

Clinical Communications

A three-level stepwise oral food challenge for egg, milk, and wheat allergy

Noriyuki Yanagida, MD^{a,b}, Takanori Minoura, MD, PhD^b,
Setsuko Kitaoka, MD, PhD^b, and
Motohiro Ebisawa, MD, PhD^c

Clinical Implication

- The 3-level stepwise oral food challenge, starting with a low dose and progressing to medium and full doses, is an effective approach to enable children with allergies to determine the maximal quantity of the allergen that they can safely consume.

TO THE EDITOR:

Oral food challenges (OFCs) are necessary for food allergy management.¹⁻³ The threshold dose varies among patients.⁴ Administration of a higher dose OFC after a low-dose OFC⁵ can avoid complete elimination.^{5,6} Our study aimed to clarify the safety and effectiveness of a stepwise OFC.

A 3-level stepwise OFC with a low-dose OFC was administered to diagnose food allergy or confirm tolerance acquisition safely at Sendai Medical Center. We included patients who first underwent a low-dose OFC for egg, milk, or wheat (STEP 1: 213 mg, 850 mg, and 374 mg, respectively) (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). Patients who tolerated the low-dose OFC received the medium-dose OFC for egg, milk, or wheat (STEP 2: 1550 mg, 3400 mg, and 2600 mg, respectively) within 12 months. If patients showed no reaction at STEP 2, a full-dose OFC for egg, milk, or wheat (STEP 3: 6200 mg, 6800 mg, and 5200 mg, respectively) was administered within 12 months. The symptoms and associated severity are described in Table E3, available in this article's Online Repository at www.jaci-inpractice.org. After a negative result for each OFC, patients were allowed to consume up to the recommended doses of protein from each suspected causative food. For suspected high-risk cases, a very-low-dose OFC for egg, milk, or wheat (STEP 0: 1.8 mg, 99 mg, and 146 mg, respectively) was implemented before STEP 1 (see detailed methods in this article's Online Repository at www.jaci-inpractice.org).

Of 909 patients, 149 did not meet our eligibility criteria (Figure 1). Of the 760 patients enrolled from 2010 to 2012, 432

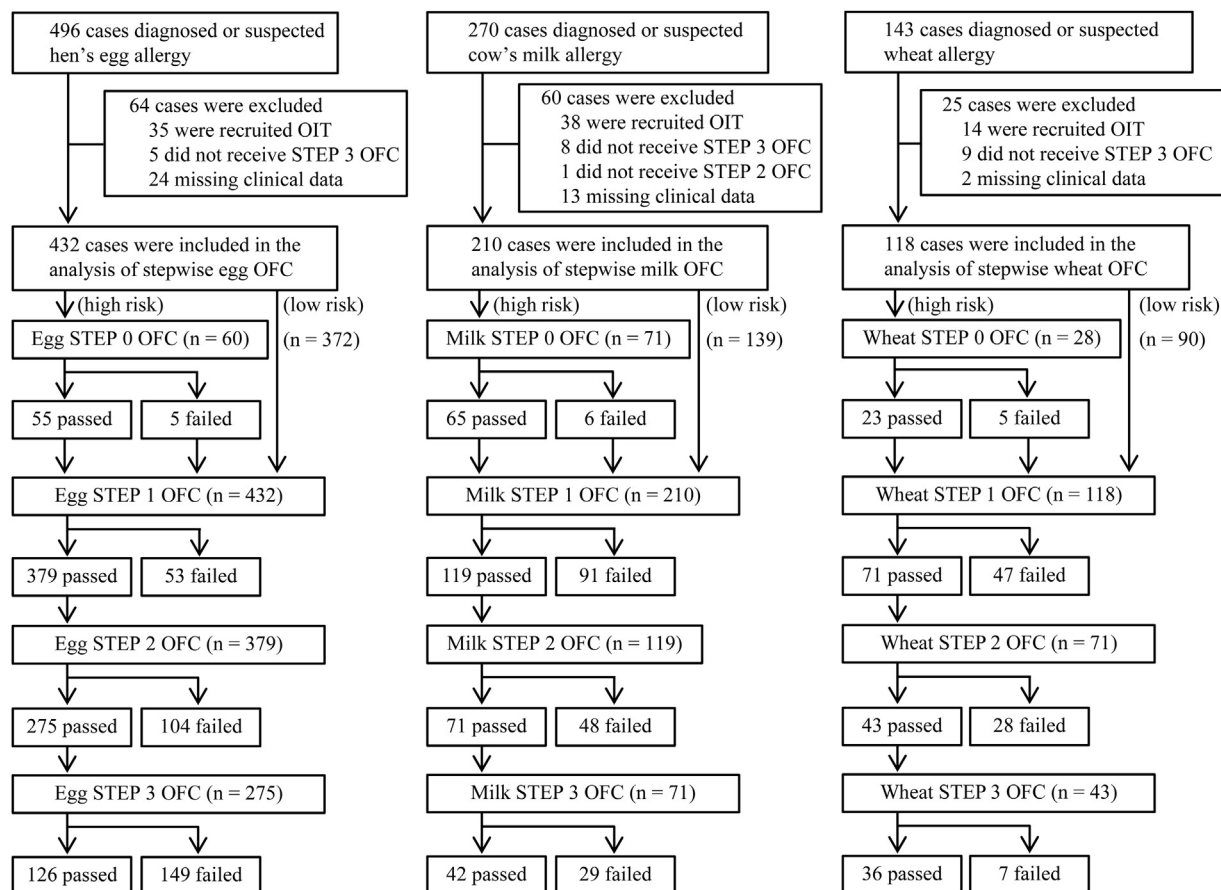


FIGURE 1. Patient enrollment. A stepwise oral food challenge (OFC) (STEP 0, STEP 1, STEP 2, and STEP 3; Table E1, available in this article's Online Repository at www.jaci-inpractice.org) was administered. OIT, Oral immunotherapy.

