

Impact of Omalizumab on Food Allergy in Patients Treated for Asthma: A Real-Life Study



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What is already known about this topic? Anti-IgE therapy is able to raise the tolerance threshold among peanut-allergic patients. Omalizumab is studied as an ancillary treatment to reduce the anaphylaxis risk related to the oral immunotherapy (OIT) protocols for food allergy. Such clinical procedures are risky, as well as time and resource consuming. However, they are justified by the very poor quality of life experienced by food allergy sufferers. OIT may be unsuccessful in the most severe forms of food allergy.

What does this article add to our knowledge? When used in severe asthma, omalizumab induces a significant increase in food tolerance thresholds. This reduces the risk of food reactions, allows for the safe introduction of some foods, and increases the quality of life of children with concomitant food allergy.

How does this study impact current management guidelines? Omalizumab is not included in any food allergy management guideline. Our data indicate that it could be considered a replacement for OIT in case of unfeasibility or unresponsiveness. Further studies are needed to evaluate its cost-effectiveness.

BACKGROUND: The effects of omalizumab on food allergy thresholds have been little studied.

OBJECTIVE: To assess the real-life effects of omalizumab on food threshold tolerability in children treated for severe asthma.

METHODS: In this observational, real-life, efficacy study, we reviewed the food allergen thresholds of patients with severe asthma, as well as their immediate reactions to 2+ foods before and after a 4-month treatment with omalizumab. We also evaluated their control of asthma and their quality of life, as measured by Pediatric Quality of Life Inventory (PedsQL).

RESULTS: Fifteen children, allergic to 37 foods, were evaluated. Omalizumab induced an increase in the allergen threshold for milk, egg, wheat, and hazelnut from a mean 1012.6 ± 1464.5 mg protein to 8727 ± 6463.3 eliciting dose ($P < .001$). A total of 70.4% of subjects tolerated the complete challenge dose after 4 months of treatment with omalizumab. These foods were reintroduced in the patients' diet without the need for any oral immunotherapy procedures. The remaining foods were partially tolerated. The number of reactions to the unintended ingestion

of allergenic foods over 4 months dropped from 47 to 2. The PedsQL increased from 61 ± 5.32 to 87 ± 7.33 (parental judgment; $P < .001$) and from 65 ± 7.39 to 90 ± 4.54 (patients' judgment; $P < .001$). The mean cost of omalizumab was €1311.63 per month.

CONCLUSIONS: During treatment with omalizumab for severe uncontrolled asthma, the food allergen threshold increases to 8.6 times its original value. The quality of life of patients also increased, due to a better asthma control and a reduction in dietary restrictions. The cost/benefit ratio of such treatment for selected cases of food allergy remains to be evaluated. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1901-9)

Key words: Food allergy; Omalizumab; Oral Immunotherapy; Quality of life; Real-life studies; Asthma; IgE

Food allergy affects up to 4% of the population, and is more common in young children. Milk, egg, peanut, nut, and fish allergies are common causes of severe—and sometimes fatal—reactions, and could persist throughout life.¹ Anaphylaxis occurs in 10% of food-allergic children, multiple food allergy in 30%. Patients with severe and/or multiple food allergies are particularly prone to severe reactions, and show worse quality of life (QoL) scores.²⁻⁴ As in asthma—where the cost of the most severe forms exceeds by 10 times the mean cost of the disease⁵—the cost of the most severe forms of food allergy is likely far higher than the mean one, evaluated at \$4184 per child per year.⁶

The current standard of care for a food-allergic subject is the avoidance of the offending food/s.⁷ Research on oral immunotherapy (OIT) indicates that the administration of incremental doses of the allergenic food reduces reactivity.⁸⁻¹⁰ However, OIT seems to be able to produce desensitization, that is, “a temporary state of immunological unresponsiveness with recurrence of

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Abbreviations used

ACT- Asthma Control Test
 EoE- Eosinophilic esophagitis
 HRQoL- Health-related quality of life
 OFC- Oral food challenge
 OIT- Oral immunotherapy
 PedsQL- Pediatric Quality of Life Inventory
 QoL- Quality of life
 SCORAD- Scoring Atopic Dermatitis
 SIT- Specific immunotherapy
 TTF- Tolerance threshold to foods

allergic reaction to offending foods after a period of discontinuation of allergen ingestion after successful OIT,” rather than a sustained unresponsiveness, that is permanent immune tolerance to food off-OIT.¹¹⁻¹³ In the course of OIT, local adverse effects—as well as systemic and potentially serious reactions—are common, particularly in children with multiple food allergies.¹⁴ During OIT, the QoL of children with food allergies improves in some subjects, while deteriorating in others.¹⁵ Being highly specific,¹⁶ OIT is most appropriate in children who suffer from allergy to a single food. For children with multiple food allergies, a “multi-food OIT” has been proposed, but the literature on this procedure is still limited.^{17,18} Thus, in this case, other therapies could be considered, such as the use of immune response modifiers. Among them, the humanized monoclonal antibody against IgE (omalizumab) has been licensed for use in severe allergic asthma, with dosing based on body weight and baseline serum IgE concentration. Preliminary data from pilot studies showed that the anti-IgE therapy achieves a reduction of the likelihood of anaphylaxis on accidental peanut ingestion.¹⁹ On this basis, this type of therapy is currently being studied as a strategy for reducing side effects and speeding up buildup phase during desensitization procedures for peanut,^{20,21} milk,^{22,23} egg,²⁴ and multiple food allergies.^{18,25} From these studies, it is difficult to extrapolate the effects of omalizumab *per se* on food tolerance threshold.

In this real-life study, we assessed the effects of omalizumab on the food tolerance threshold in children with severe asthma and food allergy, for whom OIT would be unfeasible.

METHODS

We hypothesized that when children with food allergies receive omalizumab for their asthma, their tolerance threshold to foods (TTF) is increased, warranting a partial or total harmlessness of previously eliciting foods. To this purpose, our local ethics committee authorized us to review the clinical records of children matching our inclusion criteria (December 13, 2017, Prot. 1501/17).

Patients

We reviewed the data of patients with severe asthma (Global Initiative for Asthma guidelines) and immediate reactions to foods who were treated with omalizumab between August 1, 2014, and March 31, 2017. An immediate food-allergic reaction was defined as reported symptoms of urticaria, angioedema, rhinitis, asthma, and vomiting within 1 hour of the ingestion of a food to which the

patient was sensitized as determined by skin prick and *in vitro* tests.²⁶ All patients were sensitized to at least 1 perennial aeroallergen and showed inadequate asthma control (Asthma Control Test [ACT] ≤ 19), despite a treatment with high-dose inhaled corticosteroids + another medication. The threshold dose for inhaled corticosteroids was set at 250 $\mu\text{g/day}$ fluticasone for children younger than 12, and 500 $\mu\text{g/day}$ for older patients. All patients were to have a baseline IgE between 30 and 1500 IU/mL on at least 2 consecutive determinations. They were eligible to receive omalizumab as add-on asthma therapy within the remit of the Italian tax-supported health care system. As part of their clinical follow-up, the patients had performed periodically oral food challenges (OFCs), spirometry tests, QoL questionnaires, and hematologic evaluations.

