REVIEW

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Natural history of food protein-induced enterocolitis syndrome

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Purpose of review
Because of the paucity of reports and variability in the diagnostic criteria utilized, little is known regarding the natural outcome of patients with food protein-induced enterocolitis syndrome (FPIES). Data extracted from referenced manuscripts, as well as allergists' unpublished observations from across the globe, were used to form a cohesive opinion regarding its natural outcome.

Recent findings
All authors concur that there is a generally high rate of recovery for FPIES. The most common foods causing FPIES are milk and soy. Depending upon which study is analyzed, by the age of 3–5 years, approximately 90% of patients recover from their disease. Recovery from FPIES to solid foods, occurs at a later age, but may reflect a later stage of introduction of the food into the diet. An important clinical outcome, although not common, is a shift from FPIES food hypersensitivity to an IgE-mediated food allergy. This necessitates a change in the oral food challenge protocol, if IgE-mediated sensitization is detected.

Summary
Over the past several years, there has been an increasing awareness of FPIES. This knowledge should lead to a more timely diagnosis and should reassure parents and practitioners alike regarding its favorable course.

Keywords
food hypersensitivity, food protein-induced enterocolitis syndrome, repetitive vomiting

INTRODUCTION

The first published descriptions of the food protein-induced enterocolitis syndrome (FPIES) were reported by Rubin [1] and Gryboski [2] respectively. It was not only until 19 years later that diagnostic criteria were suggested for FPIES [3]. These criteria were subsequently modified by Sicherer [4]. Although there were disagreements, historically, regarding the diagnostic criteria [5,6], most authors currently agree on the definition of this disease [6,7▪,8▪▪,9,10▪▪].

In addition to the variable definitions of FPIES, the difficulty in establishing criteria for the disease was hindered by the paucity of reports. Recently, however, several sizable series have been reported from across the globe, including Korea [11], Australia [9], Israel [10▪▪], Italy [12▪] and a very large group from the United States [8▪▪]. These reports have enabled us to summarize the natural history of this syndrome.

CLINICAL MANIFESTATIONS

FPIES is a non-IgE mediated reaction to food, manifested primarily in the gastrointestinal system. For the purpose of this review, the definition of FPIES utilized is repetitive vomiting usually with lethargy or pallor that appears 30–240 min after the offending food. In addition, by definition, other IgE-mediated associated symptoms, such as rash, urticaria and respiratory symptoms are absent. These criteria were adopted by Ruffner *et al.* [8▪▪], and are in accordance with the two most recent reviews in the field [6,7▪]. Although some authors describe a condition defined as chronic FPIES [13–15], the literature regarding the outcome of this entity is almost nonexistent and as such we have not included this entity in our review.

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KEY POINTS

- Although most patients with FPIES recover by the age of 2–3 years, there are teenagers, however, in whom FPIES persists.
- Although initial inducing doses in FPIES are relatively large, with time, much smaller doses can elicit a reaction.
- In cases of FPIES, it is not uncommon to develop IgE-mediated food allergy.
- It is neither predictable, nor uncommon, for a patient with FPIES to develop additional sensitivities to multiple foods, leading to a more protracted outcome.

The most common reported foods to cause FPIES are cow's milk (Table 1) [4,8▪▪,9,10▪▪,11,12▪,13–25,26▪▪] and soy (Table 2) [4,8▪▪,11,12▪,14,16,18,27–30]. The exception is Australia in which the food most likely to elicit a FPIES reaction was rice (Table 3) [4,8▪▪,9,12▪,13,15,18,24,26▪▪,31–37]. It is unclear whether Australia is unique because of the particular feeding habits or for some other unknown reason. It is interesting to note, however, that in response to a survey, six out of eight of the cases reported from Singapore, a country where early rice feeding is common, were to milk, as well (E. Thame and B.H. Lee, personal communication). However, the list of foods causing FPIES continues to grow. Included are foods that commonly cause IgE-mediated food allergy, such as egg (Table 4) [8▪▪,12▪,18,26▪▪,38,39], peanut (Table 5) [8▪▪,26▪▪] and seafood (Table 6) [8▪▪,9,12▪,13,36,40,41]. But in addition, the list contains many foods that are not commonly reported to induce IgE-mediated reactions such as grains (Table 7) [8▪▪,9,12▪,16–18,26▪▪,36,42], fruits (Table 8) [8▪▪,9,12▪,40,43–45], vegetables and legumes (Table 9) [4,8▪▪,9,12▪,16,28,37,46,47] and poultry and meat (Table 10) [3,4,8▪▪,9,12▪,13,16,28,48].

