



Nutritional management of food protein-induced enterocolitis syndrome

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Purpose of review

To summarize the latest information on the nutritional management of food protein-induced enterocolitis syndrome (FPIES), focusing on the foods implicated and how to avoid these whilst maintaining a nutritionally sound diet.

Recent findings

A number of foods are implicated in FPIES such as milk, soy and grains, particularly rice. The number of foods implicated in FPIES per individual differs, but the majority of reported cases have two or fewer food triggers involved.

Summary

FPIES is a complex presentation of non-IgE-mediated food allergy. Dietary management is complicated as both common food allergens as well as atypical food allergens can trigger FPIES. Sound nutritional advice is required to ensure appropriate food avoidance, adequate consumption of other foods and sufficient nutritional intake to maintain and ensure growth and development.

Keywords

cow's milk, food allergens, food protein-induced enterocolitis syndrome, non-IgE-mediated food allergy, nutritional management

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is an uncommon and potentially severe non-IgE-mediated food allergy. Usual symptoms include vomiting, diarrhoea, lethargy and, in some cases, hypovolemic shock and metabolic acidosis. It is often caused by cow's milk or soy proteins, but may also be triggered by the ingestion of other solid foods, particularly grains. The diagnosis is made on the basis of a clinical history, reported symptoms and a food challenge when appropriate.

Management of FPIES is divided into two stages. During the acute phase, fluids and intravenous steroids are used as required and discussed by Miceli Sopo *et al.* [1] in this edition. During the maintenance phase, the treatment and management strategy is avoidance of the culprit food(s). Dietary management of food protein enterocolitis also requires advice on the intake of suitable foods to ensure sufficient nutritional intake, growth and development. Development of tolerance should be considered as discussed by Katz [2] in this edition to prevent unnecessary avoidance of foods. Finally, FPIES presents a number of unique and complex dietary issues, which in most cases will require the input of a dietitian.

APPROPRIATE FOOD AVOIDANCE

Appropriate food avoidance includes knowledge of the allergens involved and the information required for appropriate allergen avoidance.

The food allergens involved

The European Union considers cereals containing wheat and gluten, shellfish, eggs, fish, peanuts and tree nuts, cow's milk, celery, mustard, sesame seeds (*Sesamum indicum*), mollusks, soy, lupine (*Lupinus spp.*) and sulphite as the most common food allergens [3]. In the USA, the main food allergens as identified by the Food and Drug Administration

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KEY POINTS

- Dietary management of FPIES is complicated by the fact that both typical and atypical allergenic foods are involved.
- The role of the dietitian to ensure adequate nutritional intake is crucial.
- Dietary management of FPIES includes advice on foods that should be avoided, safe foods that can be consumed, assessment of nutritional intake as well as assessment of growth and development.

are milk, eggs, fish (e.g. bass, flounder and cod), crustacean shellfish (e.g. crab, lobster and shrimp), tree nuts (e.g. almonds, walnuts and pecans), peanuts, wheat and soy [4].

One of the dietary challenges of dealing with FPIES is that although many infants and children present with FPIES to milk or soy, fish, egg and to a lesser extent to wheat, many infants and children will also react to foods commonly assumed to be low allergenic foods such as rice, oats, meat, fruit and vegetables (see Table 1 [5–17,18^{***},19–31] for a summary of foods reported to cause FPIES in children).

Very little information is available on foods implicated in FPIES in adults. Only one case study has been published by Fernandes *et al.* [32], confirming the previous suggestions of the role of seafood in adult FPIES [33].

Information on food allergen avoidance

Healthcare professionals should give patients and carers clear guidance about food avoidance to prevent both unnecessary restrictions and accidental exposure to allergens. Information about which foods to avoid can be obtained from qualified dietitians and credible patient groups such as UK-based (www.allergyuk.org, www.anaphylaxis.org.uk) or USA-based (www.foodallergy.org). Table 2 [34] contains information about foods commonly implicated in FPIES and the nutrients they contain.

Food allergen avoidance advice should ideally be provided by a dietitian [35] and include a discussion on understanding food labels and prevention of cross-contamination, and lifestyle issues such as time taken to shop and eating away from home [34].