This study reports data on subjects with immediate reactions to at least 2 foods. Patients with immediate reactions to a single food and a history of failure of OIT were also included. The rationale behind this choice is to focus on patients who could be considered as potential targets for immunomodulatory therapies.

The patients' sensitivity to inhalants and food allergens was documented by a positive skin prick test (wheal at least 3 mm larger in diameter than positive control ≤ 15 minutes after pricking) and/or an allergen-specific IgE level, with 0.35 kU/L as a lower limit of eligibility (ImmunoCAP, Thermo Fisher, Uppsala, Sweden). Total IgE were measured and patients exceeding the level of 1500 kU/L were not admitted to the treatment. We did not exclude patients with previous, life-threatening anaphylactic reactions. The only subjects excluded were those with chronic diseases potentially interfering with the evaluation—or the administration—of omalizumab (gastrointestinal or gastroesophageal chronic disease, chronic infections, hepatic disease, chronic nonallergic pulmonary disease). Patients on subcutaneous or sublingual immunotherapy for inhalant allergens were also not included. All patients signed a written informed consent for the challenge procedures. One of the authors (MCA) followed them before and throughout the treatment period.

Food challenges

Before inclusion, OFCs were performed to confirm food allergy, and to establish the threshold dose for each food. To evaluate the severity of the reactions—and to set the criteria for stopping the food challenge due to safety considerations—we used the standardized published American Academy of Allergy, Asthma, and Immunology/EuroPrevall protocol²⁷⁻²⁹ (see this article's Online Repository at www.jaci-inpractice.org). In case of reactions to baked food, we did not perform any challenge with the native food. We evaluated the difference between the provoking dose of the eliciting food at OFC (mg of proteins) before and after 4 to 6 months of treatment with omalizumab. To be conservative, the second challenge was administered during the 2 days before an injection of omalizumab. The information on the protein content of the foods was obtained from <https://ndb.nal.usda.gov/ndb/search/list>. In this study, we report on TTF, the number of foods fully tolerated after 4 months of treatment, and the number of subjects developing full clinical tolerance to foods. A full TTF was defined as the ability to tolerate a full serving of a specific food. For cow's milk, this was defined at 144.4 mL, corresponding to 4700 mg of proteins; for baked milk at 80 g, corresponding to 6960 mg of proteins; for hen's egg at two 45 g eggs, or 11,160 mg of proteins; for baked egg at 80 g, corresponding to 9520 mg of proteins; for hazelnut at 64 g, or 8847.5 mg of proteins; and for wheat at 220 g, that is, 10,060 mg of proteins.

TABLE I. Demographic characteristics and asthma status of the 15 patients

Patient characteristic	N (%)	Median	Range	25th, 75th percentile
Age, mo	15 (100)	144	96-276	120, 180
Total IgE	15 (100)	689	208-1491	345, 884
ACT	15 (100)	16	9-19	13, 18
SCORAD	3 (20)	21	18-34	19.5, 27.5
Duration of asthma, mo	15 (100)	61	24-112	38, 79
FEV1 % of predicted <12 y	6 (40)	91	65-106	75.5, 96.5
FEV1 % of predicted >12 y	9 (60)	70	65-74	69.7, 72.5
Asthma treatment				
Fluticasone $\geq$ 500 mcg/d	14 (93.3)			
Salmeterol	11 (73.3)			
Montelukast	6 (40)			
$\geq$ 2 drugs	15 (100)			
$\geq$ 3 drugs	4 (26.7)			
SPT +ve and/or sIgE >0.35				
Dermatophagoides farinae and pteronyssinus	7 (46.7)			
Cat dander	9 (60)			
Dog dander	10 (66.7)			
Alternaria	7 (46.7)			

ACT, Asthma Control Test; FEV1, forced expiratory volume in 1 s; SCORAD, Scoring Atopic Dermatitis; SPT, skin prick test.

Quality of life

We administered a Pediatric Quality of Life Inventory (PedsQL) 4.0 questionnaire, based on a 23-item, self-reported generic QoL scale for children in the Italian context (<http://www.pedsql.org/translations.html>). These health-related quality of life (HRQoL) measures are known to have a good reliability and construct validity in a wide variety of general and disease-specific populations, and have shown responsiveness to meaningful change.³⁰ The PedsQL 4.0 Generic Core Scales instrument consists of 4 domains: (1) physical, (2) emotional, (3) social, and (4) cognitive functioning. It includes formats for children and adolescents from 2 to 18 years of age (parent-proxy report) and from 5 to 18 (self-report). For ease of interpretation, items are scored and linearly transformed into a 0 to 100 scale. Higher scores indicate better HRQoL.

Study design

This is a real-life observational efficacy study (Table I). The cohort design did not include reference groups. Each patient underwent diagnostic food challenges, to establish the reactivity threshold before treatment. As soon as the patient was in stable clinical conditions (2-3 days after the challenge procedure), omalizumab treatment was initiated—as per the Italian Drug Agency (Agenzia Italiana del Farmaco) labeling information—at the dose of 0.016 mg/kg/IgE every 14 to 28 days.³¹ Trained nurses administered the injections at our outpatient clinic. Before the procedure, and at the end of the study, pulmonary function tests (spirometry with bronchodilator examination), ACT, and a dermatological assessment for the definition of Scoring Atopic Dermatitis (SCORAD) (in case of eczema) were performed. After 4 months of treatment, 2 days before an administration of omalizumab, oral provocation tests with previously tested foods were performed, to reassess the primary outcome (TTF) and to allow the dietary introduction of fully tolerated foods. We measured the change from baseline in total IgE and the adverse events before, during, and after omalizumab. Finally, we measured the QoL before and after the treatment, using PedsQL questionnaires.³²

Statistical evaluation

Because of its observational nature, the study was not prospectively powered to detect any particular effect. Data were analyzed with the SPSS package (IBM Corporation, Armonk, NY). The continuous variables are expressed as a median (min-max). Categorical data are provided as numbers of cases and percentages. Differences between baseline and follow-up time points for food reactivity, QoL scores, and laboratory markers were calculated using the Wilcoxon signed-rank test. A *P* value of .05 or less indicates statistical significance. We calculated the odds ratios and the corresponding 95% confidence intervals, to assess the determinants significantly associated with the variation of food tolerance threshold.

