

Letter to the Editor

Accurate oral food challenge requires a cumulative dose on a subsequent day

To the Editor:

Food allergy remains a major problem, not only in terms of an accurate diagnosis to determine the clinically relevant allergen but also to avoid unnecessary or even harmful elimination diets. Oral food challenges are the gold standard in the diagnostic workup of suspected food-related symptoms.¹ Since we observed that some of our oral food challenges were positive only on the day after a cumulative dose had been given, we aimed to investigate the percentage of this kind of positive reaction. A further end point was whether differences between the various foods would be seen.

We prospectively performed 490 oral food challenges with the 6 most common food allergens—cow's milk ($n = 109$), hen's egg ($n = 166$), wheat ($n = 35$), soy ($n = 20$), peanut ($n = 103$), and hazelnut ($n = 57$).

Oral food challenges were performed in a double-blind, placebo-controlled fashion in 151 of 490 (31%) cases, and open challenges in children younger than 1 year in the absence of severe eczema or in children with a clear history of immediate type reactions (339 of 490, 69%). Briefly, up to 7 increasing doses were administered at 30-minute intervals by using a semilog scale.²⁻⁴ For cow's milk challenges, fresh pasteurized cow's milk containing 3.5% fat was used; similarly, hen's egg challenges were performed with pasteurized hen's egg, wheat challenges with wheat powder (Kröner, Ibbenbüren, Germany), peanut challenges with roasted peanuts, hazelnut challenges with raw hazelnut, and soy challenges with soymilk (Alpro, Düsseldorf, Germany) (Table I).

The food challenges were stopped as soon as objective clinical symptoms were observed or when the highest dose was reached. Criteria for assessing an oral food challenge were used according to previous standards.⁵ In the case of a negative outcome on the first day, a cumulative dose was given (combining the 7 doses from the first day in a single challenge meal). In double-blind, placebo-controlled food challenge, this cumulative dose was still blinded. The study was approved by each local ethic committee.

Of 490 oral food challenges, 289 (59%) were assessed as positive, of which 251 (87%) were assessed as positive during the 7 increasing dose steps and 38 (13%) after having administered the cumulative dose on another day. Twenty-six of the 38 children (9% of all positives) presented with urticaria and/or angioedema,

and the other 12 with stomach ache, nausea, redness, worsening of eczema, or contact urticaria. Similar results were obtained for all foods (Table II).

Our data indicate that a considerable number of oral food challenges may be assessed as falsely negative if a cumulative dose on another day is also not administered. Children may then be at risk of unexpected sudden allergic reactions at home, or it may not be possible to recognize the clinical relevance of a food for the underlying atopic eczema. It is not yet clear whether it makes a difference if the cumulative dose is administered directly the day after or a few days later.

The most probable reason for an oral food challenge that is positive only after a cumulative dose on another day may be an induction of a short-term clinical nonreactivity during the first day when 7 increasing doses are given every 30 minutes, as suspected some years ago.⁶ A break of only 1 night combined with a following higher dose than the ones before may then lead to clinical symptoms not seen on the first day. Remarkably, the phenomenon was observed irrespective of the food given—ranging from cow's milk to peanut.

One may argue that each dose is standing alone and patients reached a threshold only when the cumulative dose was given. However, in our view, there are 2 reasons supporting our hypothesis that induction of a short-term clinical nonreactivity is the more likely explanation. First, the difference between the last dose of the first day and the cumulative dose on another day is quite small (eg, for cow's milk 100 mL vs 144 mL) compared with the half-logarithmic steps during the first day. Second, we often observe minor clinical symptoms during the increasing doses in these cases, which can be overrun by the next steps signaling an intermittent clinical reaction and not nonreactivity (data not on the database).

In children with non-IgE-mediated reactions showing gastrointestinal symptoms, late clinical symptoms are frequently observed⁷; however, our study population consisted of children with atopic eczema and IgE-mediated reactions, showing immediate skin symptoms in the vast majority.

Our interpretation may be supported by findings that show that immediate-type symptoms were seen after accidental exposure to cow's milk in children with atopic eczema after a prolonged elimination diet.⁸ Hypothetically, this may be due to an increased sensitization during the long-term elimination diet. However, in contrast, our results suggest that even only 1 night may be

TABLE I. Oral food challenge conditions

	Cow's milk		Hen's egg		Peanut		Hazelnut		Wheat		Soy	
	Food (mL)	Protein (mg)	Food (mg)	Protein (mg)	Food (mg)	Protein (mg)	Food (mg)	Protein (mg)	Food (mg)	Protein (mg)	Food (mL)	Protein (mg)
Day 1, dose 1	0.1	3	40	5	12	3	25	3	4	3	0.1	4
Day 1, dose 2	0.3	10	110	14	40	10	83	10	10	8	0.3	11
Day 1, dose 3	1.0	33	380	50	120	30	250	30	35	28	1.0	40
Day 1, dose 4	3.0	100	1,140	150	400	100	830	100	100	80	3.0	110
Day 1, dose 5	10.0	330	3,800	490	1,200	300	2,500	300	350	280	10.0	360
Day 1, dose 6	30.0	1,000	11,400	1,460	4,000	1,000	8,300	1,000	1,040	800	30.0	1,100
Day 1, dose 7	100.0	3,300	38,000	4,900	12,000	3,070	25,000	3,000	3,500	2,800	100.0	3,600
Another day, cumulative dose	144.4	4,780	54,900	7,070	17,800	4,500	37,000	4,440	5,000	4,000	144.4	5,200

TABLE II. Outcome of oral food challenges

	n (%)					
	Cow's milk	Hen's egg	Peanut	Hazelnut	Wheat	Soy
No. of challenges	109 (100)	166 (100)	103 (100)	57 (100)	35 (100)	20 (100)
Age (mo), median	27	30	43	43	14	34
Male:female	86:23	102:64	60:43	36:21	20:15	14:6
Positive challenges after cumulative dose with	9 of 72 (13)	16 of 121 (13)	6 of 54 (11)	4 of 24 (17)	1 of 12 (8)	2 of 6 (33)
Urticaria/angioedema*	7 of 72 (10%)	12 of 121 (10%)	3 of 54 (6%)	3 of 24 (13)	1 of 12 (8)	—
Contact urticaria†‡	1 of 72 (1%)	—	1 of 54 (2%)	1 of 24 (4)	—	—
Redness, pruritus‡	—	4 of 121 (3%)	1 of 54 (2%)	—	—	—
Worsening of eczema	1 of 72 (1%)	—	—	—	—	—
Vomiting	—	—	—	—	—	1 of 6 (17%)
Stomach ache, nausea	—	—	—	—	—	1 of 6 (17%)
Profound lethargy	—	—	1 of 54 (2%)	—	—	—

*Three or more hives and/or angioedema that appeared on other places than perioral.

†Hives, for example, perioral after contact with the allergen.

‡Standing alone not a criterion for a positive food challenge.

sufficient to lose clinical nonreactivity, which was acquired during the induction of a short-term clinical nonreactivity of a single day. In line, immediate-type symptoms were seen in the positive reactions on another day (though not worsening of eczema).

In conclusion, as a consequence of our observations, we propose the inclusion of a second day with a cumulative dose to ensure a correct outcome of oral food challenges, avoiding false-negative results.

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