ENSURING SUFFICIENT NUTRITIONAL INTAKE

The effect of any avoidance diet on nutritional intake will be influenced by the frequency of

consumption of the food, dependency on commercially available food, parental resources and cooking skills. Additional food avoidance not related to any allergic disease, for example, religious reasons, the number of allergens avoided, the period of elimination required and the nutrient content of the foods being avoided will also have an effect [34,36^{***}]. The nutritional content of the main foods implicated in FPIES is listed in Table 2 [34].

Of particular importance for FPIES is the number of foods involved, the role of breastfeeding, suitable formula choice, level or degree of food avoidance and appropriate weaning advice.

The number of foods involved

Globally, there are slight differences in the number of foods that are causing FPIES in an individual child. Katz *et al.* [30] report that in 44 Israeli children with FPIES triggered by cow's milk, none of the children was reacting to other foods, including soy. A number of other studies, however, indicated that more than one food is implicated in FPIES in an individual child [5,9,12]. Mehr *et al.* [28] reported that in 35 children from Australia, 17% reacted to more than 1 food, but no child reacted to both soy and cow's milk. In a multicentre trial conducted by Sopo *et al.* [18^{***}], the authors showed that 15% of children ($n=66$) reacted to more than one food, and once again, none of the children reacted to both cow's milk and soy.

In contrast, Nowak-Wegrzyn *et al.* [11] reported from the USA that 80% of children with FPIES reacted to more than one food and 65% presented with FPIES to both soy and cow's milk. Fogg *et al.* [9] found that 1 of 19 (22%) children had FPIES triggered by cow's milk and soy.

FPIES triggered by rice seems to co-exist with cow's milk [9,11,18^{***}], soy [9,11], oats [9,11,28], sweet potato and banana [28] as well as other foods [11].

Some children with FPIES may have IgE-mediated disease concomitantly with other foods [18^{***},28], although seen in less than 10–15% of cases.

The more foods that need to be avoided, the more the nutritional quality of the diet is affected. Data ($n=97$) from 13 different dietitians across the UK from two primary, eight secondary and three tertiary centres in the UK was published by Meyer *et al.* [37]. Forty-five children were classified as having IgE-mediated, 29 had non-IgE-mediated and 23 had mixed-type allergy. Sixty-six children excluded two or fewer foods and 31 excluded at least three foods from their diet. In this study, children with food allergies were more underweight and

Table 1. Foods most commonly implicated in food protein-induced enterocolitis syndrome

Number	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18 ¹⁰⁰]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	Total	
Country	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	USA	Italy	Italy	Italy	Italy	Italy	UK	Croatia	Belgium	Spain	Australia	Australia	Australia	Australia	Japan	Israel	Israel	Israel	
Date	2013	2012	2011	2011	2006	2004	2003	1998	1967	1978	1963	2013	2013	2012	2012	1996	2012	2006	1994	1982	2012	2013	2012	2009	2011	2011	2011	2003	
Milk	1				6	2	1	10	1	1	1	1	1	1	44														165
Rice	1				2	1	1	1	1	1	1	3	3	3	4	1	1	5	1	1	1	20	14	14	14				64
Soy	1				3	8	8	11	9	9	1	1	3	3								5	1	12	12			54	
Oats					1	9	9															7	2	2	2			19	
Fish												8	8	8	1	1	1	1	1	1	1							11	
Egg												4	4	4								4						10	
Chicken												2	2	2	1	1	1	1	1	2	1	1	2	2				13	
Sweet potato																												5	
Wheat												2	2	2	2	1	1	1	1	1	1							4	
Banana												2	2	2									1					3	
Pea																												4	
Barley																												2	
Corn																												2	
String bean																												2	
Turkey																												4	
Squash																												2	
Lamb																												1	
lentils																												1	
Orange juice																												1	
Tomato																												1	
Potato																												1	
Carrot																												1	
Goats milk																												1	

Table 2. Foods commonly implicated in food protein-induced enteropathy and their nutrients

