [47 <sup>°</sup> ]       | US children        | I = 0.14%                       |
| Ludman <i>et al.</i> [48]                      | UK infants         | I = 0.36%                       |
| Xepapadaki <i>et al.</i> [46]                  | Greek infants      | P = 0.47%                       |

Porphyromonadaceae than the stools of allergic-free infants that had more *Prevotella* [49].

Up to 40–60% of FPIES patients [30,50,51<sup>¶</sup>] present co-atopic diseases such as IgE-mediated food allergy, eczema, asthma, allergic rhinitis, and recently, eosinophilic esophagitis [32,44,45<sup>¶¶</sup>,47<sup>¶¶</sup>,52–54,55<sup>¶</sup>,56].

Although a family history of atopy is present in 80% of first-degree relatives [32,44], siblings with FPIES have been reported rarely, and FPIES may be more common in twins [42].

Interestingly, FPIES has been reported in patients with Down syndrome. In these children, the disease course is more protracted [57], and it is probably due to the immune dysregulation seen in children with trisomy 21 [58], which includes reduced levels of IL-10 (cytokine associated with tolerance development) and increased expression of TNF  $\alpha$  (responsible for increased gut permeability), two key cytokines implicated in FPIES pathogenesis [59,60].

FPIES to liquid food (CM and soy milk) usually present within the first weeks or months of life, whereas FPIES to solid food presents later, at 4–7 months of age, when the complementary foods are introduced in the infant's diet [31]. Rarely does FPIES occur in adulthood; it is usually triggered by seafood [61–64].

CM is the most common FPIES-trigger food around the world [42,52,65–67], with the exception of Australia [44] and the Southwest USA [55<sup>¶</sup>], where rice is the major culprit food and Spain, where fish is the main one [68,69].

In the majority of cases (up to 80%), children experience FPIES to a single food. Nonetheless, ~25% of children may react to two foods, and less than 10% react to three or more foods [32].

The pathogenesis of FPIES remains unclear. FPIES reactions are associated with systemic immune activation with increased neutrophils, decreased T cells and eosinophils, activated monocytes and natural killer T cells, increased cytokine, and increased C-reactive protein [70–74]. Nonetheless, the exact mechanism of activation to a specific food remains unknown.

Although the SPT and s-IgE to the trigger food are typically negative in patients with FPIES, up to 20% of patients could have detectable IgE to the trigger foods at the initial evaluation (atypical FPIES) [32,50,52].

As said, the diagnosis of FPIES is mainly based on clinical history; however, in cases where the history is less clear or not all the diagnostic criteria are satisfied, the gold standard to diagnose acute FPIES still remains the OFC [31,75<sup>¶</sup>].

For chronic FPIES, since well-defined criteria do not exist, an OFC with the culprit food after a period

of its elimination is mandatory to confirm the diagnosis with the occurrence of acute symptoms [31].

Furthermore, the OFC is the only way to validate whether or not the acquisition of tolerance has been reached; it is generally performed at least 12–18 months from the most recent reaction [31].

The OFC should be conducted under medical supervision for prompt therapeutic support [31]. So far, despite the 2017 consensus, different OFC protocols are still debated.

The management of FPIES consists of avoiding the suspected culprit food [31] and treating the acute symptoms with fluid rehydration along with the possible administration of ondansetron and/or methylprednisolone [31].

Commonly, FPIES has a good prognosis with the acquisition of tolerance at a young age, although differences have been found in different countries and for different culprit foods; for example, in Israel [42], 90% of children tolerated CM by the age of 3 years, which is very similar to Australia [76] (88% by the age of 3 years). In South Korea [67], patients with CM-FPIES reached the tolerance earlier (27.3% by 6 months of age and 100% by 2 years); in contrast, in a study from the USA [32], the median age of tolerance development to CM was higher (53% by 5 years of age), whereas in Italy [52], it was 63% by 24 months of age. FPIES to fish and egg have been considered more persistent in the USA [32] and Australia [76]. In Spain, most children with FPIES to fish develop tolerance later (75% by 5 years of age) than those with FPIES to CM (50% by 29 months of age) [69].

## CONCLUSIONS

The non-IgE-mediated food allergies comprise a spectrum of diseases with similar and different features (highlighted in Table 2) affecting infants and young children.

The most prominent features of these diseases are symptoms that affect the gastrointestinal tract.

There is a gradient of symptom severity of non-IgE-mediated food allergies: FPIAP represents the milder one, whereas FPIES represents the more severe expression of this spectrum of diseases; in fact, it is the only one that could present itself in an acute form.

FPIAP remains a benign and self-resolving common cause of rectal bleeding in infants whereas FPIES appears to be on the rise and FPE seems to be decreasing in incidence.