RESULTS

Of 115 patients treated with Xolair for severe asthma between 2014 and 2017, 15 children (12 M, 3 F) satisfied the inclusion criteria (Figure 1). Their demographic characteristics are reported in Table I. Despite treatment with high-dose inhaled corticosteroids + at least another medication, their median ACT was 16 (mean, 15.13 $\pm$ 2.92). Only 3 patients had atopic dermatitis (AD), with SCORAD ranging from 18 to 34. Their prevalent inhalant sensitization was dog and cat dander. The patients had clinical histories of immediate reaction to 37 foods. Reactions included the reported onset of symptoms and signs of an allergic reaction (see Appendix A, available in this article's Online Repository at www.jaci-inpractice.org). Six of them were reactive to 1 single food for which the OIT had been unsuccessful. All these 6 patients, and 5 of 9 of the others, were equipped with auto-injectable epinephrine devices. In the 4 months before the administration of omalizumab, the 15 patients reported 47 reactions, 3 of which required the use of epinephrine.

Baseline reactivity threshold was measured by OFC for 23 foods including milk, baked milk, egg, baked egg wheat, and hazelnut (Table II). Challenges were performed openly, except in 2 cases of older children with a possible psychological component

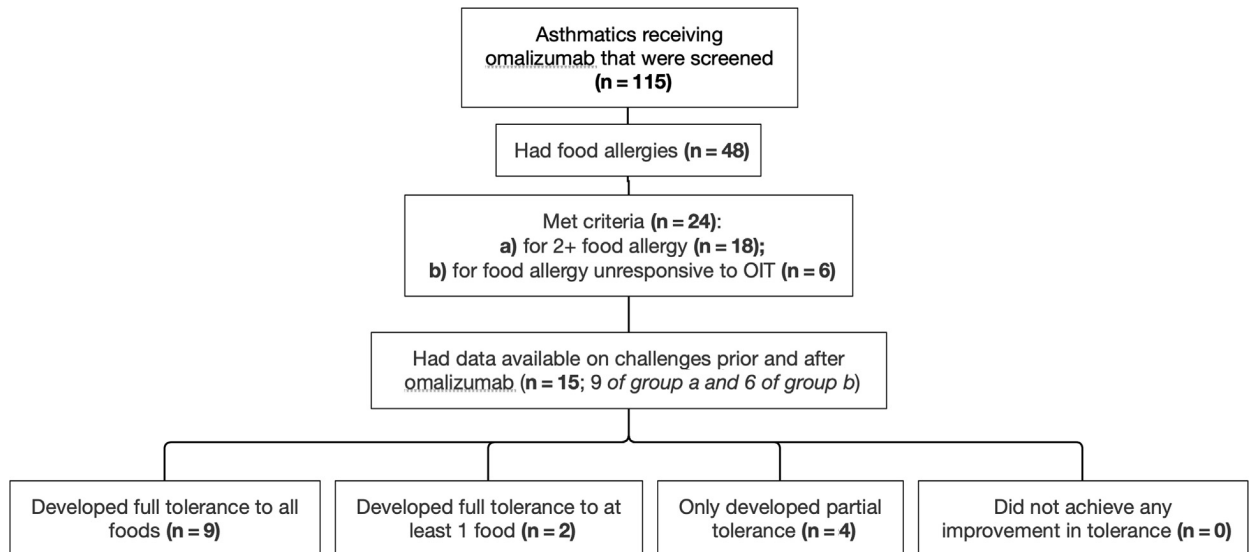


FIGURE 1. CONSORT flow diagram of the population screened and included. *OIT*, Oral immunotherapy.

TABLE II. Patient characteristics per single participant

ID	Age	Sex	Eliciting foods	Failed OIT	Initial threshold*	Omalizumab dose	Threshold on omalizumab	Tolerance full/partial
1	15	M	Egg	Egg	31.00	450.00	11,160.00	Egg
2	23	M	Milk		512.00	600.00	4096.00	Milk
	23	M	Egg		545.60		5580.00	Egg
3	19	M	Wheat		1170.00	150.00	9360.00	Wheat
	19	M	Milk		2048.00		8192.00	Milk
4	11	M	Milk		8.00	525.00	2048.00	Milk
	11	M	Egg		31.00		11,160.00	Egg
5	11	M	Baked egg		3332.00	300.00	9520.00	Baked egg
	11	M	Baked milk		191.40		6960.00	Baked milk
6	12	M	Milk	Milk	32.00	900.00	4096.00	Milk
7	10	M	Baked milk		2436.00	300.00	6960.00	Baked milk
8	14	M	Baked milk	Milk	34.80	450.00	5568.00	Baked milk
9	15	F	Egg	Egg	5580.00	1,200.00	11,160.00	Egg
	15	F	Baked milk		3480.00		6960.00	Baked milk
10	8	F	Milk	Milk	8.00	75.00	8192.00	Milk
11	12	F	Wheat		845.00	600.00	10,400.00	Wheat
12	12	M	Milk	Milk	140.80	150.00	2304.00	Milk
13	10	M	Egg		57.04	900.00	11,160.00	Egg
	10	M	Milk		460.80		8192.00	Milk
14	9	M	Baked milk		1740.00	225.00	7830.00	Baked milk
	9	M	Hazelnut		13.80		35,328.00	Hazelnut
15	18	M	Wheat		585.00	600.00	10,400.00	Wheat
	18	M	Milk		8.00		4096.00	Milk
Mean $\pm$ SD					1012.6 $\pm$ 1464.5		8727 $\pm$ 6463.3	$P < .001$
Median (range), [25th, 75th percentile]					460.8 (8-5580), [31, 1740]		8192 (2048-35,328), [5568, 10,400]	

OIT, Oral immunotherapy; *SD*, standard deviation.