LOW BUT INCREASING AWARENESS OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

The first manifestation of FPIES usually begins with the first or second introduction of the offending food [4,9,10▪▪,12▪,15,30,32]. Not uncommonly, however, it is only after repeated episodes that the actual diagnosis is finally made (see Tables 1–10 for the number of prediagnosis episodes). Until then, unfortunately, unnecessary procedures or medical treatments may be performed. For example, a sepsis work up was performed at many centers (A. Fiocchi, personal communication, 19–23, 49) ranging up to 28% [9] and 50% of cases [16]. Furthermore, up to 22% of cases had a surgical consultation [9]. The only population-based prospective study [10▪▪] estimated the incidence of milk FPIES as 0.34% of the newborn population. This compared with 0.5% for that described for IgE-mediated cow's milk protein (CMP) allergy, in the same population [10▪▪]. The results of a 1-year surveillance study [24] of FPIES in Australia, however, noted an incidence of 0.01%. The most likely explanation accounting for the differences in these two studies may relate to the low level of awareness and familiarity with this condition, among physicians at large. In fact, there were several regions of Australia in which there was not even a single report described (S. Mehr, personal communication). The low degree of awareness may be related to the lack of mortality in this disease and the high rate of spontaneous recovery. In addition, the challenge procedure is time consuming, as the reaction might be delayed up to 3–4 h after the last dose and may continue for up to 48 h [6,49]. This makes it difficult to carry out a FPIES oral food challenge (OFC) in an office-based or even a day care hospital setting. This limited availability of performing an OFC, coupled with the dramatic nature of the reaction lead to a tendency to postpone the challenge. Even in the presence of a very suggestive history, if the challenge is performed by 18 months; for example it is not uncommon that most challenges are negative (S. Mehr, personal communication). One interesting aspect of this low familiarity to FPIES is that it may explain why foods perceived to have a low allergenic profile such as rice have a greater number episodes occurring prior to diagnosis, compared with milk and soy (4 versus 2, for rice versus milk or soy, respectively) (Tables 1–3).

In recent years, however, there appears to be an increased interest in FPIES. This increased interest has translated into an increased number of publications. More than 29 publications appeared between 2011 and 2013, compared with between 2008 and 2010. Furthermore, at least two multicenter registries, in Italy (Sopo, personal communication) and Australia [50], were recently initiated. Finally, educational intervention programs successfully implemented in Italy (A. Fiocchi, personal communication) should reduce the time to diagnosis and decrease unnecessary procedures to be performed. These trends will hopefully provide important and validated information in the next several years.

DURATION OF DISEASE AND RATE OF RECOVERY

All experts agree that there is a high and rapid rate of recovery from FPIES. Optimally, the loss of reactivity to the offending food would be determined by a

Table 1. Reported cases of milk-food protein-induced enterocolitis syndrome

Year	Ref. no.	No. of cases	Symptoms			Age onset (m)	Outcome (a = accidental, c = challenge)		No. of other food FPIES	No. of PD	Remarks
			Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
1982	[13]	1	1	1	1	1.25	14	NA	Ch(1)	0	Chronic CM?
1993	[14]	1	+	–	+	1	NA	NA	S(1)	0	Methemoglobinemia, fever
1998	[4]	13	13	4	9	0.25–5	6(6–25)	7(12–84)	S(5)	NA	5 methemoglobinemia. 1 reacted to EHCF, 2 atypical
2000	[15]	1	+	+	+	0.5	NA	72		NA	Tolerated soy
2003	[16]	4	4	2	3	0.1–6	28 (a,c),	25, 16? 19m	O (3) S(3) Ba(2), R(3)	1	Most with FPIES to multiple foods; 3 had chronic FPIES
2005	[17]	1	+	+	±	3	NA	30		3	Tolerated soy; sepsis treatment
2006	[18]	8	7 (>1in 6)	NA	6	0.5–4	NA	NA	R+S(1)	NA	
2007	[19]	1	+	+	+	8	24	9	None	1	Sepsis work up
2009	[11]	23	+	+	33%	0.5–2	100% 20 m	NA	R(1), Be, E (1), F+ shellfish (1)	NA	Hypotension (11%), diarrhea later 3/23 methemoglobinemia
2009	[9]	7	7	4	2	4.1 ± 1.8	Most by 24 m		None	2	
2010	[20]	1	–	+	+	48	NA	NA	NA	NA	Gastrostomy, hypotension
2010	[21]	1	+	+	–	1 day	NA	NA	NA	NA	Very delayed diagnosis
2011	[10▪▪]	44	44	40	11	0.1–6	90% by 36	1 at 44	NA	NA	Study restricted to CMP
2012	[22]	1	+	+	–	2	NA	5	None	3	Breast fed, chronic FPIES
2012	[12▪]	44	98%	80%	54%	3.5 ± 2.4	24 ± 8		B(2), F(3), P(3), R(2), W(2)	2.7	10/44 with multiple food FPIES
2011	[23]	2	+	+	+	1.1, 8		Converted to IgE			
2013	[24]	1	+	+	+	4	NA	NA	R	NA	
2013	[25]	1	+	+	+	3	NA	3(c)	NA	0	Started with IgE, lost SPT
2013	[26▪▪]	1	+	+	–	NA	NA	12y(c)	NA	NA	Ondansetron
2013	[8▪▪]	310	All*	All*	~ 50%	6.3 ± 0.7	32 ± 24.1	80% by 5	>50% to 2 or more	NA	2 teenagers with persistent FPIES. *Diagnostic criteria

