

Resolution of acute food protein-induced enterocolitis syndrome in children



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Clinical Implications

- The type of food triggering acute food protein-induced enterocolitis (FPIES) is one of the main factors influencing tolerance. Children with rice and cow's milk FPIES achieved tolerance significantly earlier than those with egg and fish FPIES.

TO THE EDITOR:

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food allergic disorder that usually presents by 4–6 months of age.¹ Cow's milk, soy, grains, and eggs are amongst the commonest triggers.¹ Standard practice to ascertain tolerance has been a medically supervised challenge to the triggering food at 3–4 years of age.² However, limited data exist regarding time to tolerance and factors that affect its attainment, particularly in children with solid food FPIES.^{1,3–9} We aimed to determine whether tolerance in children with acute FPIES occurred earlier than previously reported and whether this was affected by the type and number of food triggers.

We performed a retrospective study of children with acute FPIES who underwent open food challenges (OFCs) from 1995 to 2015 at the Children's Hospital at Westmead (CHW), New South Wales, Australia. We identified all children with FPIES who had a medically supervised OFC at our hospital to determine tolerance. Children were included for analysis if their original presenting acute FPIES episode satisfied the following criteria: repetitive vomiting (0.5–4 hours) after eating a suspect food(s) and at least 2 of the following: (1) a second (or more) episode of repetitive vomiting (0.5–4 hours) after eating the same suspect food, (2) repetitive vomiting episode (0.5–4 hours) after eating a different food, (3) associated floppiness, pallor, and/or diarrhea (within 24 hours) during at least one episode, and (4) need for an emergency room visit and/or intravenous fluid therapy during at least one reaction. Children with multiple FPIES were defined as having at least 2 separate food triggers.

At CHW, children with FPIES are offered an in-hospital-supervised OFC to the triggering food 6–12 months after their last reaction. OFCs consisted of a single serving size of the food allergen (at least 3 g of food protein, rice at least 1 g), with a 4-hour observation period. Children with a skin prick test (SPT) >2 mm to the food challenge had a standard graded OFC to the same total cumulative dose. Reaction at the OFC was defined as follows: (1) the triggering food was the same as the one causing the original FPIES reaction; (2) vomiting occurred within 0.5–4 hours of ingestion; and (3) no cutaneous or respiratory symptoms of an allergic reaction occurred. Children with multiple FPIES were challenged to each food on separate occasions.

Statistical analyses were performed using JMP Version 11 Software for Windows (SAS Institute Inc., Cary, NC). Time to tolerance was described as the time from the initial reaction to the time of the OFC in months. Children who were not tolerant were censored at their last OFC. Time to tolerance was described using the Kaplan-Meier method, and predictors of time to tolerance were tested using proportional hazards regression models. Only rice, cow's milk, egg, and fish were evaluated because of smaller numbers caused by other triggering foods. There was no adjustment made for multiple statistical comparisons. Approval for the study was obtained from the ethics committee at the CHW (LNR.15.SCHN.15).

Patient characteristics and FPIES triggers are summarized in Table 1. A total of 81 OFCs were conducted on 69 children. Eleven children had more than 1 OFC (8 children had FPIES to 2 different foods challenged separately, 1 child had 4 different food triggers challenged [egg, rice, banana, cow's milk; this particular child had cow's milk rechallenged a second time], and 3 children had challenges to the same food [1 reacted to soy at 17 months but tolerant by 25 months, and 2 reacted on rechallenge: egg at 37 months and 49 months; cow's milk at 5 months and 14 months]). Rice, cow's milk, egg, and fish were the most common triggers at initial presentation and therefore the most common foods challenged at OFC (Table 1). There were 33 OFCs to grains, of which 27 (82%) were to rice, 3 to wheat, 2 to oats, and 1 was to barley. There were 20 (25%) positive challenges. The characteristics of OFC reactions and treatment administered are shown in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

The proportion of children who remained reactive to rice, cow's milk, egg, and fish over time is shown in Figure 1. Attainment of tolerance for rice and cow's milk was achieved at a significantly younger age than for fish and egg (Figure 1). By 3 years of age, 87% and 88% of children with rice and cow's milk FPIES were tolerant; in comparison only 12.5% of egg and 25% cases of fish FPIES achieved tolerance (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Older age at initial FPIES episode and diagnosis were both associated with slower acquisition of tolerance (age first episode hazard ratio [HR] 0.9 per month, 95% confidence interval [CI] 0.80–0.97, $P = .008$; age at diagnosis HR 0.96 per month, 95% CI 0.94–0.98, $P = .0015$). These associations remained significant when adjusted for food groups. Children with a positive SPT to the triggering food (at the time of diagnosis and/or OFC) achieved tolerance more slowly (median age tolerance 54 months, 95% CI >32 months) than those with a negative SPT (median age tolerance 16 months, 95% CI 14–22; HR 0.29, 95% CI 0.09–0.94, $P = .04$). Gender, presence of any atopic disorder, and the number of food triggers (ie, single vs multiple FPIES) were not associated with the rate of tolerance acquisition (data not shown). The severity of the initial FPIES reaction (as defined by the presence of hypotension, hypothermia, and/or the need for IV fluid therapy) did not influence the rate of tolerance acquisition (HR 0.72; 95% CI 0.38–1.39). Nor was there an association between the severity of the initial FPIES reaction and the eliciting food trigger ($P = .58$). Unlike other studies, this study specifically examined