Main foods implicated in FPIES	Common food sources	Nutrients
Milk	Butter/most fat spreads, cheese, cow/sheep/goat milk evaporated/condensed milk, cream, ghee, yoghurt, ice creams, custard, dairy desserts and manufactured foods using milk or butter in their ingredients	Protein, carbohydrate, fat, vitamin A, vitamin D, riboflavin, pantothenic acid, vitamin B12, calcium, magnesium, phosphate [34]
Soy	Soy sauce, soy products, meat substitutes, breads, vegetarian/vegan foods, processed meat, for example, hot dogs, foods labelled as 'diet' and 'high-protein'	Protein, thiamin, riboflavin, pyridoxine, folate, calcium, phosphorus, magnesium, iron, zinc, protein and fibre [34]
Egg	Egg white and yolk, cakes, biscuits, speciality breads and mayonnaise	Protein, riboflavin, biotin, protein, vitamin A, vitamin B12, vitamin D, vitamin E, pantothenic acid, selenium, iodine and folate [34]
Fish and seafood	All types of white and fatty fish, anchovy (Worcester sauce), aspic, caviar, surimi, Caesar salad, Gentleman's Relish, Kedgeree, fish sauce, paella, bouillabaisse and gumbo	All fish: protein, iodine
	Some people may tolerate canned fish	Fish bones: calcium, phosphorus and fluoride
	Fish oil capsules may cause reactions in highly sensitised individuals	Fatty fish: vitamins A and D, omega-3 fatty acids
	Crayfish, crab, lobster, shrimp, prawns	Shellfish and molluscs: zinc, selenium, copper, iron [34]
	Clams, mussels, oysters, octopus, squid, snails, scallop	
Grains: wheat/barley/oats	Bread, breakfast cereals, pasta, cakes, biscuits, crackers, cold cooked meat, pies, batter, flour, semolina, spelt, couscous, bottled sauces and gravies, barley water, soup, flapjacks or cereal bars, porridge	Carbohydrate, fibre, thiamine, riboflavin, niacin, calcium, iron and folate if fortified [34]
Rice	Rice-based dishes: Sushi, paella, curries, gumbo and risotto	Carbohydrate, calcium, iron, phosphorus, potassium, thiamine, riboflavin, niacin, folate and pantothenic acid
	Rice cereal	
	Rice pudding	
Chicken, turkey, lamb	Any meat containing dishes	Protein, (fat), selenium, phosphorus, potassium, zinc, iron Vitamin B6 and niacin
Sweet potato	Sweet potato and dishes containing sweet potato such as curries or vegetarian meals	Beta-carotene (vitamin A), pantothenic acid, thiamine, niacin, riboflavin, magnesium, manganese and potassium
Peas	Vegetarian meals	Folic acid, pantothenic acid, niacin, thiamine, pyridoxine, ascorbic acid, vitamin K, vitamin A, calcium, iron, copper, zinc and manganese

FPIES, food protein-induced enterocolitis syndrome.

stunted than the general population (as published by others) [38,39], which appears to be linked to the number of foods excluded.

In addition, avoidance of a large number of foods increases the likelihood of food refusal and aversions, which may have an additional impact on food intake, particularly in children [40].

The role of breastfeeding

Most breastfed infants with FPIES appear to tolerate breast milk from an unrestricted maternal diet [41]. Nowak-Wegrzyn *et al.* [11] reported that in their study, infants with FPIES did not seem to react to the allergens in breast milk. In addition, an Australian group [27] presented data on 34 mothers

of infants with FPIES. Of these 34 mothers, 21 lactating mothers were instructed to continue to eat the implicated food, in 7 cases it was unclear what advice was given, in 3 cases the infants were not being breastfed and in only 3 cases the mother was told to exclude the food trigger from her diet. Although they could not determine how many of the 21 mothers continued to eat the trigger food, no infant re-presented to their clinic with a history of breast-milk-induced FPIES.

Recent reports, however, question this observation. Tan *et al.* [27] presented a case of an infant reacting to soy protein after maternal consumption of a portion of soy ice cream. Previous maternal consumption of smaller amounts of soy in foods did not, however, lead to FPIES in the infant. Very interestingly, Monti *et al.* [42] reported on an infant who was reacting to maternal consumption of a dish of pasta with a sauce containing butter and cream. This questions the use of milk-containing foods in a small minority of breastfed infants with FPIES triggered by cow's milk.

Mane *et al.* [5] reported a case of an infant reacting to trace amounts of rice protein after the infants licked a wrapper that covered a rice cracker. In view of this reaction to 'trace' amounts of rice protein, this mother was subsequently asked by the authors to avoid rice from her diet, despite no previous obvious reacting of the infant to rice protein in breast milk.