*mg proteins eliciting dose.

in their reactions (2 double-blind placebo-controlled food challenges were carried out with milk, 1 with egg and 1 with hazelnut). Fourteen foods, including beef (patients 5 and 8), hazelnut (patient 4), egg (patient 11), walnut (patient 14), pea-nut (patient 14), soy (patient 4), pea (patient 4), tomato (patient

3), peach (patient 14), apricot (patient 14), kiwi (patient 2), fig (patient 2), and chestnut (patient 2), were not evaluated at challenge. Omalizumab was administered at the median dose of 450 mg/month (mean, 535 $\pm$ 287.5). The total dose of omalizumab administered in the whole group was 8025 mg/month,

TABLE III. Median PedsQL score before and after the treatment with omalizumab in 15 children

PedsQL	Parents group		Patients group	
	Before treatment	After treatment	Before treatment	After treatment
Total score median (range), [25th, 75th percentile]	61 (50.5-72), [57, 63.7]	87 (69.5-98.7), [84.5, 92]	65 (46.5-77), [59.6, 67]	90 (79.5-98.7), [87.3, 91.2]
Physical functioning median (range), [25th, 75th percentile]	59.7 (30-70), [45, 65]	92.5 (62-100), [84, 97]	66 (46-100), [57, 77]	94 (75-100), [85, 100]
Emotional functioning median (range), [25th, 75th percentile]	57 (32-75), [50, 62]	87 (68-100), [78, 91]	59 (30-71), [45, 65]	90 (78-100), [85, 93]
Social functioning median (range), [25th, 75th percentile]	57.5 (40-80), [53, 64]	87.5 (68-95), [78, 91]	62 (30-78), [50, 66]	90 (80-100), [85, 95]
Cognitive functioning median (range), [25th, 75th percentile]	68 (45-90), [67, 75]	91 (75-100), [82, 95]	69 (59-90), [64, 75]	85 (80-100), [85, 100]

PedsQL, Pediatric Quality of Life Inventory 4.0.

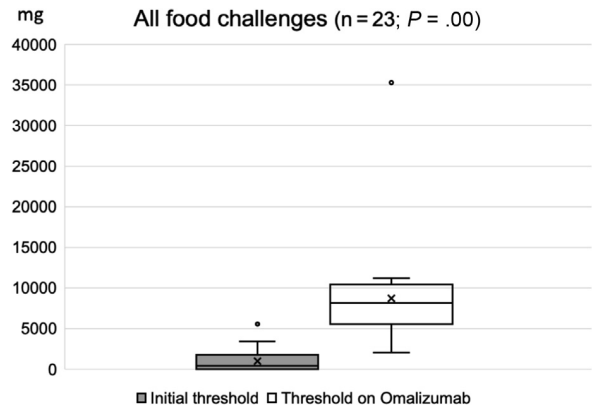


FIGURE 2. Box and whisker plot showing initial threshold (mg) and threshold after omalizumab treatment (mg) for 23 food challenges in 15 patients. The bars, box, and whiskers indicate the medians, 25th and 75th percentiles, and the ranges, respectively.

with individual doses ranging from 150 to 1200 mg/month. Considering the price in Italy, 1 month of omalizumab supply for these patients cost between €376 and €1478.4, for an average monthly cost of €1311.63.

Omalizumab was well tolerated in all children. After 4 months of treatment, the ACT score was significantly increased (median 22, mean 21.85 ± 2.74 ; $P < .001$). The 3 children with AD were completely clear (SCORAD, 0). Full challenge dose was administered without symptoms to 9 patients for 16 foods. Two patients ingested the full challenge dose to one food, and the partial challenge dose to a second; in these cases, the reactive food after treatment was milk. In total, full desensitization was reached for 19 foods (70.4% of the foods tested). Besides the 11 patients who developed full TTF to at least 1 specific food, 3 patients reacted to the post-treatment challenge for the only food tested (milk and baked milk), and 1 to both the foods tested (milk and egg). Though not completely tolerant, all these patients registered a substantial increase in their TTF: at the OFC, the first showed an 8-fold increase in his tolerance threshold to milk (4096 vs 512 mg protein) and a 10-fold increase in his tolerance threshold to egg (5580 vs 545 mg). The second reacted to a 128-fold greater dose of milk (4096 vs 32 mg protein); the third tolerated a 164-fold greater dose of baked milk (5568 vs 34 mg). The final TTF, expressed in mg of protein tolerated, was significantly increased by the treatment ($P < .001$; Figure 2). The differences in tolerance thresholds are significant for egg ($P = .04$), baked milk ($P = .04$), milk ($P = .001$), and wheat ($P = .01$) (Figure 3). Overall, food tolerance thresholds increased from a mean 1012.6 ± 1464.5 mg protein to 8727 ± 6463.3 eliciting dose ($P < .001$), with an 8.6-fold increase after the treatment with omalizumab (Figure 2). The median threshold was found increased by 17.8 times (Table II).

The 16 foods fully tolerated during the challenges were then successfully reintroduced in the diet of 11 children. The 7 recipes for children who tolerated food in an incomplete way were not introduced in the form of ingredients, but were permitted in the form of traces. The number of allergic reactions to the unintentional ingestion of foods dropped from 47 (1.74 ± 1.02 per patient) in the 4 months before the treatment to 2 (0.50 ± 0.32

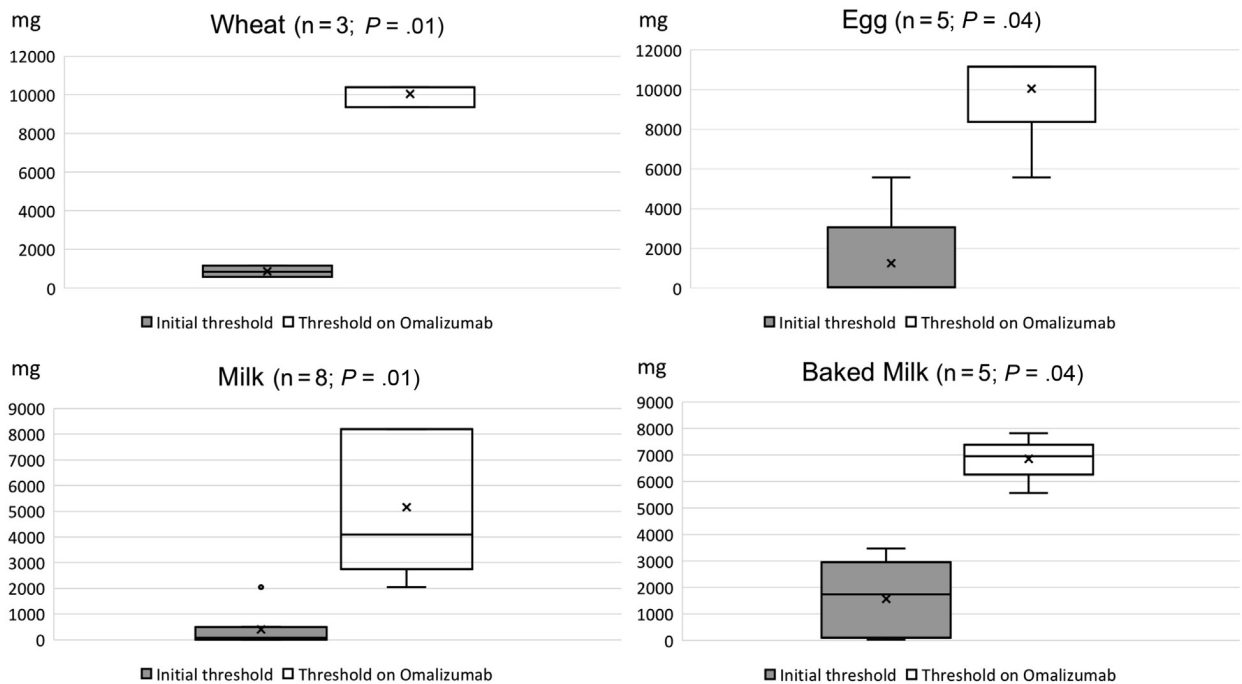


FIGURE 3. Box and whisker plot showing initial threshold (mg) and threshold after omalizumab treatment (mg) for four foods in 15 patients. The bars, box, and whiskers indicate the medians, 25th and 75th percentiles, and the ranges, respectively.