B, banana; Ba, barley; Be, beef; Ch, chicken; D, diarrhea; E, egg; EHCF, extensively hydrolyzed cow's milk formula; F, fish; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; O, oat; P, poultry; PD, prediagnosis episodes; R, rice; Rep V, repetitive vomiting; S, soy; T, turkey; To, tomato; W, wheat.

Table 2. Reported cases of soy-food protein-induced enterocolitis syndrome

Year	Ref. no.	No. of cases	Symptoms			Age onset (m)	Outcome (a = accidental, c = challenge)		Other food FPIES (*n*)	No. of PD	Remarks
			Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
1993	[14]	2	2	2	2	2, 1.5	NA	NA	CM (1)	0	1+ milk, 2 methemoglobinemia
1998	[4]	14	13	2	11	0.25–7	2 (24–36)	9 + 3 lost to FU	CM(7), P(1)	NA	
1998	[27]	7	7	6	6	2–5	12–24 in 5, 2 NA	NA	None	NA	
2003	[16]	7	7	3	4	0.5–6	2 (24–31)	5 (16–63)	R(6), CM(3), O(5), Ba(1), SB(1), [1+ CM, O, R, B, SB}	1–3	7/7 multiple food FPIES; 1/7 with chronic FPIES
2003	[28]	2	2	1	1	1–2	0	24, 90, one 19 years (Pt #1)(a)	P,T(1), CM, C(1)	Several	Methemoglobinemia
2006	[29]	2	2	2	2	1	NA		EHCF (tolerated neocate)	A	Chronic? Sepsis work up methemoglobinemia
2006	[18]	4	4	NA	2	0.25–4	NA	NA	CM(2), R(1)	N	2 with multiple food FPIES
2009	[11]	?	+	33%	33%	?					
2009	[9]	12	12	10	2	5.4 ± 3.1	NA	NA	R(2)	2	
2012	[12▪]	3	98%	80%	54%	10.6 ± 6.7	22		None	2	Described with other FPIES cases
2012	[30]	1	+	+	+	5	NA	6(a)	NA	3	Maternal soy ingestion, transferred through breast milk
2013	[8▪▪]	189	All*	All*	~ 50%	7.7 ± 8.9	33.9 ± 23	NA, one 16 y/o(c)	Most		*Diagnostic criteria

?, probably; B, banana; Ba, barley; C, corn; Ch, chicken; CM, cow's milk; D, diarrhea; EHCF, extensively hydrolyzed cow's milk formula; FPIES; food protein-induced enterocolitis syndrome; FU, follow-up; L/P, lethargy or pallor; NA, not available; O, oat; P, poultry; PD, prediagnosis episodes; R, rice; Rep V, repetitive vomiting; S, soy; SB, string bean; T, turkey; W, wheat.