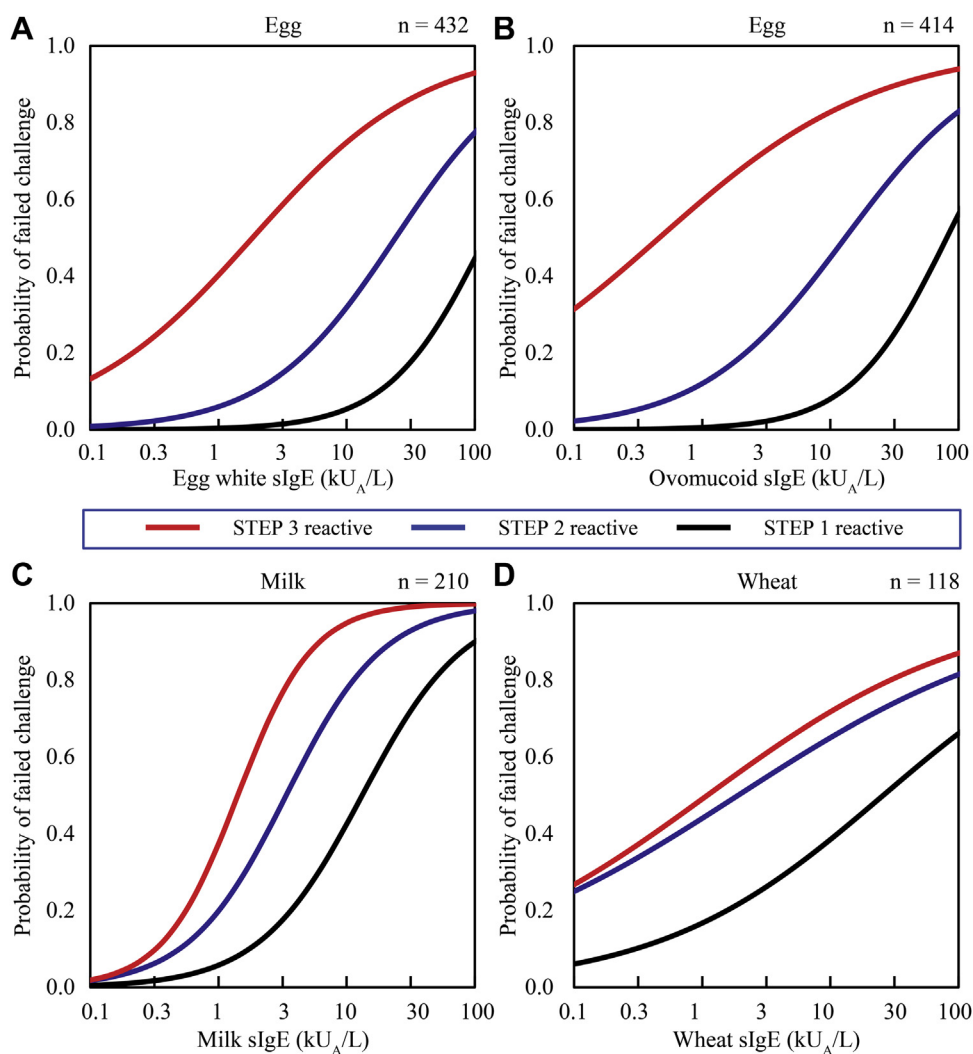


FIGURE 2. Fitted probability curves demonstrating stepwise oral food challenge (OFC) outcomes with respect to immunoglobulin E levels against (A) egg white, (B) ovomucoid, (C) milk, and (D) wheat. The probability curve was subdivided by the total cumulative dose of 3 different OFCs. *sIgE*, Specific IgE.

had a suspected egg allergy, 210 a suspected milk allergy, and 118 a suspected wheat allergy. As shown in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org), 516 patients (68%) reported a prior immediate reaction to a causative food, and 238 patients (31%) experienced food-related anaphylaxis. The median age of patients enrolled was 4 years.

As shown in Figure 1, 379 suspected egg-allergy patients (88%), 119 suspected milk-allergy patients (57%), and 71 suspected wheat-allergy patients (60%) passed STEP 1. STEP 2 was implemented approximately 195 days after completing STEP 1. Of these, 275 suspected egg-allergy patients (64%), 71 suspected milk-allergy patients (34%), and 43 suspected wheat-allergy patients (36%) passed STEP 2. STEP 3 was implemented approximately 190 days after completing STEP 2. Per our results, 126 suspected egg-allergy patients (29%), 42 suspected milk-allergy patients (20%), and 36 suspected wheat-allergy patients (31%) passed STEP 3. Patients in the 4 groups, divided by their threshold doses, differed significantly in serum specific IgE (sIgE) levels against causative foods (Fig E1, available in this article's Online Repository at www.jaci-inpractice.org). Probability curves based on OFC results for each step

showed intergroup variability (Figure 2). Probability curves subdivided by age (≤ 4 years or >4 years) were different in wheat allergic patients (Figs E2 and E3, available in this article's Online Repository at www.jaci-inpractice.org) as previously reported.⁷

Analyses of the best and worst cases, including data for excluded patients, revealed little change in the outcome (Figs E4 and E5, available in this article's Online Repository at www.jaci-inpractice.org). The positive rate of rechallenge after approximately 182 days since the initial positive OFC was 44% (97/222) (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

Among high-risk patients with a previously documented reaction, 159 ($n = 60$ [egg]; $n = 71$ [milk]; $n = 28$ [wheat]) underwent STEP 0 OFC before STEP 1. Of these patients, 16 exhibited reactions ($n = 5$ [egg]; $n = 6$ [milk]; $n = 5$ [wheat]), and no patients passed STEP 1 with the decreased total amount. The 90% positive predictive value (PPV) of STEP 1 for any of the foods was >100 kU_A/L (Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

Among the 556 patients who showed a positive reaction at any step, 14 showed a severe reaction (3%). Intramuscular adrenaline

was needed in 1 patient (0.2%), and the most severe reactions occurred in STEP 1 for milk (Tables E7 and E8, available in this article's Online Repository at www.jaci-inpractice.org).

