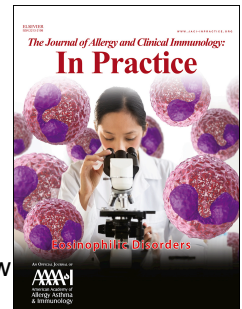


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An Observed Serving Dose May Not Be Necessary Following a Standard Divided Dose FPIES Oral Food Challenge (OFC)

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Title Page

Title: An Observed Serving Dose May Not Be Necessary Following a Standard Divided
Dose FPIES Oral Food Challenge (OFC)

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Dr. Bird reports personal fees from Food Allergy Research and Education, personal fees and non-financial support from American College of Allergy, Asthma and Immunology, grants from Nestle Health Sciences, personal fees from Nutricia North America, personal fees from Pharm-Olam International LTD, personal fees and other from Pfizer Pharmaceuticals, grants, personal fees and non-financial support from Aimmune Therapeutics, personal fees from Prota Therapeutics, personal fees from Allergy Therapeutics, Ltd, grants from NIH-NIAID, grants from Novartis, personal fees from AllerGenis, personal fees from Abbott Nutrition International, grants and personal fees from DBV Technologies, outside the submitted work.

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Maria Crain reports being on an allied health advisory board for DBV Technologies and Aimmune Therapeutics for their peanut products.

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Clinical Implications:

FPIES OFCs can be safely performed in the outpatient setting using a single serving protocol, and the additional observed feeding is unlikely to yield useful information. Additional study is necessary to refine the approach to conducting a FPIES OFC.

TO THE EDITOR:

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy that typically presents during the first year of life. In the majority of patients, history alone is sufficient to make the diagnosis and identify trigger foods. If the diagnosis is not clear after taking a careful history, an oral food challenge (OFC) is used as the gold standard to confirm the diagnosis. OFCs are highly useful to determine whether FPIES has been outgrown and are usually attempted within 12-18 months after the most recent reaction.^{1, 2}

The FPIES OFC method has not been systematically studied and reported practices vary. International consensus guidelines recommend administering the challenge food at a dose of 0.06-0.6g of the food protein per kilogram of body weight (not to exceed 3g of protein or 10g of total food) in 3 equal doses over 30 minutes.¹ When a very low dose of food protein is administered and if there is no reaction after 2-3 hours of observation, some experts advocate administration of an age-appropriate serving, followed by an additional 4 hours of observation.¹ We reviewed our experience with FPIES OFCs to evaluate whether an observed serving is necessary 2-3 hours following the initial divided dose OFC.

A retrospective chart review was performed for all patients who underwent FPIES OFCs from July 2010-July 2018. Patient histories were reviewed for age, sex, symptoms, whether symptoms prompted emergency department (ED) visit, and implicated foods. OFC-related data were also collected including age at the time of challenge, cumulative dose of food

administered, challenge outcome, time to reaction, and reaction treatment. Chart review approval was granted by the Institutional Review Board of UT Southwestern Medical Center.

All patients underwent open OFCs in the Children's Health Food Allergy Center. Intravenous (IV) catheters were placed at the provider's discretion. OFC doses ranged from 0.03-0.6g food protein per kilogram of body weight divided in 3 equal doses over 30 minutes. An age-appropriate serving could be given 3 hours later at the discretion of the provider. OFCs were retrospectively categorized as high-risk if the patient had any previous reaction requiring ED evaluation or if the OFC was performed to the food to which the patient previously reacted. Low-risk foods included those not previously introduced but which the patient was avoiding due to high-risk nature of the food(s) for FPIES.

We reviewed 88 OFCs conducted for 46 patients (25 female, 21 male) during the study period. Of these 88 OFCs, 68 (77%) were retrospectively categorized as high-risk. The median age at time of OFC was 18.5 months (range 6-118 months, 0.5-9.8 years). Three of 27 subjects with a history of skin prick or serum specific IgE testing demonstrated sensitization to their reported food trigger. Subject characteristics are shown in Table 1.

Fifty-one percent (45/88) of OFCs involved administration of the initial divided doses without the additional age-appropriate serving. Reactions occurred in 11% (10/88), all of which occurred in the high-risk OFCs and only after the initial divided dose. No subject had a reaction after administration of an age-appropriate serving following the initial divided dose. Eight of the 10 positive reactions occurred upon challenge to previously reported food triggers; the other 2 positive challenges occurred to peanut and pork in separate patients who had historical reactions consistent with FPIES to oat. Symptoms developed after a median cumulative dose of 0.35 g/kg (range 0.2-0.6 g/kg, serving size 50-100% based on age-appropriate serving size

estimates) and all reactions occurred within 2-3 hours after completion of the initial divided dose. The total dose administered did not differ between high-risk (mean=0.429 g/kg) and low-risk (mean=0.41 g/kg) OFCs ($p=0.74$) (Figure 1). There was no association found between likelihood of reaction and time interval since last clinical reaction to the culprit or any other food.

Reactions occurred to uncooked milk ($n=3$), soy, rice, lightly cooked egg, baked egg, cooked cheese, peanut, and pork (all $n=1$). Treatments used for positive challenges included: IM ondansetron ($n=3$), PO ondansetron ($n=2$), IV ondansetron ($n=2$), PO and IM ondansetron and IM epinephrine ($n=1$), IM ondansetron and IV fluids ($n=1$), and no treatment ($n=1$). Two of 3 subjects with evidence of detectable serum specific IgE to their reported food trigger had positive OFCs (uncooked milk and baked egg). All subjects with positive OFCs were successfully managed in the clinic.