Table 3. Reported cases of rice-food protein-induced enterocolitis syndrome

Year	Ref. no.	No. of cases	Symptoms			Age onset (m)	Outcome (a = accident, c = challenge)		No. of other food FPIES	No. of PD	Other
			Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
1963	[31]	1	–	–	+	1		11	NA	NA	Chronic at the beginning
1982	[13]	1	+	–	+	6	30		CM	NA	Chronic diarrhea, malnutrition, resolved with EHCF, FPIES?
1992	[32]	1	+	+	+	1.25	NA	11	NA	4	
1996	[33]	4	4	3	–	3, 4, 2, 5	NA	NA	NA	1–3	Hypotension, first introduction of food
1998	[4]	1	1	1	–	6	NA	16	S(1)	NA	
2000	[15]	10	10	5	4	3–6 (5 cases described)	4 (21–45)	5 (12–63)	O(5), CM(3), P(1), S(6), SP(1), Ba(2)	1–>4	1 case with chronic FPIES, 8/10 with multiple food FPIES
2003	[16]	9	9	7	5	4–6	3 (21–45)	6 (12–63)	B (1), CM(3), O(5), Pe(1), S(6), SB(2), SP(1)		Additional 1 – immediate response
2004	[34]	1	1	1	–	11	NA		Ba		
2006	[35]	5	5	5	5	5–6	2, 36 m	2, +1 lost to FU	None	>1	1 patient had sepsis work up performed twice
2006	[18]	2	2	NA	1	4–9	NA	NA	CM(1), O(1), S(1)	NA	None alone
2009	[9]	14	14	13	3	5.2 ± 0.8	80% 36 m		S(2), SP(1), B(1), O(1)	4	(36%) other food
2012	[12▪]	3	98%	80%	54%	10.6 ± 6.7	53 ± 17		R(2), CM(1)	3	
2012	[36]	1	+	+		4	Still/4y	Can have cooked	None	4	10g first reaction, few grains last
2013	[8▪▪]	88	All*	All*	~50%	7.3 ± 5.1	43.1 ± 5.1	NA	Most		*Diagnostic criteria
2013	[37]	1	+	+	+	5.5	NA	7(c)	SP(1)	2	Oral mucosal contact
2013	[26▪▪]	1	+	+	–	NA	NA	10y(c)	NA	NA	Ondansetron
2013	[24]	1	+	+	+	8	NA		CM	0	Hypotension

B, banana; Ba, barley; CM, cow's milk; D, diarrhea; EHCF, extensively hydrolyzed casein formula; FPIES; food protein-induced enterocolitis syndrome; FU, follow-up; L/P, lethargy or pallor; NA, NOT available; O, oat; P, poultry; PD, prediagnosis episodes; Pe, peas; R, rice; Rep V, repetitive vomiting; S, soy; SP, sweet potato; T, turkey; W, wheat.

Table 4. Reported cases of egg-food protein-induced enterocolitis syndrome

Year	Ref. no.	No. of cases	Symptoms			Age onset (m)	Outcome (a = accident, c = challenge)		Other food FPIES	No. of PD	Remarks
			Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
2006	[18]	1	+	NA	+	9	NA	NA	None	NA	
2011	[38]	1	+	+	+	11	NA	22(c)	None	4	
2012	[12▪]	4	4	3	2	10.6 ± 6.7	53 ± 17		None	2.5	
2013	[26▪▪]	1	+	+	–	NA	NA	36(c)	NA	NA	Ondansetron
2013	[8▪▪]	51	All*	All*	~50%*	11.3 ± 9.6	41.8 ± 39.2		NA		*Diagnostic criteria
2013	[39]	4	4	4	2	6, 9,48, 6,	24(1)	3(24–72)	None	1–12	2 with positive SPT. Worst outcome to patient with negative SPT to egg

D, diarrhea; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; PD, prediagnosis episodes; Rep V, repetitive vomiting; SPT, skin prick test.

scheduled OFC. In real life, however, many patients experience an accidental exposure without a reaction and report subsequently, usually not voluntarily, that they are not sensitive any more. In Tables 1–10, the available information regarding the various foods causing FPIES, the age of first presentation and the outcome to the best of our knowledge are presented. In our cohort of milk FPIES [10▪▪], over 90% lost their reactivity by the age of 3 years and only a single patient had a challenged-proven reaction after the age of 3 years. Similar results were obtained in Korea (11 and Hwang, personal communication), Australia [9] and Italy [12▪]. The largest group of cow's milk FPIES, consisting of 310 patients identified by retrospective chart review, yielded different and less favorable results [8▪▪]. Only 35% outgrew their FPIES disease by the age of 2, and only 70% outgrew their sensitivity by 3 years. However, by school age (5 years old) more than 85% lost their reactivity to milk. It is possible that the differences noted with regard to the age of resolution between the studies reflect the variability in the mode of collection of data.