This study examined the effectiveness and safety of a 3-level stepwise OFC. Although most patients did not tolerate the full allergen dose, most could tolerate the low or medium doses, thereby safely avoiding complete elimination of the causative food. Taking a low dose may enable patients to tolerate the higher dose more quickly. Severe symptoms were rare, and only one case of adrenaline required anaphylaxis occurred, further supporting the safe approach of this stepwise protocol. The 90% PPV of STEP 1 for any of the foods was $>100 \text{ kU}_A/\text{L}$. Therefore, STEP 1 OFC need not be avoided because of a high sIgE level against causative foods. More than half of the patients passed the rechallenge OFC after approximately 6 months. This may be because most participants were young and most participants underwent an egg OFC. The positive rates of rechallenge of the egg OFC have been reportedly low.⁸

The PRACTALL guidelines³ recommend a general challenge schedule consisting of 3, 10, 30, 100, 300, 1000, and 3000 mg of food protein at intervals of at least 20 minutes. This method provides information on patients' reactions to the cumulative dose of food protein but does not examine the highest safe dose, as most symptoms develop after 20 minutes.⁹ The 3-level stepwise OFC can determine whether patients with allergies to egg, milk, or wheat can safely consume these foods at low or medium doses.

Our study had several limitations. First, OFCs were not double-blinded or placebo-controlled. However, most symptoms induced were objective, limiting assessment bias. Second, almost 25% of patients reacted to STEP 1, and 10% reacted to STEP 0. For safety reasons, we may recommend a 4-level stepwise OFC with all patients starting at STEP 0. Third, we should consider the inherent differences in antigenicity of heated foods. Lastly, most patients were young children who will likely outgrow these food allergies. Findings may be different in older children or children with peanut, tree nut, sesame, fish, and/or shellfish allergies. Therefore, multicenter, prospective studies should be conducted in the future to confirm the safety and effectiveness of this approach for various food allergens and for older children.

In conclusion, the 3-level stepwise OFC proposed here will help to avoid complete elimination of suspected food allergens, and contribute to improved food allergy management.

Acknowledgments

N.Y. conceived of this study, wrote this manuscript, analyzed the data, and generated figure. T.M. revised this manuscript and figures critically. N.Y., T.M. and S.K. collected data. S.K. helped to undergo this study. M.E. advised study design and helped

to conceive of this study. All authors read and approved the final manuscript.

The authors thank the pediatricians and nurses who participated in the recruitment of study subjects and data collection at Sendai Medical Center.

^aDepartment of Pediatrics, Sagami National Hospital, Kanagawa, Japan

^bDepartment of Pediatrics, Sendai Medical Center, Miyagi, Japan

^cDepartment of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagami National Hospital, Kanagawa, Japan

This study was supported by funds from the National Hospital Organization in data collection, analysis, and JSPS KAKENHI Grant Number 16K00899 in the interpretation of data and decision to submit the article for publication.

Conflicts of interest: M. Ebisawa is on the scientific advisory board of DBV Technologies and has received lecture fees from Pfizer and Siemens. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 1, 2016; revised June 16, 2017; accepted for publication June 23, 2017.

Available online ■■

Corresponding author: Noriyuki Yanagida, MD, Department of Pediatrics, Sagami National Hospital, 18-1, Sakuradai, Minami-ku, Sagami, Kanagawa 252-0392, Japan. E-mail: n-yanagida@sagami-hosp.gr.jp.

2213-2198

© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jaip.2017.06.029>

REFERENCES

- Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906-20.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008-25.
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-74.
- Turner PJ, Wainstein BK. Crossing the threshold: can outcome data from food challenges be used to predict risk of anaphylaxis in the community? *Allergy* 2016;72:9-12.
- Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. *Allergol Int* 2016;65:135-40.
- Yanagida N, Minoura T, Kitaoka S. Butter tolerance in children allergic to cow's milk. *Allergy Asthma Immunol Res* 2015;7:186-9.
- Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. Usefulness of wheat and soybean specific IgE antibody titers for the diagnosis of food allergy. *Allergol Int* 2009;58:599-603.
- Yanagida N, Sato S, Asaumi T, Ogura K, Borres MP, Ebisawa M. Safety and feasibility of heated egg yolk challenge for children with egg allergies. *Pediatr Allergy Immunol* 2017;28:348-54.
- Yanagida N, Minoura T, Kitaoka S. Allergic reactions to milk appear sooner than reactions to hen's eggs: a retrospective study. *World Allergy Organ J* 2016;9:12.

ONLINE REPOSITORY**METHODS****Oral food challenge test**

A 3-level stepwise oral food challenge (OFC) with a low-dose OFC was administered to diagnose food allergy or confirm tolerance acquisition safely, according to European Academy of Allergology and Clinical Immunology Guidelines^{E1} at Sendai Medical Center from 2010 to 2012. We included patients who first underwent a low-dose OFC for egg, milk, or wheat (STEP 1: 213 mg, 850 mg, and 374 mg, respectively) (Tables E1 and E2). Patients who tolerated the low-dose OFC received the medium-dose OFC for egg, milk, or wheat (STEP 2: 1550 mg, 3400 mg, and 2600 mg, respectively) within 12 months. If patients showed no reaction at STEP 2, a full-dose OFC for egg, milk, or wheat (STEP 3: 6200 mg, 6800 mg, and 5200 mg, respectively) was administered within 12 months. For suspected high-risk cases, a very-low-dose OFC for egg, milk, or wheat (STEP 0: 1.8 mg, 99 mg, and 146 mg, respectively) was implemented before STEP 1. The symptoms and the associated severity are described in Table E3.

Subjects

We excluded patients with missing clinical information or laboratory data, those who did not complete the subsequent OFC after a negative result for STEP 1 or STEP 2, and those who started oral immunotherapy.

ImmunoCAP analysis

Patients' levels of serum specific IgE (sIgE) against egg white, ovomucoid, milk, and wheat (Immuno CAPTM; Thermo Fisher Scientific/Phadia, Uppsala, Sweden) were measured within 6 months of OFC. If the sIgE for causative foods was >100 kU_A/L, dilution measurement was applied.

Statistical methods

The Mann-Whitney *U* test or Fisher exact test was performed, and a *P* value $<.05$ was considered statistically significant. We calculated predictive decision points (positive predictive value [PPV]) and probability curves, as previously described.^{E2,E3} To create probability curves and determine the PPV, we used regression analysis after logarithmic transformation of sIgE values.^{E3}

$$\text{Logit}(\Pr[Y = 1 \mid \ln(kU_A/L)]) = \alpha + \beta \ln(kU_A/L)$$

PPVs were applied within ranges that have the exact number of patients.

All analyses were performed using SPSS software (version 24.0 SPSS, Chicago, Ill).

