

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication May 23, 2020; Revised May 27, 2020; accepted for publication May 28, 2020.

Corresponding author: Ronald A. Strauss, MD, Cleveland Allergy and Asthma Center, 20455 Lorain Road, #T03, Fairview Park, OH 44126. E-mail: straussallergy@yahoo.com.

REFERENCES

1. Patel GB, Kern RC, Bernstein JA. Clinical management review. Current and future treatments of rhinitis and sinusitis. *J Allergy Clin Immunol Pract* 2020; 8:1522-31.
2. Holgate ST, Polosa R. Treatment strategies for allergy and asthma. *Nat Rev Immunol* 2008;8:218-30.
3. Boushey HA. Drug use in asthma. In: Katzung BG, editor. *Basic and Clinical Pharmacology*. 11th ed. San Francisco, CA: McGraw-Hill; 2009:333-349.
4. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122(Suppl):S1-84.

<https://doi.org/10.1016/j.jaip.2020.05.058>

Reply to "Nasal cromolyn in the treatment of rhinitis"



To the Editor:

Strauss,¹ as a response to our review,² suggests intranasal cromolyn sodium (NasalCrom) as a treatment option for patients with allergic rhinitis (AR).

As stated by Strauss, the clinical benefits of intranasal cromolyn sodium are inferior to intranasal corticosteroids based on randomized clinical trials.^{3,4} Intranasal cromolyn sodium has shown efficacy when compared with placebo, and thus is an option for patients as an over-the-counter medication.⁵ Given its safety profile and current evidence, its use is likely most favorable for those who cannot tolerate intranasal corticosteroids or require short-term prevention before known exposures.^{6,7} In addition, intranasal cromolyn sodium is an option for treatment of AR in pregnant patients.⁶

In summary, intranasal cromolyn sodium is a pharmacological treatment option, particularly as an add-on or second-line treatment for AR.

Gayatri B. Patel, MD
Anju T. Peters, MD, MSCI

Division of Allergy and Immunology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Ill.

The study was funded by Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine; and Ernest Bazley Foundation.

Conflicts of interest: A. T. Peters is a consultant for Sanofi-Regeneron; and consultant at and receives research support from AstraZeneca and OptiNose. G. B. Patel declares that she has no relevant conflicts of interest.

Received for publication June 6, 2020; accepted for publication June 8, 2020.

Corresponding author: Anju T. Peters, MD, MSCI, Division of Allergy and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611. E-mail: Anjupeters@northwestern.edu.

REFERENCES

1. Strauss R. Nasal cromolyn in the treatment of rhinitis. *J Allergy Clin Immunol Pract* 2020;8:2841-2.
2. Patel GB, Kern RC, Bernstein JA, Hae-Sim P, Peters AT. Current and future treatments of rhinitis and sinusitis. *J Allergy Clin Immunol Pract* 2020;8:1522-31.

3. Bousquet J, Chantal I, Alquié MC, Charpin D, Didier A, Germouty J, et al. Prevention of pollen rhinitis symptoms: comparison of fluticasone propionate aqueous nasal spray and disodium cromoglycate aqueous nasal spray. A multicenter, double-blind, double-dummy, parallel-group study. *Allergy* 1993;48:327-33.
4. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;62:125-34.
5. Meltzer EO. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther* 2002;24:942-52.
6. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122(Suppl):S1-84.
7. Wise SK, Lin SY, Toskala E. International consensus statement on allergy and rhinology: allergic rhinitis-executive summary. *Int Forum Allergy Rhinol* 2018;8: 85-107.

<https://doi.org/10.1016/j.jaip.2020.06.014>

Oral food challenge protocol for food protein-induced enterocolitis syndrome: time for a change?