per patient) in the observation period ($P < .001$). None of these reactions required epinephrine. Fourteen months after the introduction of egg, one of the children experienced symptoms compatible with eosinophilic esophagitis (EoE). Because the diagnostic esophagoscopy did not confirm the clinical suspicion (eosinophils per field: 5), egg was not withdrawn from the diet.

To establish the factors associated with TTF, we examined the following variables: age at the time of reaction, basal food reactivity, basal ACT, basal total IgE, and the individual mg/kg dose of omalizumab. Logistic regression revealed no significant association of all these factors with TTF (basal food reactivity [$P = .3$], age [$P = .1$], ACT [$P = .5$], basal total IgE [$P = .2$], mg/kg dose of omalizumab [$P = .2$]).

We administered the PedsQL questionnaire to parents and patients. In both groups, the physical, emotional, social, and cognitive functioning was significantly increased by the treatment. The physical health summary score and the psychosocial health summary score were greatly increased (Table III).

During the 4-month treatment, patients reported only 2 reactions to the unintentional ingestion of foods (1 to peanut, 1 to peach), with a 95.7% reduction in the number of reactions. None of these reactions required epinephrine.

DISCUSSION

The utility of omalizumab in altering food allergen thresholds has not been investigated extensively. We aimed to assess the effects of omalizumab in a patient population that may have difficulty with OIT, namely those who failed OIT or have multiple food allergies complicating OIT administration. In peanut allergy, the administration of the drug for 24 weeks was reported to increase the reactivity threshold from 80 to 6500 mg protein.³³ In this study, complete tolerance (defined as the threshold of 10,000 mg of peanut) was reached in one third of

patients. In another study, which defined the threshold at 1000 mg of peanut, 44.4% of patients reached a complete tolerance over a similar period.³⁴ In this study, omalizumab increased the mean cumulative threshold dose from 63 mg peanut protein at baseline to 2881 mg at week 24. On this premises, omalizumab has been proposed as a pretreatment, to improve the safety of the OIT. In the desensitization procedures for peanut,^{20,21} milk,^{22,23} egg,²⁴ and multiple food allergies,^{18,25} omalizumab reduces the risk of the induction phase. Some of these studies on the omalizumab treatment, whose duration ranges from 8 to 18 weeks, exclude children with the most severe forms of allergy, including severe anaphylaxis,^{21,23} severe asthma,¹⁸ or both.²⁰ One open-label study offered omalizumab in case of treatment failure,¹⁸ but the results in terms of food allergen thresholds have not been reported. Thus, no information can be obtained from these studies on the effects of omalizumab on the reactive food allergen threshold *per se*, and the only available data remain those relative to peanut.

We decided do not report here the effects of omalizumab in patients with a single food allergy, unless they did fail an OIT course. OIT is generally able to increase the threshold for the specific food, taking 6+ months to be established.³⁵ For children with multiple food allergy, “multi-food OIT” has been proposed, but the literature on this procedure is still limited.¹⁷ Thus, we focused on patients for which omalizumab could be considered an alternative to the OIT, as potential targets for immunomodulatory therapies.

Our data show that children with severe asthma and food allergy may reach full TTF to 70.6% of the foods tested. Omalizumab is more effective in our children than in previous experiences.^{33,34} Because our thresholds in baseline conditions are similar to those of peanut in the published studies,^{19,33,34} it is unlikely that this difference could be explained by a different

severity of the caseloads. It may instead be due to the longer treatment period, different age groups (children vs adults), or to different food allergens (milk, egg, wheat, and hazelnut vs peanut).

In our patients, when a full TTF was not reached, the reactivity threshold was found to be increased by 8 to 164 times. Although in this limited caseload the number of reactions to the exposure to allergenic foods was reduced after the treatment, because the relationship between the threshold and severity of the reactions is not linear,³⁶ our data do not guarantee that omalizumab can automatically protect against anaphylactic reactions. However, the increase in TTF reduces the risk of reactions to tiny amounts of food allergens—including traces—and may allow us to cautiously introduce little amounts of food in these children's diet, opening the way for an exposure-induced reduction in the anaphylactic risk.

Studies evaluating the QoL by PedsQL in open populations of similar age reported a score of 72 (child-reported) and a score of 64 (parent-reported) in children with chronic health conditions.³² Our children with severe asthma and food allergy reported a lower score (62.99 and 60.47) before treatment. After treatment, the score steadily increased to values even higher than those found in the healthy populations (89.71 and 87.25 vs 81 and 78, respectively). Thus, a better asthma control and the perception of a reduction in food allergy risk translate into a very significant improvement of the QoL, involving not only the physical, social, and cognitive aspects, as in the OIT studies,¹⁵ but the emotional functioning as well.

We recorded a steady reduction in the number of immediate reactions to the unintentional ingestion of foods. Because uncontrolled asthma is a known risk factor for severe reactions, this may reflect the better asthma control. The only suspected food-allergic manifestation—EoE—was not confirmed. This does not mean that the consumption of previously eliciting foods under omalizumab is completely risk free. EoE has been described in 10% of cases after the reintroduction of peanut in an omalizumab/OIT protocol,²¹ and our children are continuously monitored for symptoms of food allergy. Larger studies will be necessary to establish the esophageal safety of food consumption while on omalizumab. On the other hand, because we were able to introduce all the 16 tolerated foods without any specific induction phase, our data indicate that omalizumab could be considered not complementary to, but substitutive of OIT.