TABLE 1. Characteristics of episodes

	Reactor	Nonreactor	Total
Total episodes (vs number of patients)	20 (16)	61 (53)	81 (69)
Male (n)	8	21	29
Median age (mo) at initial episode (IQR)	6 (4-9.3)	4.5 (4-6)	5 (4-6)
Median age (mo) at diagnosis (IQR)	8 (4.3-41.5)	8.5 (6-14.8)	8 (6-16.8)
Median age (mo) at OFC (IQR)	17 (10.8-51.3)	20 (15.5-27)	19 (14-32)
Interval between initial episode and OFC (mo) (IQR)	11.5 (4.5-31)	15 (11-22)	14 (10-28)
Comorbid atopy (n)			
Eczema	5	22	27
Asthma	1	7	8
Allergic rhinitis	1	4	5
IgE food allergy (previous clinical reaction to a food)	2	10	12
Positive SPT to triggering food (either at diagnosis or before OFC)*	1	3	4
Single food trigger (n)	13	28	41
Foods challenged at OFC (n)			
Rice	3	24	27
Cow's milk	4	21	25
Egg	6	2	8
Other grains (barley, oats, wheat)	2	4	6
Fish	3	1	4
Soy	1	3	4
Fruits	0	3	3
Chicken	0	2	2
Potato	0	1	1
Peanut	1	0	1

IQR, Interquartile range; OFC, open food challenges; SPT, skin prick test.

*Of the 4 cases with a positive SPT, 1 was to cow's milk, 1 to soy, and 2 to egg.

the time to tolerance based on the standardized case definition of FPIES and only included those who had in-hospital-supervised challenges. We found that patients with rice and cow's milk FPIES achieved resolution more quickly than for other foods. Our resolution rate for cow's milk is in keeping with figures reported by Katz et al⁶ (94% by 30 months of age) and Hwang et al⁷ (100% by 20 months), but in contrast to most US reports, where rates of resolution are much lower (20%-60% by 3 years of age^{3,8}). The reasons for these variations remain unclear, although may be explained in part by differences in rates of cow's milk sensitization,⁸ which has been associated with a delay in tolerance acquisition.⁸ We found that sensitization detected by SPT also delayed tolerance acquisition. In our study, by 3 years of age, 90% of children with rice FPIES and 75% of those with grain FPIES were tolerant. This is higher than that reported by Nowak-Węgrzyn et al³ (40% for rice by 3 years) and Caubet et al⁸ (25% for rice by 3 years, and

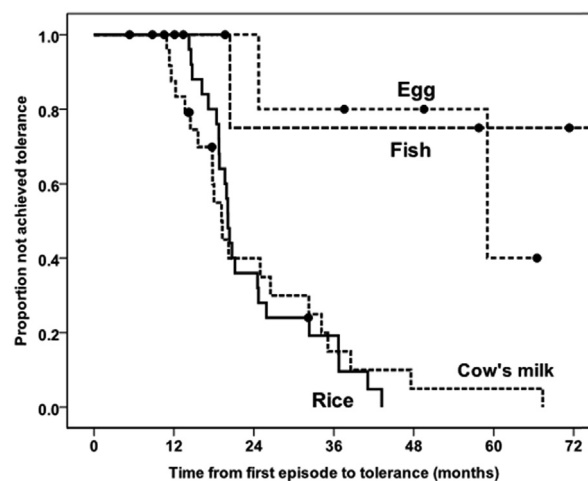


FIGURE 1. Kaplan-Meier curves for time to tolerance to cow's milk, egg, fish, and rice.

65.5% for grains by 5 years). This discrepancy cannot be explained by the presence of IgE sensitization to rice, which is rarely reported, and did not occur in any of our rice FPIES cohort. We found that those with egg and fish FPIES had a poorer prognosis with respect to time to tolerance. This has been reported by others for fish,^{8,9} but no studies have previously examined resolution rates for egg FPIES.

Like other reports, our data are not based on OFCs at regular intervals, and are thus susceptible to bias. Only with prospective studies with regular challenge intervals, will it be possible to fully understand the natural history of FPIES. Nevertheless, similar to IgE-mediated food allergy, the type of food triggering FPIES is one of the main factors influencing tolerance. We did not find that children with multiple food FPIES were slower to achieve tolerance. We suggest that children with rice or cow's milk FPIES should have an OFC by at least 2 years of age, whereas challenges to egg and fish could be delayed until 5 years of age.

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TABLE E1. Characteristics of reactions at oral food challenge (OFC) (n = 20)

Median time to reaction in hours (IQR)*	2.5 (2-3)
Symptoms and signs, number (%)	
Vomiting	20 (100)
Pallor	5 (25)
Floppiness	6 (30)
Diarrhea (within 4 h of the OFC)	2 (10)
Hypotension	1 (5)
Treatment, number (%)	
Required overnight admission	1 (5)
Intravenous fluids	6 (20)
Intravenous ondansetron	13 (65)

IQR, Interquartile range; SPT, skin prick test.

*Only 3 children reacted within 30 min of receiving the full challenge dose (cow's milk, soy, and fish). All had negative SPT to the food challenge.

TABLE E2. Proportion of children outgrowing FPIES at 12-mo intervals

Age at OFC (mo)	Proportion of children tolerant n, %				
	All foods	Rice	Cow's milk	Egg	Fish
12	7, 9%	0, 0%	3, 12%	0, 0%	0, 0%
24	42, 52%	17, 63%	14, 56%	1, 12.5%	1, 25%
36	53, 65%	22, 87%	22, 88%	1, 12.5%	1, 25%
48	59, 73%	27, 100%	24, 96%	1, 12.5%	1, 25%
60*	60, 74%	27, 100%	24, 96%	2, 25%	1, 25%

FPIES, Food protein-induced enterocolitis; OFC, open food challenges; SPT, skin prick test.

*There were 4 children who reacted at OFC > 60 mo (1 to cow's milk at 66 mo of age, 1 to egg at 67 mo of age, and 2 to fish at 71 and 121 months of age, respectively; only the child with egg FPIES had a positive SPT at the time of OFC).

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