For now, however, routine avoidance of the allergenic food by the breastfeeding mother is not recommended for most infants with FPIES. This is in particular of relevance in those infants who did not present with FPIES whilst being breastfed, although the mother was consuming the allergenic food. If maternal avoidance of any food is, however, required, it should ideally be instructed with the help of a dietitian.

Choice of formula

The choice of formula when dealing with cow's milk allergy has been touched on by the food allergy guidelines published over the last few years as summarized by Venter *et al.* [43,44] in two publications. In brief, the United States (U.S.) National Institute of Allergic and Infectious diseases guidelines [35] recommend a hydrolyzed formula for the treatment of FPIES. The United Kingdom National Institute of Clinical Excellence (UK NICE) guidelines [45] made no recommendation on formula choice. The Australian Consensus guidelines [41] recommend the use of an extensively hydrolyzed formula for the treatment of FPIES. The Diagnosis and Rationale for Action against Cow's Milk Allergy

(DRACMA) guidelines [46] from the World Allergy Organisation (WAO) recommend the use of an extensively hydrolyzed formula, and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines [47] recommend the use of an amino-acid-based formula for the treatment of FPIES, particularly if in association with growth faltering. Although the choice of formula is a clinical decision, it is worth noting the use of extensively hydrolysed formula (eHF) is not suitable for the treatment of FPIES in all infants [48–50]. There is some limited evidence as well that some children may catch up on their growth sooner when placed on an amino acid formula [51,52].

On a more practical note, infants, particularly those who are breastfed, may initially refuse hypoallergenic formulas because of taste issues. Dietitians are ideally suited to give advice regarding this problem. Some suggestions may be to mix breast milk with the formula, gradually increasing the amount of formula whilst reducing the breast milk, adding flavouring to the formula (e.g. vanilla drops) or to use beakers or sippy cups in older infants. Another option is to use the formula in baking and cooking, and a dietitian can provide mothers with suitable recipes.

Level of avoidance

There is very little published data, but some anecdotal evidence that children with FPIES may tolerate baked forms (e.g. milk or egg) or smaller and trace amounts of the food they are allergic to. It is, however, also known that if the allergenic food is part of the regular diet, infants and children may present with chronic symptoms and although these chronic symptoms are usually less dramatic, they can develop to be more severe [53].

Being able to identify whether a particular food is causing these more chronic symptoms in the absence of severe or acute symptoms is one of the more challenging aspects of managing FPIES.

Another question that arises is 'Should children be allowed to eat cooked/baked/smaller amounts of a food that is implicated in their FPIES?' This is certainly not a standard of care at this time and there is no published evidence supporting such an approach. One empiric approach is that if a child is already tolerating baked milk or egg or small amounts of the offending food in their diet without any obvious symptoms and normal growth, these foods may be continued. However, in children with a history of severe reactions to small amounts of food, supervised food challenges are prudent to introduce the baked foods.

Weaning

The majority of children present with FPIES at weaning age (between 4 and 6 months) and often to first known introduction of the food, indicating ‘sensitization’ to the allergenic food protein via breast milk or during pregnancy. This fact, and the fact that many of the foods causing FPIES are considered to be atypical allergenic foods and usually first weaning foods, can complicate the weaning process and highlights the need for a dietitian to be involved.

Traditionally, mothers start weaning with baby rice, oats, corn-based porridge, fruit and vegetables, followed shortly by fromage frais and yoghurt [54]. Once finger foods are given, bread sticks or toast fingers with butter and soft cheese are also popular choices. These foods as well as other favourites like broccoli in a cheese sauce in the UK often cannot be given to infants with FPIES. First weaning foods do, however, differ across countries and cultures [55].

Very importantly, the variety of tastes and textures and the timely introduction of these directly affect or prevent fussy eating behaviour [56,57]. Food refusal is commonly seen during infancy. It is thought that 16.7% of 8-month-old and up to

18.8% of 12-month-old infants have severe aversive feeding behaviour [58]. These figures are even higher in children with non-IgE-mediated food allergies [59,60]. The food refusal may be related to the symptoms experienced to liquids or foods in the past or maternal fear of introducing new foods [61].