It would appear that the age of recovery of FPIES to soy is similar to that of milk. Among the children with FPIES to soy who were challenged, five out of six lost their reactivity by the age of three [9]. There is no information regarding the other six soy allergic children in that study, but it is reasonable to assume that the patients who were not challenged lost their sensitivity at even a higher rate. In another study [27], five out of seven soy allergic children lost their sensitivity by the age of 2 years, whereas the other two were lost to follow-up. Although other series similarly noted that the age of recovery for FPIES to soy was similar to that of milk [8▪▪,12▪], there are case reports in which FPIES persists to an older age [8▪▪,26▪▪,27–51]. To our knowledge, the two cases in which FPIES persisted the longest were to soy, at age 18 [8▪▪] and 19 years old (Y. Levy, Personal communication). In addition, a patient with a late onset of FPIES at age 33 persisted through age 53 [41].

FPIES to solid foods tend to appear at a later age, likely reflecting the later age of introduction of these foods to the diet [8▪▪,16]. Furthermore, in the Italian cohort, the age of resolution of FPIES to solid foods

Table 5. Reported cases of peanut food protein-induced enterocolitis syndrome

Year	Ref. no.	No. of cases	Symptoms			Age onset (m)	Outcome (a = accident, c = challenge)		Other food FPIES	No. of PD	Remarks
			Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
2013	[26▪▪]	1	+	+	–	NA	NA	60 (c)	NA	NA	Ondansetron
2013	[8▪▪]	9	All*	All*	~50%*	7.3 ± 5.1 ?	42.1 ± 3.8	NA	NA	NA	*Diagnostic criteria

?, probably; D, diarrhea; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; PD, prediagnosis episodes; Rep V, repetitive vomiting.

Table 6. Reported cases of food protein-induced enterocolitis syndrome induced by fish and shellfish

				Symptoms				Outcome (a = accidental, c = challenge)				
Year	Ref. no.	No. of cases	Fish	Rep V	L/P	D	Age onset (m)	Recovery age (m)	Persistent (last known age, m)	Other food FPIES	No. of PD	Remarks
1982	[13]	1	NA	+	+	+	4	NA	28m	?CM		Malnutrition
2005	[40]	14	7 sole; 10 –hake; small hake – 4; cork float – 4	12	3	5	9–12	4 tolerant; 3 tolerant to single fish	2 parent refuse challenge; 2 positive challenge; 2 too early; 1 not challenged	Wa	3–6	
2009	[9]	1	?	+	+	–	9	NA	NA	None		
2012	[41]	1	Scallops, clams	+	+	+	33 years		53			The oldest case of FPIES reported. Persisted through age 53
2012	[36]	1	Cod	+	+	–	9	NA				5 g induced the first reaction to 0.25 g last reaction
2012	[12▪]	8	Cod, sole, + other	+	+	54%		Mean 60		CM(1), P(2)	2.8	Some species of fish tolerated
2013	[8▪▪]	4	Salmon and crab	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria

?, probably; CM, cow's milk; D, Diarrhea; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; PD, prediagnosis episodes; Rep V, repetitive vomiting; Wa, watermelon.

was later than that of milk or soy [12▪]. The median age of resolution for FPIES to fish and egg was exceptionally high, at approximately 60 months (Tables 4 and 6). On the contrary, Ruffner *et al.* [8▪▪] found no difference in the age of resolution between FPIES reactions mediated by solid foods and liquids (42.1 ± 3.8 versus 32.9 ± 0.95, respectively). Confounding the data is the low catchment for the age of resolution for those reported in this study [8▪▪]. In many of the studies ([11,16,28,52], A.S. Bansal, personal communication), resolution of FPIES was determined by reports after accidental exposure

Table 7. Reported cases of food protein-induced enterocolitis syndrome induced by grains