In food allergy, the use of omalizumab instead of OIT is unquestionably economically unfavorable. In the United States, a 1-month supply of omalizumab costs between \$541 and \$2706.³⁷ In our group of severe asthma with food allergy, the monthly cost of €1311.63 converts to \$1637.00, similar to the US cost. The monthly cost of a food allergy, irrespective of its severity, has been calculated at \$348.6.⁶ Our patients present multisensitization, severe asthma, and food allergies: these characteristics are associated with a particularly severe phenotype of allergic disease, with a poor prognosis.^{38–41} From the studies on other allergic diseases, it is known that the severe forms are the most resource consuming. Uncontrolled asthma costs 4 times more than the controlled disease;⁴² severe asthma 10 times more than its intermittent forms.^{5,43} From these observations, it is reasonable that also in food allergy the cost of the most severe forms largely exceeds the mean costs. If we assume that the cost of the most severe forms exceeds by 10 times the average cost of food allergies, the mean monthly cost would amount to

\$3486.6.⁶ Under these conditions, the use of omalizumab as a substitute for avoidance and OIT would become economically plausible. Pharmacoeconomic studies based on a shared definition of severe food allergy are necessary to indicate the possibility of such approach in selected cases.

The study presents a number of weaknesses. Its design is purely observational; although we developed from the start the curiosity to evaluate what happens when patients with asthma treated with omalizumab also suffer from immediate food allergy, this cannot be defined a prospective trial. It has not been registered in any register, nor has it been supervised. Another limitation, inherent in its clinical nature, is the use of open challenges. In EuroPrevall, we used blind challenges, because open challenges are not completely exempt from subjectivity, and thus are unfit to finely evaluate thresholds. However, we required objective symptoms for positivity. Three patients did not undergo the entry challenges for recent anaphylaxis. In these patients, second-hand reporting of food reactions in their history may have led to an overestimation of the initial reactivity. Also, we decided to consider children reactive to baked milk and egg, positive to the minimum reactive threshold. This introduces a further element of arbitrariness, because we could have overestimated the postomalizumab improvement by artificially lowering the reaction threshold for nonbaked food.

Had we had the chance to use food allergy–specific QoL questionnaires, instead of generic ones, our study would have been more focused. To evaluate this aspect, we decided to rely primarily on instruments validated in the Italian context. So far, none of the specific QoL instruments has such validation.^{44,45} For this reason, we used the generic tool, which we are familiar with in our everyday practice. Despite these limitations, we are not aware of other observational efficacy studies that seized the opportunity to observe the effect of the treatment with omalizumab on food allergy thresholds when the medicinal product is administered to the same patients for the clinical indication of severe/refractory asthma. For all these reasons, the study is not free from potential bias. We offer it as a small set of preliminary data that could serve as the basis for further studies and/or clinical trials to be conducted on larger sample populations and with adequate means.

The study also allows for further considerations.

Because of its nature, omalizumab could improve the immediate food allergy symptoms, but not the chronic ones. This potential limitation—also intrinsic to the OIT—should arouse particular attention to possible non–IgE-mediated symptoms when patients consume allergenic food while on omalizumab. In our case, a suspect case of EoE was excluded by esophagoscopy.

When will it be possible to discontinue the administration of omalizumab in the population of patients with severe asthma and food allergy? The question is not clear for asthma, because patients generally experience a rebound of its symptoms after discontinuation of treatment.⁴⁶ For food allergy, after the OIT, a daily administration of the offending food may ensure a safe consumption, even without a sustained unresponsiveness.³⁵ For the moment, all the children of our group are continuing their pharmacological treatment, freely consuming the 16 reintroduced foods. Many of them also spontaneously introduced other offending foods without any formal challenge, and 13 of 15 started a 3-year course of specific immunotherapy (SIT) for their perennial allergen after 6+ months of treatment with omalizumab. We intend to start reducing omalizumab at the end of these

SITs, recommending a daily administration of the previously offending foods. The occurrence of unintentional ingestions of food allergens is being continuously monitored.

CONCLUSIONS

Although our study does not have sufficient statistical power to recommend omalizumab as a treatment for food allergy, our work adds to the literature arguing in favor of this proposal/suggestion. In this real-life study, omalizumab substantially increased the threshold of sensitivity to foods on OFCs. This collateral effect in patients with severe asthma offered protection against most unintentional ingestions of food allergens. Our observation could serve as the basis for a series of adequately powered, supervised, and controlled prospective studies, conducted to assess the extent of the benefits and risks related to the introduction of foods while on omalizumab. In fact, it is possible that—especially in the most severe forms of food allergy—the cost-effectiveness of a treatment with omalizumab is favorable. To measure the cost-effectiveness of this and other potentially useful biologic therapies, a shared definition of severe food allergy is needed. Using such a definition, studies will be able to precisely estimate the burden of severe food allergy for the single individual and the society alike.³

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ONLINE REPOSITORY

DOUBLE-BLIND PLACEBO-CONTROLLED AND OPEN ORAL FOOD CHALLENGE (OFC): OPBG PROTOCOL

1. Whom to challenge with what

- Children should be challenged with every food that is suspected to cause symptoms independently of sensitization and age.
- Children with multiple sensitizations, start with the food dependent on age (see table below) and level of sensitization (start with food with highest level). In the end, all suspected foods should be challenged.
- If the food-specific IgE and/or SPT are positive, but the child consumes the food on regular basis without having symptoms, an OFC is not necessary.
- If the food-specific IgE and/or SPT are positive and the child has any atopic disease, for example, AD, the following criteria should be followed:

At any age	cow's milk can be challenged
If the child is 6 months or older	Everything except seeds, tree nuts, peanuts, fish, shellfish
If the child is 12 months or older	No limitations

- DBPCFC is the standard** challenge method within OPBG. However, in certain cases, an open challenge may be considered but **after internal consultation and agreement** (see point 3 below).
- If atopic dermatitis (eczema) is present but there is no suspicion that it is associated with food and there is no elevated IgE or positive SPT, an elimination diet should be given for **at least 14** days:
 - If there is no change, do not challenge the child.
 - If there is improvement in the atopic dermatitis (change in SCORAD ≥ 10), challenge with the most relevant foods (eg, milk, egg, wheat, soy, peanuts) according to the age of the child (see the table above).
- Elimination diet: instead of cow's milk formula give highly hydrolyzed formula, for example, Nutramigen or amino acid formula, for example, Neocate. (In children with a suspected non-IgE-mediated gastrointestinal food allergy an amino acid formula is recommended.) If the child is taking **some solid food**, the following foods may be given:
 - Pears
 - Broccoli
 - Rice
 - Chicken
- If the child is **fully breast-fed**, do **not** perform a food challenge:
 - If the child has gastrointestinal and skin symptoms **and is sensitized**, remove that food from the mother's diet.

2. Elimination diet

The suspected allergen(s) should be excluded from the child's diet for a **minimum of 1 week** before challenge. Cow's milk should be replaced by hydrolyzed OR amino acid formula.

Nutramigen OR Neocate is the preferred formula, then any other highly hydrolyzed formula. No partially hydrolyzed formula or soy formula should be used, no sugar added. Highly hydrolyzed or amino acid formula without lactobacillus GG should be used.