This poses a particular challenge when managing children with food allergies, for example, making sure that the allergenic foods are avoided whilst providing sufficient variety in the diet to prevent long-term food aversions, restriction of food choices and nutritional deficiencies. In the absence of clear guidance, it can be difficult to know which foods to introduce during weaning and in which order. The authors have provided a suggested ‘weaning guidance’ for infants with FPIES (Table 3), but clinical judgment and using sensible reasoning in dealing with each case should always be first priority.

ASSESSING AND MONITORING NUTRITIONAL INTAKE

A nutritional assessment can provide useful information that can be used as a baseline for monitoring

Table 3. Suggested weaning guide for infants with FPIES

	Stage 1 begin by 6 months, but not before 4 months (17 weeks)	Stage 2, 6–9 months	Stage 3, 9–12 months
Textures	Smooth purees moving on to mashed foods	Mashed foods with soft lumps	Minced and chopped foods
		Soft finger foods	Hard finger foods
Suggested suitable foods but may depend on each individual case	Vegetables: start with parsnip, pumpkin, broccoli (sweet potato, squash, tomato, carrot and string beans may be a problem) Fruit: any fruit (banana/orange may be a problem)	Vegetables and fruit – expand current selection	As stage 2 with increasing frequency and variety
	Grains: millet and quinoa (delay introduction of other grains if not already tolerating and allergic to a grain)	Grains: start with corn, followed by barley, oats and rice (if not a cause of FPIES)	
	Meat and alternatives: start with beef (lamb, chicken, turkey and fish may be problem)	Meat and alternatives: continue to expand current consumption (do not give chicken or fish if a cause of FPIES)	
	Pulses: start with beans (peas and lentils may be a problem)	Soy-based yoghurt and milky puddings may be introduced in some children after discussion with physician and not a cause of FPIES	
	Soy (delay the introduction of soy if not already tolerating and has a diagnosis of cow’s milk FPIES)		

FPIES, food protein-induced enterocolitis syndrome.

the nutritional status and the impact of the avoidance diet. For example, a young child with faltering growth related to multiple food allergies will require avoidance advice as well as advice on how to increase energy [62], protein and vitamin and mineral intake.

Parents are often concerned about the growth of their children, particularly if they suffer from gastrointestinal disease. The simplest way of monitoring nutritional deficiencies in children is to assess their growth using the nationally recognized growth charts. Measuring the growth of infants, toddlers and children plays two important roles: it can provide reassurance that the child is growing well, but it can also help to detect growth-related concerns.

Monitoring dietary intake

Growth alone, however, does not indicate sufficient dietary intake and assessment of dietary intake is of great importance.

A variety of measures can be used to determine dietary intake and may include 24-h recall, food frequency questionnaires and 3–7 day food diaries. All of these have their limitations and dietitians may use the most practical option or a variety of methods [63].

The nutritional analysis, coupled with biochemical markers, can give useful information on any nutritional supplements required. National guidance on nutritional supplementation differs and it is suggested to follow these guidelines and take into account the risk of developing nutritional deficiencies based on the food or foods being avoided (see Table 2 for common foods implicated in FPIES and their main nutrients).

It is particularly important to consider iron and vitamin D intake in infants who are breastfed only (i.e. no supplementation of an infant formula) whilst solid foods are being introduced [36[¶]]. Calcium may be a problem in some cases, but this will be highlighted during a dietary analysis.

DETERMINE THE DEVELOPMENT OF TOLERANCE

As many food allergies of early childhood resolve over time, regular assessment for the development of tolerance is required to avoid unnecessary dietary avoidance. It is recommended to wait 12–18 months [64] before a food is reintroduced. It is known that FPIES can present severely after a period of avoidance, typically occurring hours after ingestion [12]. It has also been found that FPIES may convert from a non-IgE-mediated form

to an IgE-mediated form [18^{¶¶},30] of food allergy. Therefore, the rate and order and where foods will be reintroduced after a period of avoidance should be discussed and performed under the supervision of the physician.

CONCLUSION

In summary, nutritional management of FPIES requires the identification of the offending allergen followed by appropriate avoidance and use of substitute food. Of particular importance is advice to breastfeeding mothers, choice of formula and weaning guidance. The nutritional status and dietary intake should be monitored and advice on added protein, kcal and micronutrients should be provided when required. It is important to regularly consider the resolution of FPIES in order to reintroduce the food into the diet, but this decision should be made in discussion with the overseeing physician.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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