				Symptoms				Outcome (a = accidental, c = challenge)				
Year	Ref. no.	No. of cases	Grain	Rep V	L/P	D	Age onset (m)	Recovery age (m)	Persistent (last known age, m)	No. of other food FPIES	No. of PD	Remarks
2003	[16]	8	O	8	8	7	3–6	3 (18–36)	5 (19–63)	R(5), CM(3), S(5), SB(2), SP(1), P(1)	1–5	1 case with chronic FPIES, 1 case to grain alone
2005	[17]	1		1	+	+	6		36	None	2	Treated for sepsis
2006	[18]	1		1	–	–	4	NA	NA	R(1)	NA	
2009	[9]	2		2	+	+	5–6.4	NA	NA	R(2)	2	
2013	[8▪▪]	74		All*	All*	~50%	9.3 ± 6.2	37 ± 25.6		NA		*Diagnostic criteria
2012	[36]	1	W	1	+	+	6		39(c)	None	NA	15 g in first reaction to 0.5 g last
2012	[12▪]	2		NA	NA	NA	NA	NA		CM (2)	NA	
2013	[26▪▪]	1		1	+	+	–	NA	7y (c)	NA	NA	
2013	[8▪▪]	46		All*	All*	~50%	11.7–14.5	31.1.3 ± 14.5		NA	NA	*Diagnostic criteria
2003	[16]	2	Ba	2	1	–	4–6.5	1 (24)	1 (21)	O, CM, (1); CM, S, R, SB, P (1)	1	None alone
2013	[8▪▪]	18		All*	All*	~50%	11.7–14.5	55.3 ± 51.9		NA	NA	*Diagnostic criteria
2012	[12▪]	2	C	2	80%	54%	NA	NA	NA	R(2)	1	
2012	[42]	1		1	+	+	+	7	NA	None	2	
2013	[8▪▪]	37		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria

Ba, barley; CM, cow's milk; C, corn; D, diarrhea; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; O, oat; PD, prediagnosis episodes; R, Rice; Rep V, repetitive vomiting; S, soy; SB, string bean; W, wheat.

Table 8. Reported cases of food protein-induced enterocolitis syndrome induced by fruits

Year	Ref. no.	No. of cases	Fruit	Symptoms			Age Onset (m)	Outcome (a = accidental, c = challenge)		Other food FPIES	No. of PD	Remarks
				Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
2009	[9]	1	B	+	+	−	6	?		1 = R		
2012	[12▪]	2		+	+	?	NA	NA		CM(2) T(1)		
2013	[43]	1		+	+	+	6	NA	19 (a)	NA	3	Only
2013	[8▪▪]	16		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	8	A	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	7	Pea	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2008	[44]	1	Peach	+	+	−	4		12	CM	1	
2013	[8▪▪]	4		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	4	Plum	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	4	St	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	4	Wa	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2005	[40]	1		NA	NA	NA	13 Years	NA		Fish		NA
2013	[8▪▪]	3	Av	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2012	[45]	1	Or	+	+	+	10	NA	24	None	5	
2013	[8▪▪]	11	other	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria

A, apple; Av, avocado; B, banana; CM, cow's milk, FPIES; food protein-induced enterocolitis syndrome; Or, orange; D, diarrhea; L/P, lethargy or pallor; NA, not available; PD, prediagnosis episodes; Pea, pear; Rep V, repetitive vomiting; St, strawberry; Wa, watermelon.

Table 9. Reported cases of food protein-induced enterocolitis syndrome induced by vegetables and legumes

Year	Ref. no.	No. of cases	Vegetable	Symptoms			Age onset (m)	Outcome		Other food FPIES	No. of PD	Remarks
				Rep V	L/P	D		Recovery age (m)	Persistent (last known age, m)			
1994	[47]	1	SP	+	+	−	5	NA	NA	Sq	None	Sepsis work up
2003	[16]	1		+	+	−	6	34	13	O, R, S, SB,	2	
2007	[8▪▪]	19		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2009	[9]	2		2	1	1	7.6	NA		O(1), R(1)		
2013	[37]	1		1	+	+	5.5	7 (c)	NA	R(1)	2	
1998	[4]	1	P	+	−	−	5	NA	Not tested	S(1)	NA	
2003	[16]	1		+	−	−	4.5	14 (a)	4.5	CM, S, R, O, Sq	1	
2003	[28]	1		+	+	+	8	NA	80			
2013	[8▪▪]	13		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2003	[28]	1	Lentils	+	+	−	8	NA		S, T(1)		
2013	[8▪▪]	8	Potato	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	7	Carrot	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
1994	[46]	1	Sq	+	+	−	5	NA		SP	None	Hypotension
2013	[8▪▪]	6		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2003	[16]	2	SB	+	−	−	6	24	46	S(2) (and other)		
2013	[8▪▪]	3	Kidney bean	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	2	Green bean	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2012	[12▪]	1	To	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2013	[8▪▪]	5	Other	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria

B, banana; CM, cow's milk; D, diarrhea; FPIES; food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; O, oat; PD, prediagnosisepisodes; R, rice; Rep V, repetitive vomiting; S, soy; SB, string bean; SP, sweet potato; Sq, squash; To, tomato.