Ethical considerations

This retrospective study was approved by the ethical committee of Sendai Medical Center. Written consent was obtained from all patients or guardians. All data were anonymized before the analysis.

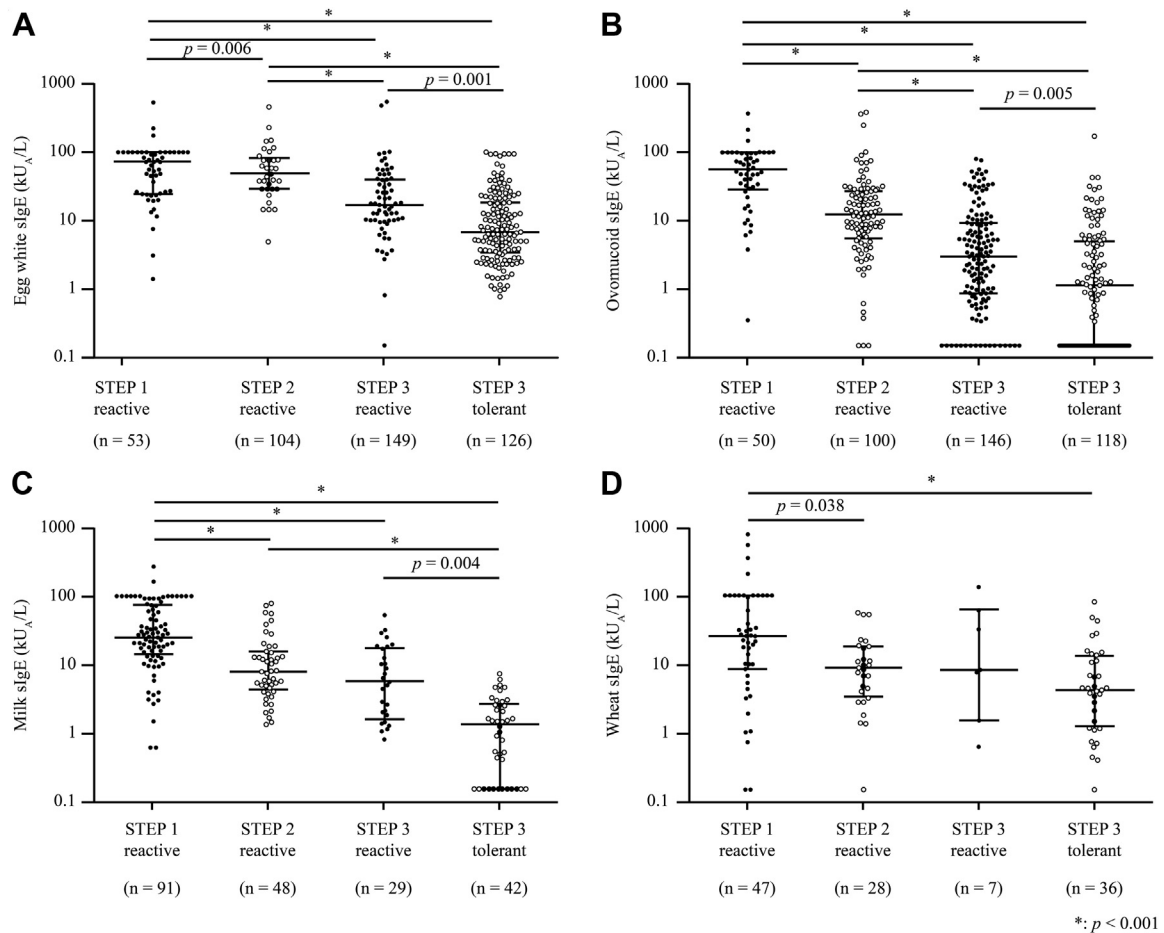


FIGURE E1. Differences in specific IgE (sIgE) titers for causative foods. Patients in the 4 groups differed significantly in sIgE levels when exposed to causative foods.