If the child is reluctant to take the formula at first, a small amount of sugar may be added at the start of the elimination diet, but must be eliminated as quickly as possible and be null by the DBPCFC.

3. Internal revision

The following members of the OPBG Unit of allergy are available for decision support in food challenges:

Carla Riccardi
Lamia Dahdah
Vincenzo Fierro
Alessandro Fiocchi

4. Timetable

- If IgE determination or SPT has been performed more than 2 months before the challenge, repeat the test at the time of the OFC.
- In DBPCFC procedures, active and placebo challenges have to be carried out on separate days in a random order. Neither the family nor the supervising medical and nursing team should be aware of this but they should have the ability to find out if this becomes necessary for medical reasons.
- If eczema worsens after the first challenge part, then the second part is not to be carried out until eczema has returned to the prechallenge state. The same nurse and doctor should assess both parts (active and placebo) of the challenge.
- Doses should be given at least 20 minutes apart.
- If possible ensure each complete dose is taken in less than 5 minutes.
- If there are only subjective symptoms to a dose, wait to see if symptoms worsen. If symptoms have not worsened **within 40 minutes**, progress with the next dose or repeat the previous dose (decision to be made by the supervising clinician).
- After a challenge has been completed, the child has to remain under observation for a minimum of 2 hours. After this time, the child may be discharged if medical condition allows this. Details of what to do in the event of a delayed reaction must be given to the family before discharge.
- A follow-up phone call should be made to the family on the morning after the challenge to ensure that there have been no late onset symptoms.
- With an expected delayed reaction (eg, every child with AD), the second part of the food challenge should occur at least 48 hours after the first part.

Preparation of the challenge food

- Preparation of each dose should be made according to [Appendix C](#).
- Normally, only 1 food should be challenged at a time in a double-blind placebo-controlled way. However, in children who are unlikely to react more than 1 food may be challenged

together at the same time. If the challenge is positive, the individual foods have to be rechallenged one after the other.

3. In the case of multiple sensitizations to various foods and a return visit for an additional food challenge is in doubt, performing a DBPCFC with 2 allergens and 1 placebo in random order can be considered. In the case where 3 allergens should be tested, at least 2 placebos should be conducted. **The ideal goal remains conducting 1 allergen and 1 placebo.**

5. Undertaking the food challenge

Before the challenge

1. All challenges must be supervised and conducted by children's nurses and medical staff experienced in performing food challenges and recognizing and managing an anaphylactic reaction.
2. The pediatric medical team supervising challenge should assess the child before the challenge and determine whether or not they are fit for the challenge.
3. The child must be 3 days without fever and free from infectious symptoms.
4. Ensure antihistamines have not been taken within the previous 4 days.
5. Patients with a history of hay fever should not have challenges performed during the hay fever season.
6. Admit child in early morning. Child may have a light breakfast of food they have eaten previously without symptoms or prescribed diet before admission.
7. The nurse caring for the child undergoing the challenge must be present at all times throughout the challenge to assess the child, or this must be delegated to another appropriately skilled member of staff.

Food challenge procedure

8. Obtain written informed consent from the parent for the food challenge, if required by hospital policy.
9. Documentation of the food challenge must be done on the OPBG challenge documentation sheet.
10. Record weight, temperature, and pulse. Examine skin and record SCORAD score. Obtain blood for IgE and perform SPT if indicated (see points 4.1 and 4.2). Auscultate chest and record. Optional examination: respiratory rate, saturations, and blood pressure.
11. Calculate the dosage of appropriate rescue medication (intramuscular adrenaline, inhaled bronchodilator, oral or intravenous antihistamine, oral or intravenous corticosteroid). This should be prescribed on the medication chart and available for immediate use. Record the child's weight and the doses on the DBPCFC documentation sheet.
12. Site venous cannula if warranted by history. This will be decided by the responsible clinician.
13. Child must remain on ward throughout the whole procedure and for at least 2 hours after the completion of the challenge.
14. Challenge food should be covered in the clean kitchen area and only handled by the person performing the challenge. The food should be directly handled by the staff to prevent contamination; either a clean spoon or latex-free gloves should be used.
15. Commence challenge and administer challenge substance as per protocol for specific substance (see the dosages in Tables E1-E3).

16. Record all doses, times, and observations. Contact the supervising clinician if there are any symptoms or signs of an allergic reaction; the nurse should simultaneously commence treatment if appropriate
17. Child may play throughout the challenge, but should not be overactive, to reduce risk of exercise exacerbating potential allergic reaction.
18. Child may drink throughout challenge only water, tea, or juice previously safely consumed. Additional food should not be given. However, if the child is extremely hungry and upset and these measures have not calmed him or her, a very small amount of formula (less than 100 mL) may be given. Care must be exercised so that the child continues to take the challenge material.
19. The challenge arm will be stopped after any objective symptom or after any severe, persistent (over 40 minutes) subjective symptom. If in doubt, wait to see if symptoms worsen. If symptoms have not worsened in 40 minutes, then either repeat the previous dose or give the next dose (decision to be made by responsible clinician). Reactions should be treated according to the severity of the reaction (Appendix B) and the medical team informed.

After the challenge

20. Following a positive reaction, the child should remain under medical observation until fully recovered (minimum of 2-4 hours) and monitored (eg, pulse, respiration, saturation, BP, and auscultation of chest) until stable. The child may be admitted for overnight observation.
21. When a negative challenge has been completed, the child should rest or play quietly for 2 hours, and remain on the ward for that time.
22. Child must be assessed by the responsible clinician before discharge.
23. Before discharge ensure that the child and caretaker:
 - a. understand the need for restricting strenuous activities for 24 hours to reduce the risk of exercise-induced reaction;
 - b. are aware of the appropriate action to take if the subject develops further symptoms;
 - c. have appropriate contact details to access help/advice;
 - d. if reaction was positive, have antihistamine and, where necessary, self-injectable adrenaline available;
 - e. have understood dietary inclusion or exclusion with input from dietitian if appropriate; and
 - f. have appropriate follow-up arrangements.
24. Call the family on the morning after the challenge to ensure that there have been no late onset symptoms.

Completing the challenge

In case of DBPCFC, the second arm of the challenge will be undertaken on a separate day. Where a subject has had a reaction and has been treated with an antihistamine, it will be necessary to postpone the second stage for 4 days (see point 4 above).

Only when both parts have been completed and the challenge "code" broken will the challenge be considered as having been completed.

If the challenge is negative, the family should give the child a normal portion of the food at home. The family should be called the next day to ensure that there have not been any adverse effects. In addition, if the parents report that the child's atopic dermatitis has worsened in the 48 hours (maximum) after the

completion of the challenge, the child should be seen in the clinic.