Table 10. Reported cases of food protein-induced enterocolitis syndrome induced by poultry and meat

				Symptoms				Outcome (a = accidental, c = challenge)				
Year	Ref. no.	No. of cases	Food	Rep V	L/P	D	Age onset (m)	Recovery age (m)	Persistent (last known age, m)	Other food FPIES	No. of PD	Remarks
1982	[13]	2	Ch	2	1	2	1.25, 6	1–19	1–25	2-CM, 1-R	NA	
1994	[47]	1		+	+	+	5	NA	NA	None	4	
1998	[4]	1		–	+	+	24	9y		T(1)	NA	Atypical
2003	[16]	1		+	–	–	6		12y(c)	T	NA	
2003	[28]	4		4	3	1	3, 4.5, 7, 12	1– 3 years	3 cases (24, 36, 24)	S(1), CM(2), T(1)	Several	3/4 with multiple food FPIES; hypotension reported
2009	[9]	1		+	+	?	8	0	36	None	NA	
2012	[36]	1		+	–	–	8	60 or earlier		None	NA	5g to 0.25 g
2013	[8▪▪]	21		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
1998	[4]	1		–	+	+	24	9 years				
2003	[16]	1	T Beef	+	–	–	7		12y	Ch(1)	2	Unchallenged
2003	[28]	2		2	1	–	6, 11	NA	36, 80	Ch(1), P(1), S(1)		
2013	[8▪▪]	19		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2009	[8▪▪]	11		All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2009	[8▪▪]	7	Pork	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria
2012	[12▪]	2	P	98%	80%	53%	10.6 ± 6.7	53 ± 17		F(2)	4	
2009	[9]	1	Lamb	+	+	–	11.2					
2013	[8▪▪]	2	Lamb	All*	All*	~50%*	14.5 ± 13.5	60.4 ± 33.7		NA	NA	*Diagnostic criteria

Ch, chicken; D, diarrhea; F, fish; FPIES, food protein-induced enterocolitis syndrome; L/P, lethargy or pallor; NA, not available; O, oat; P, poultry; PD, prediagnosis episodes; R, rice; Rep V, repetitive vomiting; S, soy; T, turkey.

that could have been many months after the true resolution.

MULTIPLE FOODS CAUSING FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Not uncommonly, a patient may have FPIES reactions to multiple foods. Thus, an important question arises as to what the replacement food should be and as to how other foods should be introduced into the diet. This problem is reinforced by the fact that there is no laboratory test such as a skin prick test (SPT) or a sIgE that could exclude the possibility of sensitivity. For example, the most common food to cause FPIES is cow's milk, a situation in which a soy-based formula would be considered as a natural candidate for replacement. But, many using a 'common knowledge' assume that patients with FPIES to cow's milk are reactive to soy as well [11]. With regard to this issue, there is a sharp discrepancy in the reported prevalence of FPIES to soy in cases of milk-mediated FPIES. Although in the cohorts described from Australia [9], Israel [10▪▪] and Italy [12▪] not a single case of milk-mediated FPIES reacted to soy, in reports emanating from the United States, soy-mediated FPIES was not uncommon among patients with FPIES to milk [8▪▪]. Although in one study [16] this was noted in a tertiary highly selected population, in a more recent and largest report of FPIES to date, 29% of patients with milk mediated FPIES also had FPIES to soy [8▪▪]. In this last study, those that were positive to soy were sensitive to other foods and not only milk. The issue of soy reactivity among cow's milk-mediated FPIES patients, is only one of the questions that will have to be answered by future large-scale population-based multicenter international prospective studies.

In solid food-mediated FPIES, it is common to have FPIES to an additional food. In the recent data from the United States over 40% of patients with grain FPIES had sensitivity to two or more grains and 20% with grain FPIES additionally reacted to soy, milk or both [8▪▪]. In the study [9] from Australia, patients with FPIES-mediated reactivity to both rice and oat were common. On the contrary, in the few reports of FPIES to egg and peanut, no other FPIES-type reactions were mentioned to other foods (Tables 4 and 5).