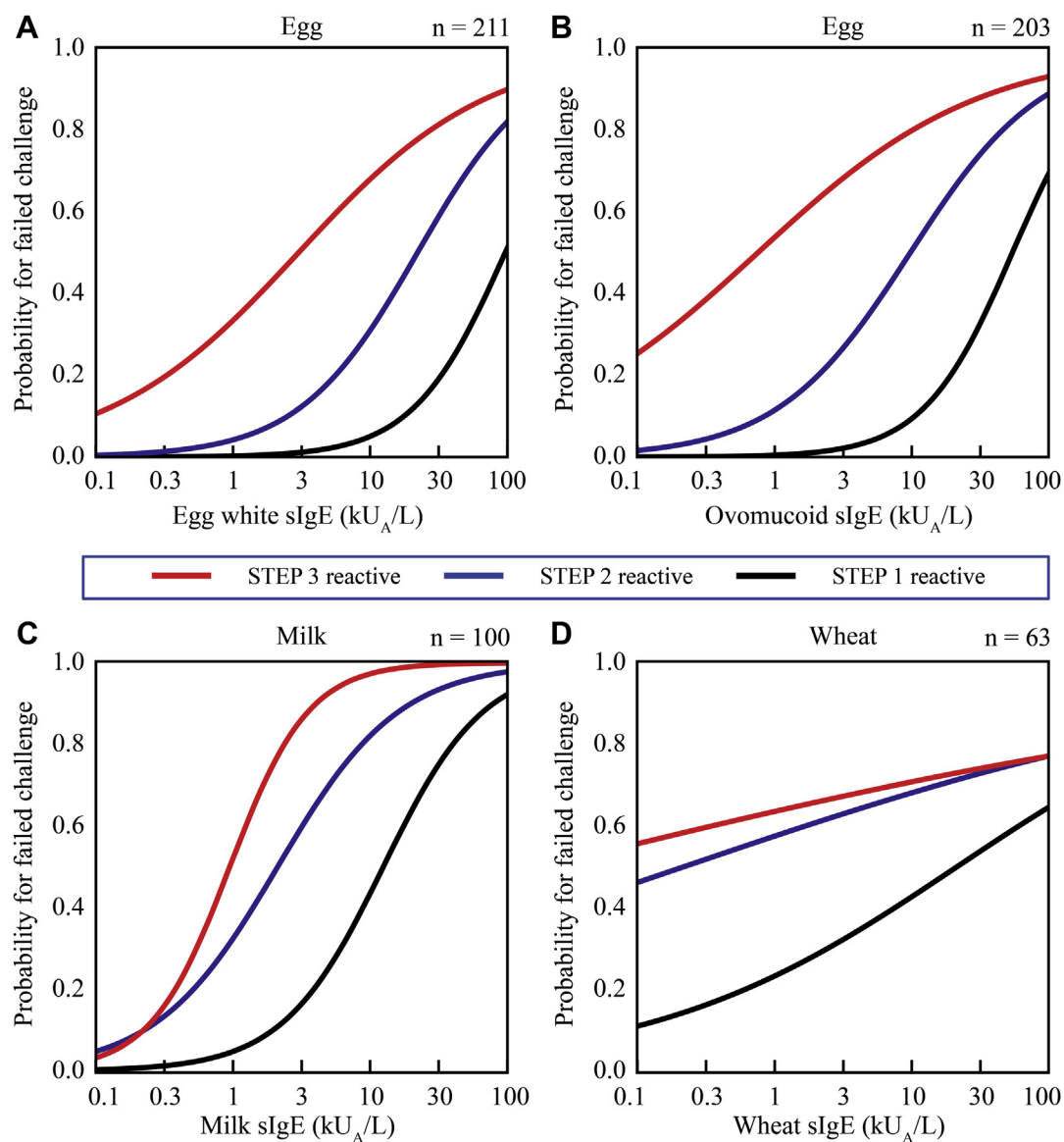


FIGURE E2. Fitted probability curves demonstrating stepwise oral food challenge (OFC) outcomes among patients aged 4 years or younger with respect to immunoglobulin E levels against (A) egg white, (B) ovomucoid, (C) milk, and (D) wheat. sIgE, Specific IgE.

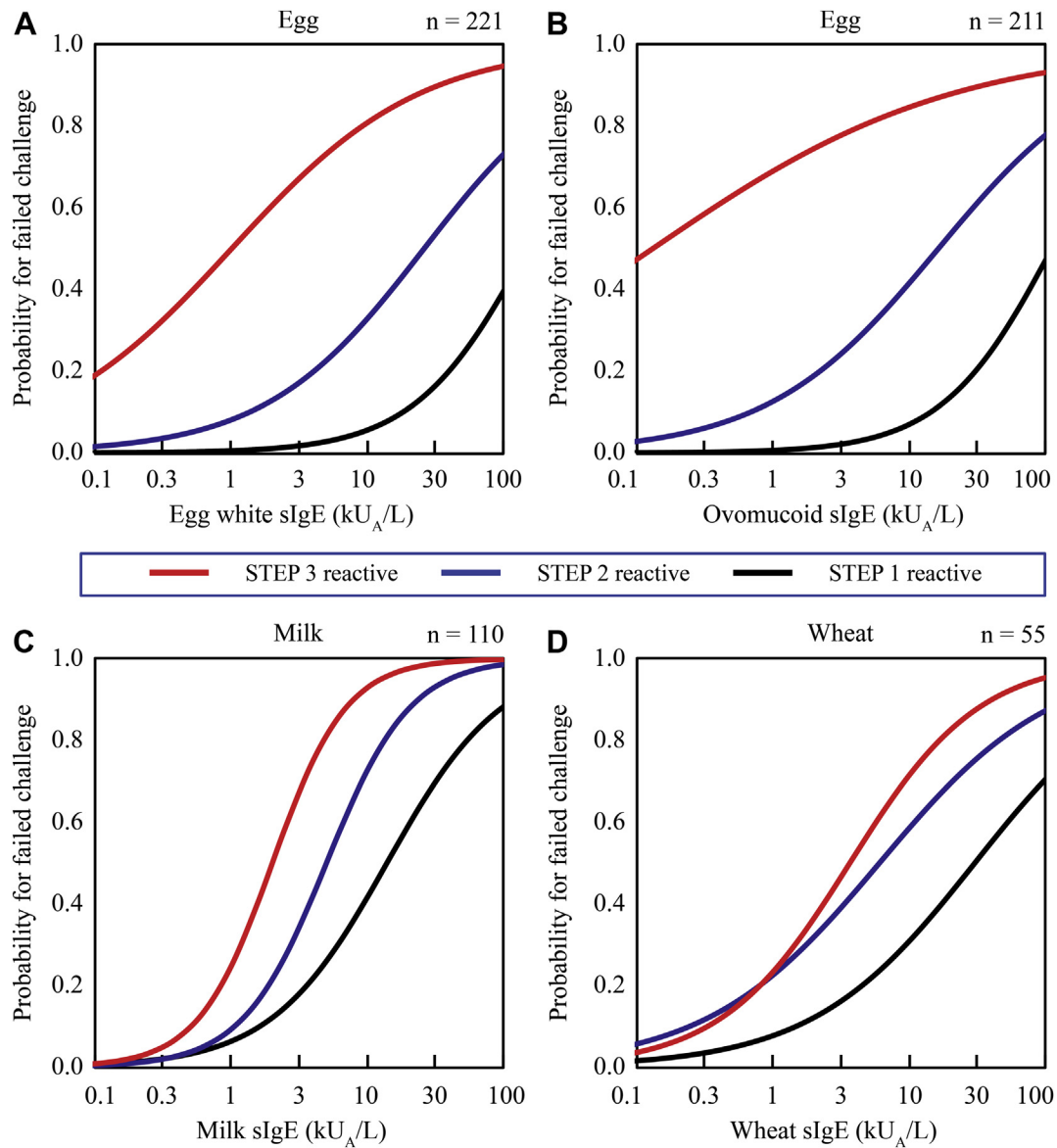


FIGURE E3. Fitted probability curves demonstrating stepwise oral food challenge (OFC) outcomes among patients older than 4 years with respect to immunoglobulin E levels against (A) egg white, (B) ovomucoid, (C) milk, and (D) wheat. sIgE, Specific IgE.