To the Editor:

We read with interest the paper by Guenther et al¹ on the food protein-induced enterocolitis syndrome (FPIES) oral food challenge (OFC). In particular, their study aimed to assess whether a single-serving dose was sufficient to elicit FPIES symptoms, or an additional serving dose, after 2-3 hours of observation, was needed. Indeed, the international consensus guidelines² on FPIES suggested administering the challenge food at the dose of 0.06 to 0.6 g/kg of body weight divided into 3 equal doses over 30 minutes, followed after 2-3 hours by a full-serving dose, when a low amount of food protein was given. The authors¹ found that all positive OFCs (10 of 88 [11%]) occurred after the single divided dose, and not even 1 reaction occurred after the administration of the additional full dose. The study concluded that, as the additional serving dose was not necessary to provoke symptoms, the actual FPIES-OFC protocol² should be refined.

Our group has recently published a study³ on a modified FPIES-OFC protocol; because FPIES is a non-IgE-mediated allergy, we believe that, to unveil the trigger dose, a longer observation time between food doses must be taken into consideration to allow the symptoms to occur. Thus, we adopted an OFC protocol, starting from the administration of 25% of the serving dose. After 4 hours, in the absence of symptoms, we administered the remaining 75% of the serving dose. Our work demonstrated that the first single administered dose, corresponding to a quarter of full dose, calculated as 0.3 g of food protein/kg of body weight, was sufficient to trigger symptoms in all positive OFCs (19 of 54), and the symptoms occurred with a median time latency of 120 minutes (range, 60-230 minutes).

Conversely, Guenther et al's study¹ found a median trigger dose of 0.35 g/kg corresponding to 50%-100% of the full age-appropriate serving dose with a time latency between the completion of the initial divided dose and the occurrence of symptoms within 2-3 hours. However, the required trigger dose may have been overestimated because, administering 3 equal doses over 30 minutes, the authors are not enabled to know if the symptoms were elicited by the first, the second, or the last dose.

Many reports⁴⁻⁷ on the FPIES-OFC protocol have been published. Our experience is in agreement with the findings by Infante et al,⁴ which showed that 25% of the full dose is enough to provoke reactions and that the observational time between

the first and the second dose should be longer than 30 minutes. On the contrary, it is in disagreement with Wang et al's results,⁶ which showed that one-third of the serving dose was necessary to have positive OFCs (57%), but the remaining challenges failed at home at a higher food dose.

More research data are needed to find out a valid alternative OFC protocol to the one currently used.² The ideal one should elicit symptoms at the lowest dose, and for that reason, the interval from the doses should be longer at least 2-3 hours.

Simona Barni, MD^a

Lucrezia Sarti, MD^a

Giulia Liccioli, MD^a

Mattia Giovannini, MD^a

Lucia Liotti, MD^b

Elio Novembre, MD, PhD^a

Francesca Mori, MD, PhD^a

^aAllergy Unit, Department of Pediatrics, Meyer Children's Hospital, Florence, Italy

^bPediatric Unit, Hospital of Senigallia, Senigallia, Italy.

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication April 29, 2020; accepted for publication June 11, 2020.

Corresponding author: Simona Barni, MD, Meyer Children's Hospital, Viale Pieraccini, 25, 50139 Florence, Italy. E-mail: simonabarni@hotmail.com.

REFERENCES

1. Guenther MW, Crain M, Parrish CP, Bird JA. An observed serving dose may not be necessary following a standard divided-dose FPIES oral food challenge. *J Allergy Clin Immunol Pract* 2020;8:1462-4.
2. Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017;139:1111-26.e4.
3. Barni S, Sarti L, Mori F, Liotti L, Pucci N, Novembre E. A modified oral food challenge in children with food protein-induced enterocolitis syndrome. *Clin Exp Allergy* 2019;49:1633-6.
4. Infante S, Marco-Martin G, Zubeldia JM, Fuentes-Aparicio V, Alvarez-Perea A, Cabrera-Freitag P, et al. Oral food challenge in food protein-induced enterocolitis syndrome by fish: is there any room for improvement? *Int Arch Allergy Immunol* 2019;179:215-20.
5. Vazquez-Ortiz M, Machinena A, Dominguez O, Alvaro M, Calvo-Campoverde K, Giner MT, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. *J Allergy Clin Immunol Pract* 2017;5:512-5.e1.
6. Wang KY, Lee J, Cianferoni A, Ruffner MA, Dean A, Mollleston JM, et al. Food protein-induced enterocolitis syndrome food challenges: experience from a large referral center. *J Allergy Clin Immunol Pract* 2019;7:444-50.
7. Infante S, Marco-Martin G, Sanchez-Dominguez M, Rodriguez-Fernandez A, Fuentes-Aparicio V, Alvarez-Perea A, et al. Food protein-induced enterocolitis syndrome by fish: not necessarily a restricted diet. *Allergy* 2018;73:728-32.