FPIES OFCs are valuable in assessing the development of tolerance; however, the approach to conducting a FPIES OFC is not standardized. Previous reports have shown that patients with positive FPIES challenges often reacted to an amount less than 50% of the standard serving size.³⁻⁹ Barni et al recently reported that all positive challenges occurred after administration of 25% of the total serving and suggested that a single serving dose was sufficient.³ Our experience is in agreement with these findings; however, Wang et al recently reported FPIES OFC involving one-third serving size was sufficient to elicit symptoms for most patients ultimately deemed to have a positive challenge (57%), and the remaining patients did not react until they consumed larger amounts at home.⁷

In our cohort, about half of the patients received an age-appropriate dose after the initial divided dose, and the other half only received the initial divided dose. All positive challenges occurred 2-3 hours after the initial divided dose and were classified as high-risk. There were no positive challenges after an age-appropriate serving was administered, suggesting that all

patients manifested symptoms after the initial feeding and that the additional full serving dose was not necessary to elicit symptoms.

Limitations of this study include the retrospective nature of data analysis and reports from our single-center experience. In addition, roughly half of the patients in this study only received an initial divided feeding and there was limited follow-up of these patients. Twenty-three of the 35 negative challenges using the modified protocol had follow-up visits and reported continued tolerance of the food challenged; however, the remaining 12 had no further contact with our staff.

In conclusion, our data suggest that the majority of patients undergoing FPIES OFCs react to the initial divided dose. An additional observed serving may not be necessary to elicit symptoms. Additional investigation is warranted to refine the approach to FPIES OFCs.

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Figure 1: **Total food protein dose administered in high risk (blue) versus low risk (orange) FPIES**

OFCs. No significant difference in the total dose of protein administered during FPIES OFC between patients categorized as high-risk or low-risk based on clinical history.

Characteristics of subjects with FPIES	
No. of patients	46
No. of OFCs	88
Sex, no. (%)	
Female	25 (54)
Male	21 (46)
Age at diagnosis (mos)	
Median	10
Range	0.5 – 32
Age at OFC (mos)	
Median	18.5
Range	6 – 118
History of atopy, no. (%)	17 (40)
Family history of atopy, no. (%)	34 (74)
ED visit for FPIES reaction, no. (%)	23 (50)
FPIES reaction to: no. (%)	
1 Food	18 (39)

>1 Food	28 (61)
Incriminated food by history, no. (%)	
Milk	18 (39)
Soy	8 (17)
Rice	16 (35)
Oat	18 (39)
Wheat	2 (4)
Other solid foods	21 (46)
Median eliciting dose during OFC, g/kg (no.)	
Uncooked milk	0.4 (3)
Soy	0.3 (1)
Rice	0.2 (1)
Lightly-cooked egg	0.2 (1)
Baked egg	0.2 (1)
Cooked cheese	0.5 (1)
Peanut	0.4 (1)
Pork	0.4 (1)
IgE sensitization, no. (%)	
FPIES food	3 (7)

Other foods	7 (15)
OFCs categorized as high risk, no (%)	68 (77)

Table 1. Characteristics of subjects who underwent FPIES OFCs.

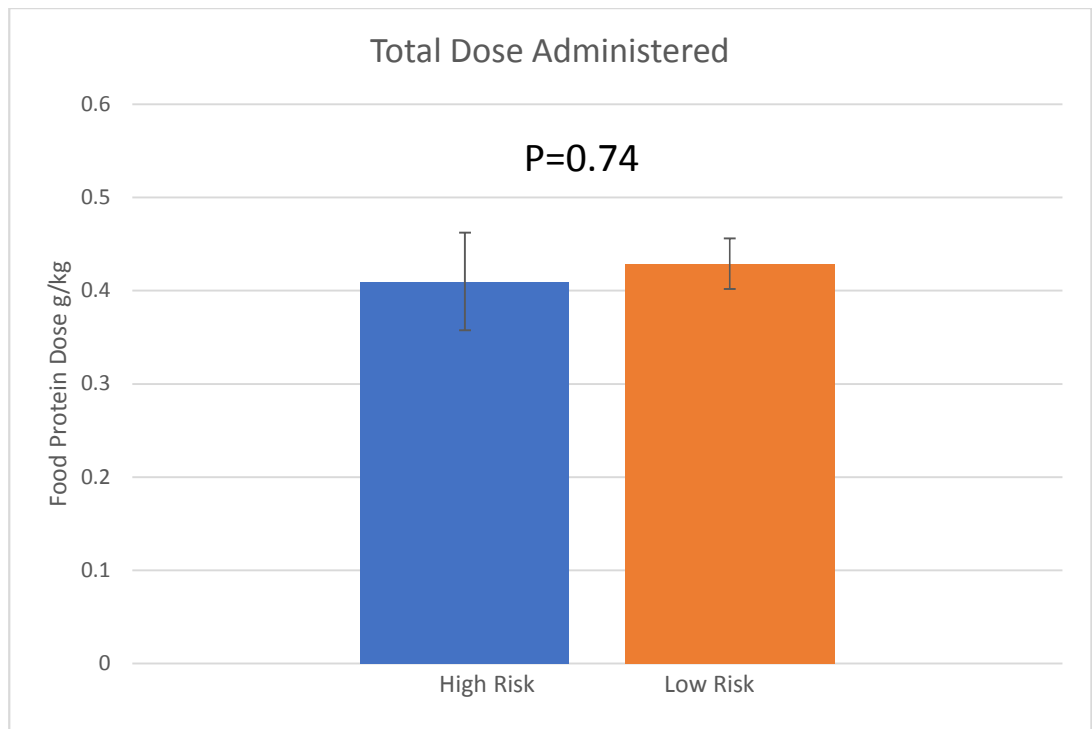


Figure 1. Total food protein dose administered between high risk and low risk OFCs.