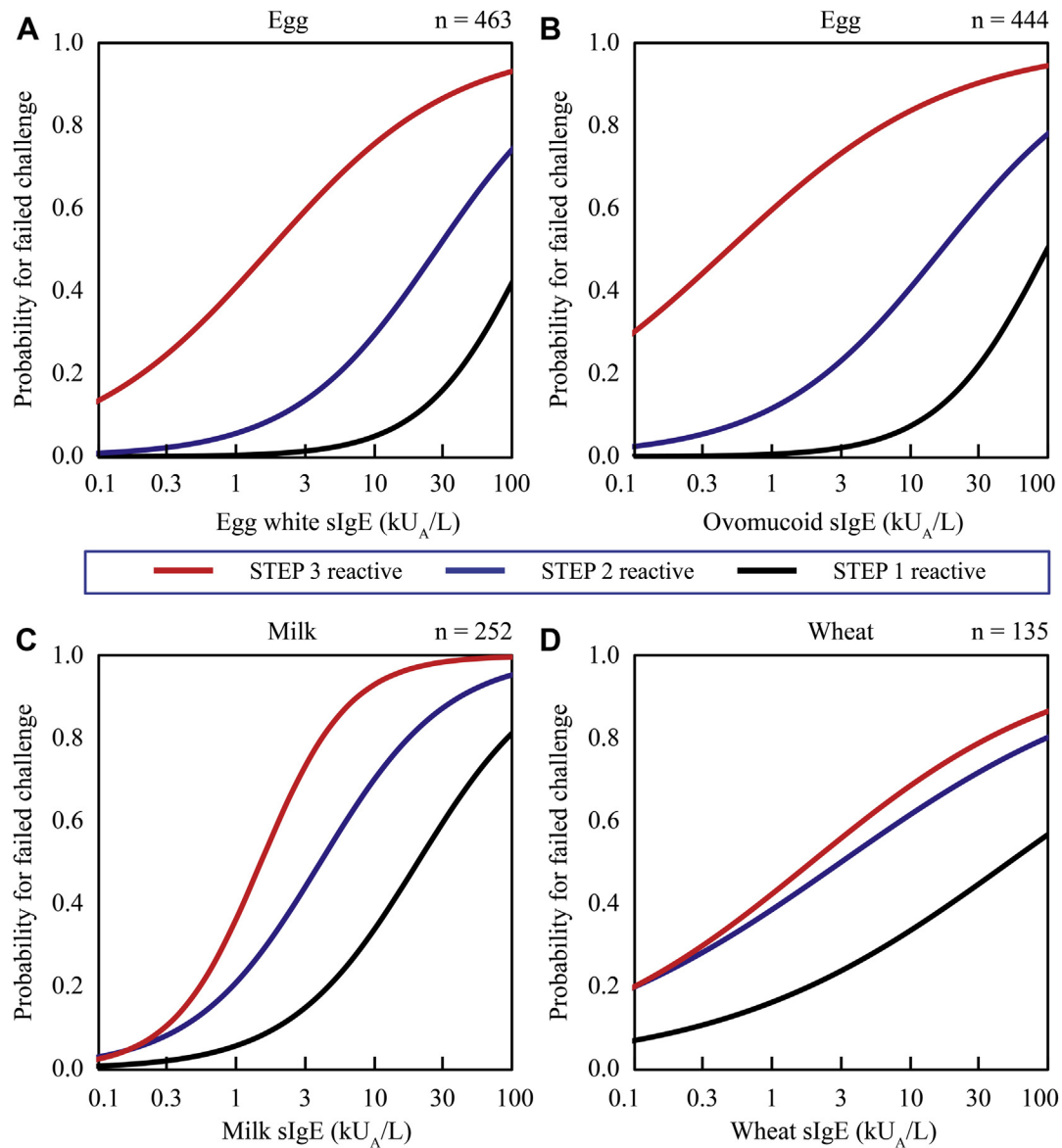


FIGURE E4. Fitted probability curves demonstrating stepwise oral food challenge (OFC) outcomes for the best case with respect to immunoglobulin E levels against (A) egg white, (B) ovomucoid, (C) milk, and (D) wheat. This analysis included patients who received oral immunotherapy or patients who did not undergo STEP 2 or STEP 3 oral food challenges. Patients who did not undergo STEP 2 or STEP 3 were regarded as those who tolerated STEP 3. sIgE, Specific IgE.