<https://doi.org/10.1016/j.jaip.2020.06.024>

Reply to "Oral food challenge protocol for food protein-induced enterocolitis syndrome: time for a change?"



To the Editor:

We would like to thank Barni et al for their comments.¹ Food protein-induced enterocolitis (FPIES) is a non-IgE-mediated food allergy in which infants and toddlers present with delayed vomiting with or without diarrhea, 15% in shock.² There is currently no biomarker to aide in diagnosis, no biomarker to aide in determination of causative food(s), and no biomarker to assess when one has outgrown the allergy. Oral food challenges (OFC) are currently the only way to clearly identify if a

particular food is a trigger and whether a child has outgrown the allergy.

In 2017, the International Guidelines on FPIES were published.² Within the guidelines, a suggested FPIES OFC protocol based on literature at that time was described (administer challenged food at a dose of 0.06 to 0.6 g/kg of body weight divided into 3 equal doses over 30 minutes, often followed by a full serving 2 to 3 hours later with a second observation period). Although clinicians may use this protocol, questions as to the necessity of a divided dose early on and/or reaching full serving size have been raised. As such, there are additional publications using modified approaches to FPIES OFC.³⁻⁵

In 2019, we published our experience with the modified FPIES OFC protocol using single dose one-third serving size, based on food and age of child, followed by a 4-hour observation period and home introduction over 9 to 12 days.³ We performed 169 FPIES food challenges in which 30 patients (18%) had positive challenges, 17 on day of the challenge (57%) and 13 during up dosing at home (43%).³ Of the 13 who reacted at home, all were characterized by delayed diarrhea and 3 had vomiting. These reactions occurred early on in up dosing either day of initial challenge or within first few days (not reaching a serving size) and only 1 sought additional medical care but did not need intervention.

In 2019, Barni et al⁴ published their experience with a modified FPIES OFC protocol in which patients were given the initial dose equivalent to 25% serving size, followed by a 4-hour observation period, and those who did not react received the remaining 75% serving size followed by an additional 4-hour observation period. In their cohort of 54 patients, 19 patients (35%) had positive challenges, all of whom reacted after the 25% serving size. The remainder who did not react never reacted.

Most recently, in this *JACI in Practice* commentary, the difference was highlighted. In our cohort, we have children who have delayed reactions after FPIES OFC, albeit mild, and they do not. However, the real question is: why is there a difference? First, we know that the patient population (children) and dosing amounts are similar. We give a third of a serving size and they give a quarter of a serving size. Is the difference due to the number of patients in each cohort, 54 versus 169? We do see more patients but do not think that is the answer or the whole answer. Interestingly, we had an overall reaction rate of 18% compared with their 35%. What about history of prior reaction? Although we may be able to explain diarrhea recurrence in 5 of the patients with a more chronic FPIES-type reaction history, we cannot use this to explain the other 8 patients. What about severity of the original reaction? We did not find this to be associated with delayed reaction in our cohort. What about the food itself? Although there were some differences in foods challenged, milk was the most common food challenged in both populations. What about actual patient cohorts or geographical region? We know there has been different temporal patterns established for presentation and acquisition of tolerance in FPIES across different geographic areas.² Additional data from cohorts in other regions may help to establish if different patterns in food challenge reactions can be expected as well. What about age of the patient undergoing FPIES OFC or the time between last reaction and OFC? Although we are unsure of the age group challenged in Barni's cohort outside of those with a positive food challenge, we do know that in our overall 169 patients, the mean age at the time of challenge was 37 months and the mean time to rechallenge from original exposure was 31.4 months. Of the 13 patients with delayed reaction, we found the timing to be similar, the mean age of time of challenge was 35 months and the mean time to rechallenge was 29 months.