Documentation of the food challenge

Complete the electronic documentation sheet. The decryption of the challenge should be documented in the child's file on the **OPBG clinical record**.

If the child has suffered a severe reaction (wheeze/stridor with signs of respiratory distress, hypotension, etc.) during the food challenge, a member of the expert committee (see point 3 above) should be notified for a case discussion.

Appendix A. Symptoms and signs of an allergic reaction

1. Skin

Erythema—flushed irritability

Urticaria—nettle rash

Pruritus—itch

Tingling—mouth/lips

Oedema—swelling

Eczematous rash

Cold peripheries—shut down

2. Nasal

Sneezing—plus itchy nose

Congestion—sniffing

Rhinorrhoea—runny nose

3. Ophthalmic

Ophthalmia—inflamed sore eyes

Runny eyes

Swollen eyes

Glazed expression

4. Respiratory

Tight/itchy throat

Wheeze

Hoarse voice/stridor

Tightness in chest

Use of accessory muscles

Tachypnoea

Dyspnoea—difficulty breathing

5. Gastric

Abdominal pain

Nausea

Vomiting

Diarrhea

6. Behavior (change)

Irritability

Drowsiness

Decreased activity

Uncomfortable

Anxiety

Distress

7. Cardiac

Tachycardia

Hypertension

Hypotension

Cyanosis

Appendix B. Medications for treatment of anaphylaxis

Chlorphenamine: 0.1-0.2 mg/kg PO/IV maximum 10 mg

Nebulized Salbutamol: 2.5-5 mg

Hydrocortisone:

2-12 years: 4 mg/kg IV, maximum 100 mg

13-18 years: 100-150 mg IV

Adrenaline: 1:1000 IM

Maximum IM dose 500 µg = 0.5 mL of 1:1000

Dose should be rounded up rather than down when giving **epinephrine**.

For children between 12 and 24 kg: Junior Epipen (0.15 mL)

For children 25 kg and above: Adult Epipen (0.3 mL)

Stridor can also be treated with **nebulized adrenaline** (1:1000) 1 mg/kg, maximum 5 mL diluted up to 5 mL with 0.9% saline.

Fluid resuscitation

Fluid replacement regime: 20 mL/kg bolus 0.9% NaCl.

Appendix C. Doses

There are to be 9 doses for both the active and placebo arm of the challenge. Challenge material may be prepared the previous day, if necessary.

For each active food the doses are as follows:

3 µg protein, 30 µg protein, 300 µg protein, 3 mg protein, 30 mg protein, 100 mg protein, 300 mg protein, 1000 mg protein, 3000 mg protein.

Detailed protocol for younger, bottle-fed infant:

A. Active part

1. Label 5 cups with A, B, C, D, and E. Cups A and B should hold 200 mL, cup C 1000 mL, cup D 50 mL, and cup E 300 mL.
2. A hydrolyzed or amino acid formula is to be used as the matrix for the food challenge. If the child has no symptoms of atopic dermatitis and no evidence of cow's milk allergy, normal cow's milk formula may be used.
3. In **cup A**, prepare 170 mL of hydrolyzed, amino acid, or cow's milk formula according to the manufacturer's instruction and set it aside. The water must be cooled to 40°C to 50°C to mix properly.
4. In **cup B**, measure 150 mL of cold (<50°C) water. A higher temperature could destroy the allergen.
5. Weigh the appropriate measure of food powder on a balance (see [Table E1](#) for the exact amount for each food).
6. Stir the measured food powder into the 150 mL of water in cup B and set aside.
7. In **cup C**, measure 1000 mL of cold (<50°C) water.
8. Add 1 mL of solution from cup B into the 1000 mL of water (<50°C) in cup C, stir, and set aside.
9. **Restir cup A.**
10. In **cup D**, mix 20 mL of the hydrolyzed, amino acid, or cow's milk formula from cup A with 20 mL of the solution from cup C.
11. **Restir cups A and B.**

12. In **cup E**, mix 150 mL of the hydrolyzed, amino acid, or cow's milk formula from cup A with 150 mL of solution from cup B.
13. 2 mL of cup D contains now 30 µg protein ("low protein solution") and 2 mL of cup E contains now 30 mg protein ("high protein solution").
14. If there is a color difference when the solutions are mixed, wrap the cups in aluminum foil. If desired, all cups can be wrapped in aluminum foil before performing the challenge.
15. Perform the challenge according to [Table E2](#).

B. Placebo part

1. In **cup F**, prepare 350 mL of hydrolyzed, amino acid, or cow's milk formula according to the manufacturer's instruction and set it aside.
2. Perform challenge according to [Table E3](#).

Detailed protocol for older children:

Protocol will follow when challenge material will become available.

Do not use the current dessert matrix for any child in the birth cohort.

TABLE E1. Food dose calculation

Be aware that the calculation might change with a new batch of the food powder (the protein content might be different).

Each center must double-check calculation for that batch before giving.

The calculation is made as follows: The protein dose for the whole challenge is 4.323333 g. Therefore where **x** is the protein content of the powder (in %) the formula is

$[100/x] \times 4.323333 \text{ g}$

(from the reasoning that x g of protein will come from 100 g powder so 1 g protein will come from $[100/x]$ g powder so 4.323333 g protein will come from $[100/x] \times 4.323333 \text{ g powder}$)

	Cow's milk (SMP)	Hen's egg	Wheat	Soy	Peanut	Fish
Protein content	36% $\pm$ 2.5%	44% min	10.6% $\pm$ 0.5%	50% $\pm$ 2.5%		
$\underline{X} =$	12.0 g	9.8 g	40.8 g	8.7 g		

TABLE E2. Food challenge doses: verum

Doses	Allergen	Doses given to child
1	3 μ g Cup D ("low protein solution")	0.2 mL
2	30 μ g Cup D ("low protein solution")	2 mL
3	300 μ g Cup D ("low protein solution")	20 mL
4	3 mg Cup E ("high protein solution")	0.2 mL
5	30 mg Cup E ("high protein solution")	2 mL
6	90 mg Cup E ("high protein solution")	6 mL
7	300 mg Cup E ("high protein solution")	20 mL
8	900 mg Cup E ("high protein solution")	60 mL
9	3 g Cup E ("high protein solution")	At least 200 mL

TABLE E3. Food challenge doses: placebo

Doses	Allergen	Doses given to child
1	None Cup F ("formula")	0.2 mL
2	None Cup F ("formula")	2 mL
3	None Cup F ("formula")	20 mL
4	None Cup F ("formula")	0.2 mL
5	None Cup F ("formula")	2 mL
6	None Cup F ("formula")	6 mL
7	None Cup F ("formula")	20 mL
8	None Cup F ("formula")	60 mL
9	None Cup F ("formula")	200 mL