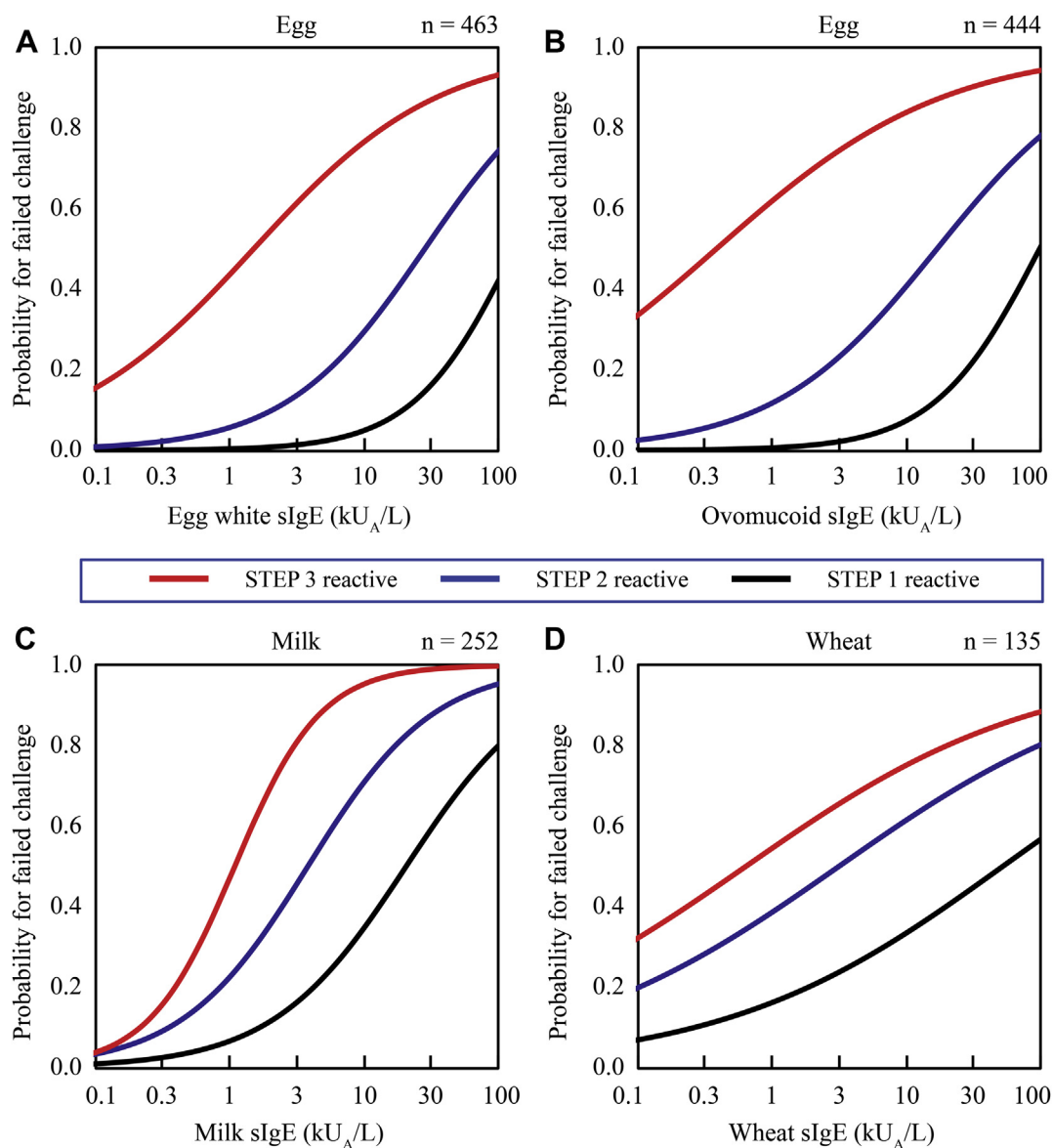


FIGURE E5. Fitted probability curves demonstrating stepwise oral food challenge (OFC) outcomes for the worst case with respect to immunoglobulin E levels against (A) egg white, (B) ovomucoid, (C) milk, and (D) wheat. This analysis included patients who received oral immunotherapy or patients who did not undergo STEP 2 or STEP 3 oral food challenges. Patients who did not undergo STEP 2 or STEP 3 were regarded as those who reacted to STEP 2 or STEP 3. sIgE, Specific IgE.

TABLE E1. Stepwise oral food challenge with the amount of protein* ingested for each challenge food

STEP	Egg	Cow's milk	Wheat
0 (very low dose)	1/4 boiled egg yolk (egg white 0.5 mg)	Sweet potato cake containing 10 g of butter (milk 99 mg)	One piece of wheat gluten cake (wheat 146 mg)
1 (low dose)	Pumpkin cake containing one heated egg yolk (egg white 148 mg)	Pumpkin cake containing 25 mL of heated milk (milk 850 mg)	2 pieces of a cookie (wheat 374 mg)
2 (medium dose)	Pumpkin cake containing 1/4 heated whole egg (egg white 1076 mg)	96 g of yogurt (milk 3400 mg)	100 g of udon noodles (wheat 2600 mg)
3 (full dose)	One scrambled egg (egg white 4303 mg)	200 mL of cow's milk (milk 6800 mg)	1 slice of white bread (wheat 5200 mg)

Challenge foods were prepared in the nutrition management room. STEP 1 was implemented in the hospital or in the outpatient clinic setting. STEP 2 and STEP 3 were implemented after hospital admission. A STEP 0 oral food challenge (OFC) (egg: whole egg protein 1.8 mg, egg yolk 0.6 mg, egg white 0.5 mg; cow's milk: milk protein 102 mg; wheat: wheat protein 146 mg) was implemented when a patient had a history of immediate reaction to a low dose of the causative food. In the OFC, 2 portions of the challenge food were administered, starting with 1/4 of the total load, followed by the remainder at 1 hour after starting the OFC. One slice of Japanese white bread contains much more wheat protein than a slice of white bread in the United States. These protein data were almost the same as those reported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan (2015) (<http://www.mext.go.jp/>).

*Amount of protein is provided in parentheses.

TABLE E2. Amounts of egg and milk protein in the challenge foods

Challenge food	Egg protein	Milk protein
1/4 of a boiled egg yolk (3.5 g) (Egg STEP 0)	1.8 mg	
Pumpkin cake containing one egg yolk (70 g) (Egg STEP 1)	213.2 mg	
Pumpkin cake containing 1/4 of a whole egg (24.2 g) (Egg STEP 2)	1657.1 mg	
Scrambled egg (45.3 g) (Egg STEP 3)	6591.5 mg	
Boiled whole egg (54.2 g)	6749.2 mg	
Raw egg (52.1 g)	6322.2 mg	
Pumpkin cake containing 25 mL of heated milk (63.3 g) (Milk STEP 1)		710.1 mg
Raw milk (200 mL) (Milk STEP 3)		6710.0 mg

The amounts of egg protein and milk protein were measured using the FASTKIT version III enzyme-linked immunosorbent assay egg kit and milk kit from NH Foods (Osaka, Japan) that detects whole egg protein and milk protein.

TABLE E3. Severity of symptoms during the oral food challenge

	1 (mild)	2 (moderate)	3 (severe)
Skin	Localized urticaria, exanthema, wheal, pruritus Swollen eyelid or lip	Generalized urticaria, exanthema, wheal, pruritus Swollen face	— —
Gastrointestinal tract	Pruritus of the throat or oral cavity Mild abdominal pain Nausea, emesis, diarrhea	Throat pain Moderate abdominal pain Recurrent emesis, diarrhea	— Cramps Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea —	Repetitive cough Chest tightness, wheezing detectable via auscultation	Persistent cough, hoarseness, “barky” cough Audible wheezing, dyspnea, cyanosis, saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	—	Pale face, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, lethargy	“Light-headedness,” feeling of “pending doom,” somnolence, headache	Confusion, loss of consciousness, incontinence

The severity score was based on the organ system that was most affected by the symptoms. Hypotension was defined as systolic blood pressure <70 mm Hg for children aged 1 month to 1 year, <70 + (2 × age) mm Hg for children aged 1–10 years, and <90 mm Hg for children aged >11 years. Mild hypotension was defined as systolic blood pressure <80 mm Hg for children aged 1 month to 1 year, <80 + (2 × age) mm Hg for children aged 1–10 years, and <100 mm Hg for children aged >11 years. Wheezing detectable via auscultation with a stethoscope was defined as mild wheezing. Audible wheezing was defined as wheezing detected without a stethoscope. This severity score was defined in the anaphylaxis guidelines for Japan. (Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. *Allergol Int* 2016; 65:135-40.)