To date, no risk factors were identified for the appearance of FPIES. Factors analyzed included breastfeeding versus no breastfeeding [8▪▪,10▪▪], the presence or absence of family history and whether the presence of an infant with FPIES increased the risk for a sibling to have FPIES [50].

SEVERITY OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

In many reports, the description of a FPIES reaction during a natural exposure or challenge is quite dramatic. As discussed above, in many cases, infants with accidental exposures to inducing foods prior to diagnosis were treated as having sepsis because of the life-threatening nature of their reaction. Furthermore, there are cases with documented decreases in blood pressure [11,24] and even shock [47]. This led to the common practice at least in some centers to perform an OFC to diagnose FPIES with an intravenous line in place [6]. However, unlike in IgE-mediated food allergic reactions [53,54], no cases of mortality have been reported in FPIES. This may be related to the early age of presentation and resolution for FPIES; no fatal IgE-mediated food allergic reactions were ever reported in infants younger than 2 years old.

Acquired methemoglobinemia, perhaps secondary to dehydration, is mentioned as evidence for the severity of reactions in this disease [14]. The data are sparse on this issue and the three reports that describe this phenomenon are to both milk and soy [9,14,29,]. They occurred both following accidental and OFC exposure [11]. Similarly, the assumption that the presence of evidence of IgE sensitization is an ominous sign [4,16,49] has not been validated [39].

ELICITING DOSE IN FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

In the four cases reported by Bansal [36], the quantity of inciting food that caused subsequent reactions was several fold less than the quantities that elicited the original reaction. This was noted for rice, wheat, cod and chicken. We made the same observation for milk and this was confirmed by Sopo (personal communication). Furthermore, this phenomenon was reported in a case of soy-mediated FPIES, as well [30]. The observed increased sensitivity upon subsequent exposures may explain the report by Monti *et al.* [55] in which an infant's threshold for reaction decreased from 50 ml in the first reaction to one spoonful and subsequently by breast milk. The latter was due, presumably, to cow's milk proteins that passed through the breast milk. However, FPIES induced by breast milk was reported in three cases where no previous FPIES reactions induced directly by a food were noted [56].

SECONDARY IgE-MEDIATED FOOD ALLERGY FOLLOWING FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME MEDIATED FOOD HYPERSENSITIVITY

Several studies reported that patients with FPIES may develop an IgE-mediated allergy to the same food. The first described case was identified in 1998 [4], and the observation was subsequently confirmed by several additional authors ([10▪▪,23,57] and Spergel, personal communication). Although this phenomenon has been demonstrated mainly for milk, we are also aware of three additional cases in which it was seen in patients who initially had FPIES to fish (Sopo, personal communication; J. Bone, personal communication) and an additional one to egg (J. Bone, personal communication). Because of the risk for the development of IgE-mediated CMA in these patients, it is prudent to examine by SPT or sIgE for sensitization to cow's milk before an OFC challenge is carried out. Needless to say, even if sensitization is noted, the patient has to be observed for an extended period of 3–4 h after the last dose, as for FPIES. The shift from a FPIES food hypersensitivity to an IgE-mediated food allergy is puzzling, as in most cases, there were no detectable IgE antibodies to milk at the initial diagnosis of FPIES. Furthermore, there were no classical IgE-mediated symptoms at the original challenge [10▪▪]. One possible explanation is the extended period of avoidance of cow's milk protein from the diet increases the risk of developing secondary IgE-CMA. The reason that this shift was not reported more frequently probably rests with earlier ambiguity in the diagnosis of IgE-mediated milk allergy and non-IgE mediated symptoms, in young infants [58]. Given that now the awareness and proper diagnosis of FPIES are increasing, it is expected that this phenomenon will be recognized more frequently, and likely with other foods, as well.

CONCLUSION

More is unknown than known about the natural history of FPIES. In general, FPIES is a benign condition with a favorable course. The duration of the disease is relatively short lived, with the vast majority growing out of the condition by the age of 3–5 years. Given the occurrence of reactions to more than one type of food in some of these patients, it is prudent to introduce alternative foods under medical supervision. In the case of FPIES to cow's milk protein, the possibility of developing IgE-mediated CMP allergy should be entertained. Finally, the possibility of a decreasing threshold for sensitivity to the offending food should be considered.

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Conflicts of interest

There are no conflicts of interest.

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