Non-IgE mediated food allergies share several common features: the age of onset, typically in infancy; the gastrointestinal symptoms, without the involvement of cutaneous and respiratory

**Table 2.** Comparison of non-IgE mediated food allergies (Created using data from Refs. [2<sup>22</sup>,77])

|                                         | <b>FPIAP</b>                                                                 | <b>FPE</b>                                                                                       | <b>FPIES</b>                                                                                                                                                                                                                               |
|-----------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Typical age of onset                    | 1 day-6 months                                                               | 2–24 months (occasionally in older children)                                                     | 1 day to 1 year                                                                                                                                                                                                                            |
| Gender (more affected)                  | Not known                                                                    | Not known                                                                                        | Male                                                                                                                                                                                                                                       |
| Risk factors                            | Not know                                                                     | Not know                                                                                         | Israeli Jewish ethnicity<br>Cesarean section                                                                                                                                                                                               |
| Culprit foods                           | Cow's milk, soy (main)<br>egg, corn, wheat                                   | Cow's milk, soy (main)<br>wheat, egg                                                             | Cow's milk, soy, rice (main)<br>Fish, poultry, fruits, vegetable                                                                                                                                                                           |
| Multiple foods                          | Occasional                                                                   | Rare                                                                                             | Frequent                                                                                                                                                                                                                                   |
| Co-atopy morbidity                      | 40–50%<br>Familiar history: up to 60%                                        | 20–40%                                                                                           | 40–60%<br>Familiar history: up to 80%                                                                                                                                                                                                      |
| Feeding at the onset                    | >50% exclusively<br>breastfed                                                | Formula                                                                                          | Formula                                                                                                                                                                                                                                    |
| Main clinical presentation              | Blood/mucus streaked<br>stools, mild diarrhoea in<br>well appearing infants  | Diarrhoea (rare bloody<br>stools), intermittent<br>vomiting, failure to<br>thrive, malabsorption | Acute: delayed, repetitive emesis,<br>diarrhoea, dehydration, lethargy,<br>pallor, hypothermia, (shock: 15%)<br>Chronic: intermittent but progressive<br>emesis, watery diarrhoea (occasionally<br>with blood or mucus), failure to thrive |
| Allergy evaluation                      | Negative (not<br>recommended)                                                | Negative (not<br>recommended)                                                                    | Negative; positive in 20% of patients<br>(atypical FPIES)                                                                                                                                                                                  |
| Diagnosis                               | Clinical history $\pm$ OFC                                                   | Clinical history $\pm$ OFC                                                                       | Clinical history $\pm$ OFC                                                                                                                                                                                                                 |
| OFC protocol                            | does not exist                                                               | does not exist                                                                                   | administering the culprit food at a dose<br>of 0.06–0.6 g per kilogram of body<br>weight in 3 equal doses over 30 min<br>followed by a 4–6-h observation.                                                                                  |
| Treatment                               | Avoidance of offending<br>foods (maternal<br>exclusion diet if<br>breastfed) | Avoidance of offending<br>foods                                                                  | Avoidance of offending foods<br>In case of acute reaction:<br>fluids $\pm$ antiemetic $\pm$ corticosteroids                                                                                                                                |
| Time to improvement                     | 72 h (up to 2 weeks)                                                         | Several weeks                                                                                    | 4–12 h (<24 h)                                                                                                                                                                                                                             |
| Re-introduction of culprit food setting | Home                                                                         | Home                                                                                             | Under medical supervision (inpatient or<br>outpatient setting)                                                                                                                                                                             |
| Typical age of resolution               | 1–2 years                                                                    | 1–3 years                                                                                        | >3 years                                                                                                                                                                                                                                   |

FPE, food protein enteropathy; FPIAP, food protein-allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; OFC, oral food challenge.

systems; the negativity of SPT and s-IgE; CM and soy as culprit foods; the co-atopy morbidity; a good prognosis, with recovery usually in early childhood; the resolution of symptoms with the elimination of the offending foods from the diet; and the recurrence of symptomatology with their reintroduction [77].

Nevertheless, these allergies have different distinguishing characteristics: FPIAP is more common in breastfeeding infants whereas FPE and FPIES usually occur in formula-fed infants; FPIES occurs more often in males whereas, in FPIAP and FPE, a more affected gender is not described; FPIES can rarely occur in adults whereas FPIAP and FPE are described merely in childhood and a small percentage of FPIES-affected infants could have positive s-IgE whereas the s-IgE is always undetectable in

FPIAP- and FPE-affected infants. Moreover, it is suggested that the reintroduction of the culprit food is performed in a hospital setting with a well-defined protocol for FPIES; for FPIAP and FPE, this could be performed at home, but there are no detailed protocols described in the literature. Lastly, solid food and atypical FPIES can persist later on in childhood, whereas the resolution of FPE and FPIAP usually occurs within 2 years of age [2<sup>22</sup>].

It is of paramount importance that clinicians know in detail the distinctive clinical manifestations of these diseases to avoid misdiagnosis and unnecessary elimination of food from the diet.

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