TABLE E4. Background of patients

	Egg (n = 432)	Milk (n = 210)	Wheat (n = 118)
Sex (male)	292 (68%)	133 (63%)	68 (56%)
Age, y (median)	4.1 (2.3-6.0)	4.1 (2.6-7.1)	3.8 (2.3-6.6)
History of immediate reaction to causative food	277 (64%)	154 (73%)	85 (72%)
History of anaphylaxis to causative food	98 (23%)	90 (43%)	50 (42%)
Atopic dermatitis, current	255 (59%)	132 (63%)	70 (59%)
Bronchial asthma, current	125 (29%)	79 (38%)	38 (32%)
Allergic rhinitis, current	43 (10%)	28 (13%)	11 (9%)
Egg white sIgE (kU _A /L)	10.4 (3.6-29.5)		
Ovomucoid sIgE (kU _A /L)	5.2 (1.0-21.2)		
Milk sIgE (kU _A /L)		11.3 (2.6-28.1)	
Wheat sIgE (kU _A /L)			10.1 (3.4-31.1)
Total IgE (IU/mL)	402.6 (153.0-910.0)	499.1 (216.0-1300.0)	458.0 (155.0-1160.0)

sIgE, Specific IgE.

Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses.

TABLE E5. Positive results of rechallenged oral food challenges

	STEP 1	STEP 2	STEP 3
Egg	10/32 (31.3%)	12/48 (25.0%)	24/53 (45.3%)
Milk	28/38 (73.7%)	7/15 (46.7%)	2/7 (28.6%)
Wheat	10/18 (55.6%)	4/11 (36.4%)	—

Among 556 subjects who showed a reaction to the oral food challenge, 222 were rechallenged after a median of 182 d (range: 18-609 d). Of these patients, 44% (97/222) experienced a positive reaction to the rechallenge.

TABLE E6. Clinical efficacy of antigen-specific IgE for predicting positive OFC

Group	5% predicted probability	10% predicted probability	50% predicted probability	90% predicted probability	95% predicted probability
Egg STEP 1 (egg white sIgE)	9.3	17.9	120.9	n.e.	n.e.
Egg STEP 2 (egg white sIgE)	0.8	1.9	24.1	305.5	n.e.
Egg STEP 3 (egg white sIgE)	n.e.	n.e.	1.8	55.7	177.4
Egg STEP 1 (ovomucoid sIgE)	6.5	12.3	80.9	n.e.	n.e.
Egg STEP 2 (ovomucoid sIgE)	n.e.	0.8	13.1	223.1	n.e.
Egg STEP 3 (ovomucoid sIgE)	n.e.	n.e.	0.5	34.4	148.6
Milk STEP 1 (milk sIgE)	0.9	1.7	13.2	100.4	200.1
Milk STEP 2 (milk sIgE)	n.e.	0.5	3.4	23.0	44.0
Milk STEP 3 (milk sIgE)	n.e.	n.e.	1.4	6.2	10.2
Wheat STEP 1 (wheat sIgE)	n.e.	n.e.	25.8	n.e.	n.e.
Wheat STEP 2 (wheat sIgE)	n.e.	n.e.	1.9	680.7	n.e.
Wheat STEP 3 (wheat sIgE)	n.e.	n.e.	1.1	202.1	n.e.

n.e., Not estimated; OFC, oral food challenge; sIgE, serum specific IgE.

IgE values are presented in kU_A/L.

The exact ranges of egg white specific, ovomucoid specific, milk specific, and wheat specific IgE are 0.1-563, 0.1-394, 0.1-273, and 0.1-795, respectively. Thus, we did not calculate the values outside of these ranges.

TABLE E7. Data related to the severity of reactions induced during a positive challenge and the subsequent treatment received

Symptom	Egg (n = 306)	Milk (n = 168)	Wheat (n = 82)
Organ system affected			
Skin	166 (54%)*	127 (76%)	69 (84%)
Respiratory	91 (30%)	121 (72%)	54 (66%)
Oral	96 (31%)	79 (47%)	19 (23%)
Gastrointestinal	214 (70%)	34 (20%)	14 (17%)
Neurological	0 (0%)	0 (0%)	0 (0%)
Cardiovascular	0 (0%)	0 (0%)	0 (0%)
Severity			
Mild (grade 1)	62 (20%)	38 (23%)	23 (28%)
Moderate (grade 2)	234 (77%)	125 (74%)	57 (70%)
Severe (grade 3)	7 (2%)	5 (3%)	2 (2%)
Treatment			
Antihistamine (oral)	220 (72%)	128 (76%)	78 (71%)
Antihistamine (intravenous or intramuscular)	5 (2%)	4 (2%)	3 (4%)
β ₂ stimulant inhalation	35 (11%)	54 (32%)	25 (31%)
Fluid infusion (intravenous)	0 (0%)	3 (2%)	0 (0%)
Steroid (intravenous)	2 (1%)	3 (2%)	0 (0%)
Steroid (oral)	116 (38%)	63 (38%)	30 (37%)
Adrenaline (intramuscular)	0 (0%)	1 (1%)	0 (0%)
No treatment	82 (27%)	37 (22%)	20 (24%)

*Data are expressed as n (%).

TABLE E8. Data related to severe reactions induced during a positive challenge among different STEPs

STEP	Egg	Milk	Wheat
STEP 0	0/5 (0%)*	0/6 (0%)	0/5 (0%)
STEP 1	2/51 (4%)	5/89 (6%)	2/42 (5%)
STEP 2	3/104 (3%)	0/48 (0%)	0/28 (0%)
STEP 3	2/149 (1%)	0/29 (0%)	0/7 (0%)

Intramuscular adrenaline was needed in 1 patient in the milk STEP 1.

*Data are expressed as severe symptoms/challenge positive cases (%).

REFERENCES

- E1. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008-25.
- E2. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
- E3. Soderstrom L, Kober A, Ahlstedt S, de Groot H, Lange CE, Paganelli R, et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. *Allergy* 2003;58:921-8.